Australian Government

Australian Pesticides and Veterinary Medicines Authority

Public Release Summary

on the evaluation of the new active fluazaindolizine in the product Salibro Reklemel active Nematicide

APVMA product number 89013

July 2021

ISSN 1443-1335 (electronic)

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This publication is available from the APVMA website.

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Preface

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator responsible for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia. Before approving an active constituent and/or registering a product, the APVMA must be satisfied that the statutory criteria, including the safety, efficacy, trade, and labelling criteria, have been met. The information and technical data required by the APVMA to assess the statutory criteria of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined on the APVMA website.

The APVMA has a policy of encouraging transparency in its activities and seeking community involvement in decision making. Part of that process is the publication of Public Release Summaries for products containing new active constituents. This Public Release Summary is intended as a brief overview of the assessment that has been conducted by the APVMA and of the specialist advice received from advisory agencies, including other Australian Government agencies and state departments of primary industries. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience to encourage public comment.

About this document

This Public Release Summary indicates that the APVMA is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

- the toxicology of both the active constituent and product
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop or animal safety.

Comment is sought from interested stakeholders on the information contained within this document.

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for approval of the new active constituent, fluazaindolizine and registration of Salibro Reklemel active Nematicide should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade, and efficacy and target crop or animal safety. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on 10 August 2021 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or organisation name (if relevant)
- email or postal address (if available)
- the date you made the submission.

Please note: submissions will be published on the APVMA's website, unless you have asked for the submission to remain confidential, or if the APVMA chooses at its discretion not to publish any submissions received (refer to the public consultation coversheet).

Please lodge your submission using the public consultation coversheet, which provides options for how your submission will be published.

Note that all APVMA documents are subject to the access provisions of the *Freedom of Information Act 1982* and may be required to be released under that Act should a request for access be made.

Unless you request for your submission to remain confidential, the APVMA may release your submission to the applicant for comment.

Written submissions should be addressed to:

Case Management and Administration Unit
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GPO Box 3262
Sydney NSW 2001

Phone: +61 2 6770 2300
Email: enquiries@apvma.gov.au

Further information

Further information can be obtained via the contact details provided above.

Copies of technical evaluation reports covering chemistry, efficacy and safety, toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA on request.

Further information on Public Release Summaries can be found on the APVMA website.

Introduction

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Salibro Reklemel active Nematicide, and approval of the new active constituent, fluazaindolizine.

Applicant

Production Agriscience (Australia) Pty Ltd.

Purpose of application

Production Agriscience (Australia) Pty Ltd has applied to the APVMA for registration of the new product Salibro Reklemel active Nematicide, containing 500 g/L, as a suspension concentrate (SC) formulation of the new active constituent fluazaindolizine.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of the product Salibro Reklemel active Nematicide, and approval of the new active constituent fluazaindolizine.

Proposed claims and use pattern

Salibro Reklemel active Nematicide is a nematicide intended for control of root-knot nematodes in cucurbits, fruiting vegetables and root and tuber vegetables. Proposed application methods are by direct injection into drip/trickle irrigation or as in-furrow soil spray, incorporated by irrigation or mechanically, either pre- or post-planting. Maximum application rates are 4 L/ha per year, either as a single treatment or as 2 applications of 2 L/ha.

Mode of action

Fluazaindolizine is a selective contact sulfonamide nematicide for the control of plant parasitic nematodes. It acts only on plant parasitic nematodes, and is not active against insect pests, plant pathogens or weeds. The mode of action is novel but remains unknown and has been designated as a Group N-UN: Unknown by the Insecticide Resistance Action Committee (IRAC 2018). Fluazaindolizine is efficacious broadly against pest nematodes species and specifically effective on root-knot nematodes (*Meloidogyne* spp.), reniform nematodes (*Rotylenchulus* spp.), dagger nematodes (*Xiphinema* spp.) and some lesion nematodes species (*Pratylenchus* spp.).

Overseas registrations

Registration of fluazaindolizine products is currently being sought in several other countries, including the USA, Canada, Japan and EU.

Chemistry and manufacture

Active constituent

The active constituent fluazaindolizine is manufactured overseas. Details of the chemical name, structure, and physicochemical properties of fluazaindolizine are listed below (Tables 1 to 2).

Fluazaindolizine is an off-white solid crystalline powder. It has a moderate solubility in water, with its solubility increased with increasing pH values due to ionization, with the Henry's Law constant showing corresponding decreases. The water solubility is 0.02 g/L at pH 4 and increases to 2.85 g/L at pH 9. Similarly, the logP of the molecule is 2.2 at pH 4 but it is -0.7 at pH 9. The vapour pressure (2.04×10^{-6} Pa at 20°C) and the Henry's law constant (0.46×10^{-6} Pa-m^3/mol at 20°C and pH 7) indicate that volatilisation is not expected to be a significant route of dissipation for fluazaindolizine. There are no flammable, explosive, self-ignition and/or oxidizing properties of safety concern for fluazaindolizine.

Table 1: Nomenclature and structural formula of the active constituent fluazaindolizine

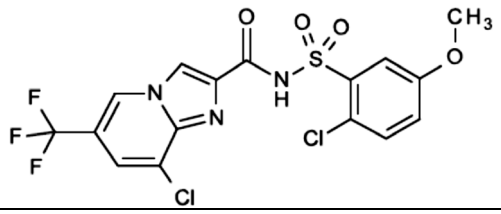
Common name (ISO):	Fluazaindolizine
IUPAC name:	8-chloro-*N*-[(2-chloro-5-methoxyphenyl)sulfonyl]-6-(trifluoromethyl)imidazo [1,2-*a*]pyridine-2-carboxamide
CAS registry number:	1254304-22-7
Molecular formula:	$C_{16}H_{10}Cl_2F_3N_3O_4S$
Molecular weight:	468.2 g/mol
Structural formula:	

Table 2: Key physicochemical properties of the active constituent fluazaindolizine

Physical form:	Technical grade (96.4% purity) – solid, purified active (99.6% purity) – solid
Colour:	Technical grade – light yellowish grey, purified active – off-white
Odour:	Technical grade – odourless, purified active – odourless
Melting point:	218.5°C
Boiling point:	The test substance decomposes at 260°C before boiling
Relative density	Bulk density – 0.619 g/mL, tap density – 0.795 g/mL
Stability:	In an accelerated model at temperature, 1% decomposition of the active is observed after 2 weeks storage at 54°C. No adverse reactions to metal or metal ions (aluminium and iron and its acetate) were observed following storage for 2 weeks at 54°C. Technical fluazaindolizine is expected to be stable during storage under normal conditions for at least 2 years.
Safety properties:	Not considered flammable. Not explosive. Auto-flammability is 218.5°C. Except for photo-degradation in water, fluazaindolizine technical does not show any chemical incompatibility with oxidising, reducing or fire extinguishing agents, and is essentially non-hazardous.
Solubility in water:	0.022 g/L (pH 4) 2.15 g/L (pH 7) 2.84 g/L (pH 9) at 20 °C
Organic solvent solubility:	Acetone 99.8 g/L Acetonitrile 35.0 g/L Ethyl acetate 27.6 g/L Methanol 3.4 g/L Dichloroethane 19.2 g/L Xylenes 1.2 g/L n-hexane 0.002 g/L n-octanol 2 g/L
Octanol/water partition coefficient (Log K_{ow}/K_{OW}):	log P_{ow} = 2.24, pH 4 log P_{ow} = -0.16, pH 7 log P_{ow} = -0.71, pH 9 at 25 ˚C
Vapour pressure:	2.04 x10^{-7} Pa at 20 °C 4.12 x10^{-7} Pa at 35 °C
Henry's law constant:	0.45 x 10^{-4} Pa m^3/mol (pH 4) 0.46 x 10^{-6} Pa m^3/mol (pH 7) 0.35 x 10^{-6} Pa m^3/mol (pH 9)
UV/VIS absorption spectra:	λ_{max}235 nm in acidic and basic solution λ_{max}298 nm in neutral solution

Formulated product

The product Salibro Reklemel active Nematicide will be manufactured overseas. Tables 3 and 4 outline some key aspects and physicochemical properties of the product.

Salibro Reklemel active Nematicide will be available in 1 L to 200 L HDPE (high density polyethylene) containers.

Table 3: Key aspects of the formulation of the product Salibro Reklemel active Nematicide

Distinguishing name:	Salibro Reklemel active Nematicide
Formulation type:	Suspension concentrate (SC)
Active constituent concentration/s:	500 g/L fluazaindolizine

Table 4: Physicochemical properties of the product Salibro Reklemel active Nematicide

Physical form:	Off-white coloured liquid
PH:	3.75 – 4.6 (1% aqueous dilution)
Relative density:	1.205 – 1.22 g/mL at 20ºC
Surface tension:	32 mN/m at 20ºC
Pourability:	Pour residue = 2.45%; rinsed residue = 0.13%
Persistent foaming:	14 ± 2 mL foam
Suspensibility:	97.5% (1% w/v dilution)
Spontaneity of dispersion:	98.7 ± 0.2%
Safety properties:	Not classified as a flammable liquid, explosive, or an oxidising substance.
Storage stability:	There were sufficient data to conclude that the product is expected to remain within specifications for at least 2 years when stored under normal conditions.

Recommendations

The APVMA Chemistry section has evaluated the chemistry of the active constituent fluazaindolizine and associated product Salibro Reklemel active Nematicide, including the physicochemical properties, specifications, manufacturing process, quality control procedures, packaging, stability, batch analysis results and analytical methods, and found them to be acceptable. The available storage stability data indicate that the formulated product is expected to remain stable for at least 2 years when stored under normal conditions.

Based on a review of the chemistry and manufacturing details, the registration of Salibro Reklemel active Nematicide, and approval of the active constituent fluazaindolizine, are supported from a chemistry perspective.

Toxicological assessment

A full data package was assessed for fluazaindolizine. There are no objections on human health grounds to the approval of fluazaindolizine.

Evaluation of toxicology

Chemical class

Fluazaindolizine is a novel nematicide, and the biochemical mode of action is currently unknown. It is selective for plant parasitic nematodes, and is the first commercialised member of a new class of halogenated indole nematicides.

Pharmacokinetics

Approximately half of the oral doses administered were absorbed, with the remainder excreted unchanged in faeces. Following absorption, fluazaindolizine was widely distributed. Levels in tissue were lower than levels in blood, and there was no potential for accumulation identified following repeat dosing. Fluazaindolizine was rapidly excreted in urine, largely as unchanged fluazaindolizine. There was limited metabolism, with major pathways involving demethylation, hydroxylation of the phenyl ring, and hydrolysis of the amide bond.

Acute toxicity (active constituent)

Fluazaindolizine has low acute toxicity after oral, dermal or inhalation administration. Fluazaindolizine was not irritating to the eyes and was not a skin sensitiser, however it was a moderate eye irritant in rabbits.

Acute toxicity (product)

Salibro Reklemel active Nematicide was of very low acute oral and inhalation toxicity, and low dermal toxicity. It was a slight eye and skin irritant, and not a skin sensitiser.

Repeat-dose toxicity

In short- and long-term repeat oral dosing studies, the main adverse effects of fluazaindolizine were histopathological lesions mainly in the urinary tract among rodents (mice and rats), or in the liver in dogs.

The no observed adverse effect level in a 28 day dietary study in mice was 6000 ppm in the diet (equal to 1,105 mg/kg bw/day), the highest dose tested. In a 90 day study in mice, histopathological effects were seen in the liver, gall bladder and kidney at 3,000 ppm in the diet, and the no observed adverse effect level was 1k000 ppm in the diet, equivalent to 146 mg/kg bw/day.

In rats, histopathological effects on the kidney were seen after 90 days of feeding fluazaindolizine at concentrations above 3,000 ppm in the diet. The no observed effect level was 1,500 ppm, equal to 84 mg/kg bw/day.

Two studies were conducted in dogs, for 3 months and 12 months. At 4,000 ppm, liver changes included pigment accumulation, and gall bladder changes included pigmented luminar content.

Effects including mortality, reduced bodyweight gain and liver changes were observed in dogs fed 1,500 ppm, equivalent to 59 mg/kg bw/day. The overall no observed adverse effect level was 1,000 ppm, equivalent to 36 mg/kg bw/day.

Chronic toxicity and carcinogenicity

Chronic dietary studies in mice and rats were conducted. In mice, deposition of amyloid was seen in several organs at 3,000 ppm (equivalent to 436 mg/kg bw/day). The overall no observed adverse effect level for the study was 1,000 ppm (equivalent to 142 mg/kg bw/day). Neoplasia was not recorded in this study, and the no observed adverse effect level for carcinogenicity was at the highest tested dose of 3,000 ppm (equivalent to 436 mg/kg bw/day).

The overall no observed adverse effect level in rats for dietary administration was 1,500 ppm (equivalent to 76 mg/kg bw/day), based on histopathological effects seen in the kidneys, along with urinalysis changes at 4,500 ppm (equivalent to 241 mg/kg bw/day). No evidence of neoplasia was recorded at any tested dose, and the no observed adverse effect level for carcinogenicity was the highest dose tested of 4,500 ppm (equivalent to 241 mg/kg bw/day).

Reproductive and developmental toxicity

In a 2-generation reproductive toxicity study, the no observed adverse effect level for parental toxicity was 500 ppm in the diet (equivalent to 36 mg/kg bw/day), based on urinary tract effects. This was also the no observed adverse effect level for offspring toxicity, based on urinary tract effects. The no observed effect level for reproductive effects was 4,500 ppm (equivalent to 273 mg/kg bw/day), the highest dose tested.

Fluazaindolizine produced decreased foetal bodyweight and maternotoxic doses in rats, with a no observed adverse effect level for maternal toxicity, embyrotoxicity and foetotoxicity of 200 mg/kg bw/day. In rabbits, no embryo or foetotoxicity was observed, and the no observed adverse effect level was 120 mg/kg bw/day, the highest dose tested. The no observed adverse effect level for maternotoxicity was 30 mg/kg bw/day, based on the presence of reduced body weight gain at 120 mg/kg bw/day. Overall, it was concluded that fluazaindolizine is unlikely to be a teratogen.

Genotoxicity

Fluazaindolizine was tested for genotoxicity in an adequate range of *in vitro* and *in vivo* assays. The overall weight of evidence indicates that fluazaindolizine is unlikely to be genotoxic *in vivo*.

Neurotoxicity/immunotoxicity

Based on the results of acute and short-term studies in rats, it was concluded that fluazaindolizine is unlikely to be a neurotoxin.

The no observed adverse effect level for the humoral immune response was equal to 393 mg/kg bw/day in a 28 day rat study, significantly higher levels than other systemic toxicity effects.

Fluazaindolizine was also tested for its potential to interact with the endocrine system in a range of studies. All studies demonstrated that there was no interaction with estrogen or androgen-receptor pathways, or thyroid pathways.

Toxicity of metabolites and/or impurities

The acute oral toxicity of several mouse, rat and plant metabolites was investigated, and found to be of low to very low acute oral toxicity. The weight of evidence suggested that all fluazaindolizine metabolites tested were unlikely to be genotoxic.

As metabolites were present in the urine of mice and rats at levels of less than 10% of the administered dose, specific toxicity could not be considered to have been adequately assessed using studies of the parent compound. As some residues were present in edible crops, repeat dose toxicity, reproduction and developmental studies were undertaken with certain metabolites. Overall they were considered likely to be equitoxic, and an ADI established for fluazaindolizine was considered to be protective for a dietary risk assessment.

Health-based guidance values and poisons scheduling

Poisons Standard

Fluazaindolizine is included in Schedule 5 of the Standard for the Uniform Scheduling of Medicines and Standards (SUSMP) in preparations containing 50% or less fluazaindolizine. Fluazaindolizine is included in Schedule 6, except when included in Schedule 5. Salibro Reklemel active Nematicide contains 50% fluazaindolizine, is therefore included in Schedule 5, and requires a CAUTION signal heading.

Health-based guidance values

Acceptable daily intake

An acceptable daily intake (ADI) for fluazaindolizine was established at 0.4 mg/kg bw/d. This was based on an overall NOAEL of 36 mg/kg bw/d for mortality, reduced bodyweight gain, and histopathological findings (i.e. single cell necrosis and periportal vacuolation) from the liver of dogs fed diets of around 1,500 ppm in 3- and 12-month studies, or equivalent to a dose of 59 mg/kg bw/d. The same NOAEL was also observed in a two-generation reproduction study in rats, with histopathological lesions occurring in the kidney, ureter, bladder and urethra in parental animals and weanlings at 88 mg/kg bw/d. To establish the ADI, a 100-fold uncertainty factor (UF) was applied to the NOAEL to incorporate differences in toxicodynamics and toxicokinetics between, and within species. The ADI (0.4 mg/kg bw/d) applies to fluazaindolizine and its metabolites, namely IN-A5760, IN-REG72, IN-TQD54, IN-UJV12, IN-F4106, IN-QEK31, IN-QZY47 and IN-TMQ01 (expressed as fluazaindolizine). However, the ADI does not apply to metabolite IN-VM862. No separate ADI or ARfD can be established for the metabolite IN-VM862, as the database is not sufficient for

this purpose. For chronic toxicity, the threshold of toxicological concern (TTC) principle for non-genotoxic substances (i.e. Cramer class III; 1.5 µg/kg bw/d) is applicable to metabolite IN-VM862.

Acute reference dose

The acute reference dose (ARfD) for fluazaindolizine was established in an acute oral neurotoxicity study at 1.3 mg/kg bw based on a NOAEL of 125 mg/kg bw for inappetence and bodyweight loss. In the absence of any chemical specific data to adjust the uncertainty factor (UF) for extrapolation from laboratory animals to humans, or take account of differences in toxicodynamics and toxicokinetics between and within species, a default 100-fold UF is applied to the NOAEL. The ARfD is applicable to the general population. The ARfD applies to fluazaindolizine and its metabolites, namely IN-A5760, IN-REG72, IN-TQD54, IN-UJV12, IN-F4106, IN-QEK31, IN-QZY47 and IN-TMQ01, expressed as fluazaindolizine. However, the ARfD for fluazaindolizine does not apply to metabolite IN-VM862.

Recommendations

There are no objections on human health grounds to the approval of fluazaindolizine.

Residues assessment

Metabolism, analytical methodology, residue trial data, fate in storage and trade aspects have been considered for fluazaindolizine.

Metabolism

The metabolism of fluazaindolizine was investigated in plants (tomato, carrot, potatoes, soybean and sugarcane) and in livestock (lactating goats, and laying hens). The metabolism of fluazaindolizine was also investigated in confined rotational crops (wheat, spinach and radish).

Metabolism in plants

In metabolism and field residue studies, parent fluazaindolizine was analysed prior to a hydrolysis step. Metabolites were generally detected as conjugates, and a hydrolysis step was required to convert them to their core structures for analysis.

Parent fluazaindolizine accounted for up to 3.7% TRR in tomato foliage (0.034 mg/kg), up to 8.4% to 13% TRR in carrot roots (0.009 to 0.011 mg/kg), up to 21% to 41% TRR in carrot foliage (0.93 to 1.3 mg/kg), up to 6.8% to 9.3% TRR in immature potato tubers (0.004 to 0.006 mg/kg) and 8.3% to 46% TRR in soybean seed (0.13 to 0.17 mg/kg). Considering rotational crops, parent fluazaindolizine was found above 10% TRR in spinach (up to 29.0%, up to 0.114 mg/kg) and radish roots (up to 17.3%, 0.048 mg/kg).

The most common post hydrolysis metabolites observed in food commodities from primary crop plant metabolism studies were IN-QEK31 at 75%, IN-TMQ01 at 60% and IN-QZY47 at 23% TRR. Metabolite IN-A5760 was a significant component of the TRR (50%, 0.033 mg/kg) in tomato fruit. IN-UNS90 was less significant in food commodities from primary crop metabolism studies (up to 20% TRR), and more significant in confined rotational crop studies where it was found at up to 67% TRR, 0.78 mg/kg in wheat forage. IN-F4106 was significant in soybean seed at 54% TRR, 0.15 mg/kg.

Metabolism in livestock

Goats dosed with ^{14}C-Ph labelled fluazaindolizine, and ^{14}C-IP labelled fluazaindolizine showed rapid elimination of fluazaindolizine and its metabolites in urine (33% and 21% dose, respectively), faeces (51% and 52% dose, respectively) and bile (2.9% and 4.8% dose respectively) at sacrifice. TRR levels in edible tissues were 0.22 mg/kg in liver, 0.36 mg/kg in kidney, 0.011 mg/kg in muscle, 0.015 mg/kg in omental fat, 0.028 mg/kg in renal fat and 0.024 mg/kg in subcutaneous fat from the ^{14}C-Ph labelled fluazaindolizine dosed goat, and 0.28 mg/kg in liver, 0.36 mg/kg in kidney, 0.010 mg/kg in muscle, 0.008 mg/kg in omental fat, 0.014 mg/kg in renal fat and 0.013 mg/kg in subcutaneous fat from the ^{14}C-IP labelled fluazaindolizine dosed goat.

In the goat metabolism study for ^{14}C-Ph labelled fluazaindolizine, parent accounted for 18% to 85% TRR in tissues and milk. In milk and tissues, the phenyl-derived metabolites included IN-A5760 (maximum 4.1% TRR), IN-F4106 (maximum 38% TRR) and IN-REG72 (maximum 7.0% TRR).

In the goat metabolism study for ^{14}C-IP labelled fluazaindolizine, parent accounted for 25% to 83% TRR in tissues and milk. In milk and tissues, the imidazopyridine-derived metabolites included IN-QEK31 (maximum 42.8% TRR), IN-REG72 (maximum 12% TRR) and IN-R2W56 (maximum 0.6% TRR).

Metabolism studies have been provided for metabolites IN-QEK31, IN-QZY47 and IN-TMQ01 in lactating goat, and a hen study is also available for IN-QEK31.

The IN-QEK31 goat metabolism study showed that unchanged IN-QEK31 accounted for the majority of residues (95% TRR) in milk, with greater than 69% TRR present in the various tissues. Formed via methylation of the carboxylic acid group of IN-QEK31, IN-R2W56 was present as a metabolite in renal fat at 17% TRR, but at a low concentration of 0.008 mg/kg.

In the IN-QZY47 goat metabolism study, metabolites present at greater than 10% TRR and 0.01 mg/kg in various tissues and/or milk included: IN-A5760 (including sulphate ~41.0% TRR in milk, glucuronide ~67% TRR in kidney and glutathione conjugates) and metabolite IN-F4106 up to 81% TRR.

In the IN-TMQ01 goat metabolism study, milk and tissues that contained greater than 0.01 mg/kg, approximately 66.1% to 100% of the total radioactive residue was characterised or identified. Unchanged IN-TMQ01 accounted for the majority of residues in the various tissues (43% to 87% TRR). IN-F4106 was identified as the major residue in milk at 98% TRR, 0.007 mg/kg, and was present in other tissues collected but only at very low concentrations (≤0.002 mg/kg).

In the laying hen metabolism studies, 93% to 94% TRR was recovered in excreta or cage washes. Whole eggs accounted for <0.1% of the dose and edible tissues accounted for <0.6% of the dose for both labels. TRR levels in edible tissues from ^{14}C-Ph labelled fluazaindolizine dosed hens were 0.732 mg/kg in liver, 0.043 mg/kg in muscle and 0.020 mg/kg in abdominal fat. TRR levels in edible tissues from ^{14}C-IP labelled fluazaindolizine dosed hens were 0.701 mg/kg in liver, 0.047 mg/kg in muscle and 0.027 mg/kg in abdominal fat.

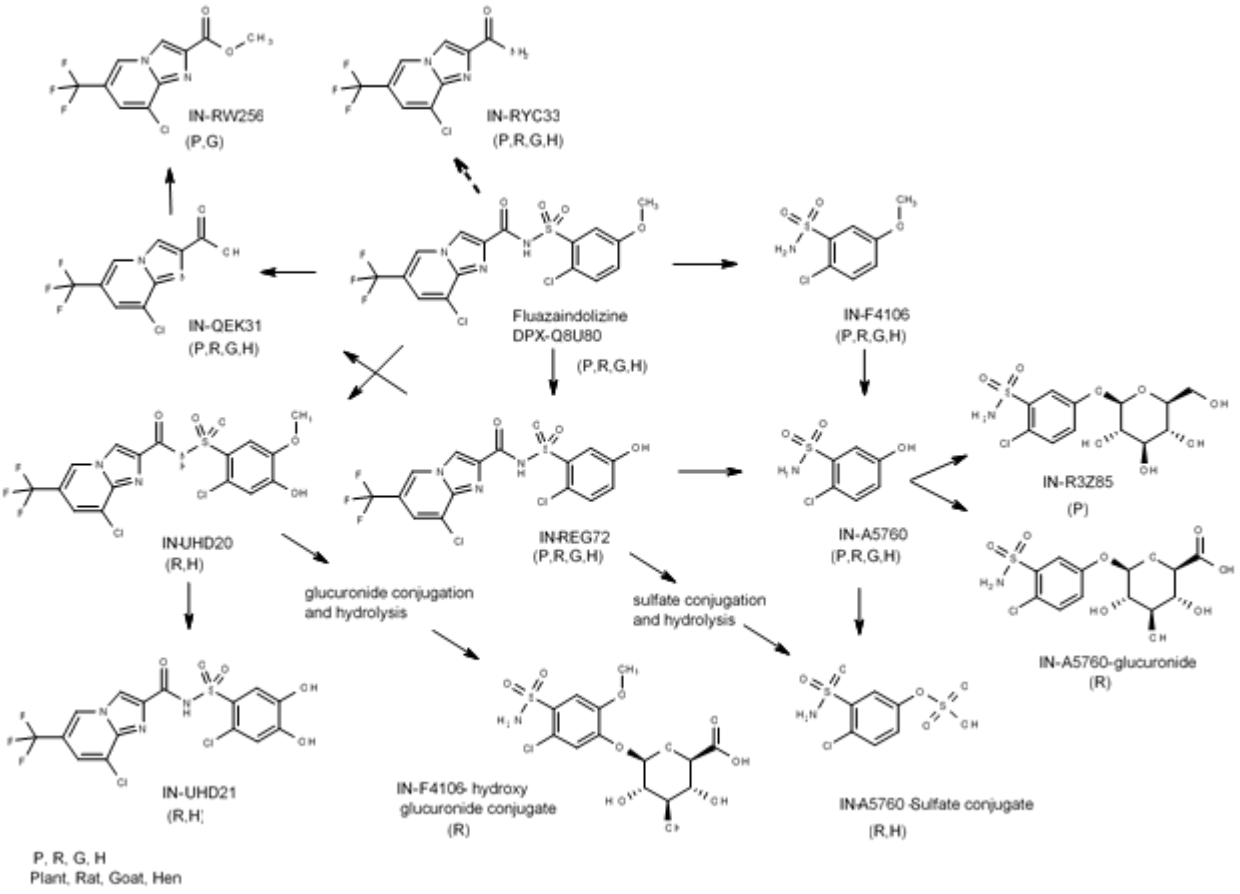
In the hen metabolism study for ^{14}C-Ph labelled fluazaindolizine, parent accounted for 67.5% to 96.5% TRR in tissues and eggs. In tissues and eggs, the phenyl-derived metabolites included IN-F4106 (maximum 5.7% TRR) and IN-REG72 (maximum 1.1% TRR).

In the hen metabolism study for ^{14}C-IP labelled fluazaindolizine, parent accounted for 66% to 97% TRR in tissues and eggs. In tissues and eggs, the imidazopyridine-derived metabolites included IN-QEK31 (maximum 4.9% TRR), IN-REG72 (maximum 1.1% TRR), IN-RYC33 (maximum 11.0% TRR) and IN-R2W56 (maximum 1.9% TRR).

In the laying hen metabolism study with IN-QEK31, unchanged IN-QEK31 was the major component found in liver (the only tissue with residues >0.01 mg/kg) at 71 % TRR.

The metabolic pathway of fluazaindolizine in plants and animals is summarised below in Figure 1.

Figure 1: Metabolic pathway of fluazaindolizine in plants and animals



Analytical methods and storage stability

Analytical methods for commodities of plant origin

The analytical methods used in residue trials for commodities of plant origin were based on analytical method DuPont-33861 by DuPont. For all matrices, the analytical method was split into 2 parts.

Samples were extracted in 70/30 methanol/water and the level of fluazaindolizine, IN-REG72, IN-F4106, IN-QEK31, IN-RYC33, IN-R2W56, IN-TMQ01 (IN-RSU03) and IN-QZY47 measured via LC/MS/MS directly after dilution, or after an optional clean-up on a Cyano solid phase extraction (SPE) cartridge (only residues of parent were extracted by this method).

The second part of the method included hydrolysing the extract overnight in 1 N HCl, and clean-up on a strong anion exchange (SAX) SPE cartridge. The concentrations of IN-UJV12, IN-TQD54 (IN-UNS90), IN-QZY47, IN-TMQ01 (IN-RSU03), IN-A5760, IN-QEK31 and IN-F4106 were then determined. The hydrolysis reaction converted metabolites of fluazaindolizine that had been conjugated to other molecules to their unconjugated forms. By analysing the samples before and after hydrolysis, the level of both free and conjugated residues were able to be measured. In all crops, the method limit of quantitation (LOQ) was 0.01 mg/kg, and the limit of detection (LOD) was estimated to be 0.003 mg/kg (3 µg/kg). The method was

validated at 0.01 and 0.10 mg/kg in each matrix using an LC/MS/MS system operating with an electrospray interface (ESI) and positive/negative polarity switching.

The method validation showed that average recoveries from fortified samples were within an acceptable range of 70% to 120% with standard deviations of ≤20%.

Analytical methods for commodities of animal origin

Analytical method DuPont-39226 was developed for the detection, quantification and confirmation of residues of fluazaindolizine and its metabolites IN-REG72, IN-QEK31, IN-F4106, IN-A5760 and IN-RYC33 in milk (cream, skim and whole), chicken eggs (yolks and whites), bovine muscle (ground beef), beef fat and beef liver.

A sample of the required matrix was placed in a centrifuge tube, and extracted with 0.01 M ammonium formate in acetonitrile/water. The resulting extracts were cleaned-up using sequential dispersive SPE steps. A Strong Cation Exchange (SCX) step was followed by Strong Anion Exchange/Octadecyl (C18) step to reduce matrix interferences. The cleaned-up extracts were then diluted and subjected to HPLC/MS/MS analysis. The HPLC/MS/MS method monitored two ion transitions for each analyte. Fortification of matrix blanks with fluazaindolizine and metabolites demonstrated that the method was free from significant matrix effects and interferences. The method limit of quantitation (LOQ) was 0.010 mg/kg and the limit of detection (LOD) was estimated to be 2 µg/kg (ppb) for each analyte.

Average recoveries of fluazaindolizine and its metabolites from fortified samples of animal tissues, milk and eggs were within the acceptable range of 70% to 120%, with standard deviations ≤20%.

Storage stability

The applicant provided details of a storage stability study for fluazaindolizine and its metabolites in various plant commodities, as summarised in Table 5.

Table 5: Storage stability of fluazaindolizine and its metabolites in various plant commodities

Commodity category	Representative commodity	Period of demonstrated stability (at ~-20°C) for analytes: Fluazaindolizine, IN-A5760, IN-F4106, IN-QEK31, IN-QZY47, IN-R2W56, IN-REG72, IN-RYC33, IN-TMQ01, IN-UJV12, and IN-UNS90
High water	Tomatoes	33 months – fluazaindolizine and most metabolites[a]
High starch	Wheat grain	24 months – fluazaindolizine and most metabolites[b]
High acid	Oranges	24 months – fluazaindolizine and most metabolites[c]
Very dry	Field corn stover, pea hay	24 months – fluazaindolizine and most metabolites[d] 22 months – fluazaindolizine and all metabolites
High oil	Soybean seeds	33 months – fluazaindolizine and most metabolites[a]
High protein	Dried pea seeds	24 months – fluazaindolizine and all metabolites

[a] The normalised recoveries of IN-REG72 declined into the 60% range after about 12 months.

[b] The normalised recoveries of IN-UJV12 declined into the 60% range after 18 months.

[c] The normalised recoveries of IN-REG72 declined into the 60% range after about 24 months.

[d] The recoveries of IN-QZY47 and IN-UJV12 declined into the 30% range after one week, and remained at that approximate level through storage intervals up to 24 months. It was suggested this was an extraction issue as the metabolites were stable in pea hay another dry commodity.

In the residue trials submitted, all samples were maintained under freezer conditions, (i.e. –18ºC) prior to analysis, and tested within 33 months of collection (most considerably less). This is acceptable for the purposes of the current application.

Residue definition

Commodities of plant origin

In primary crops, the major components of residue following hydrolysis consist of 3 metabolites: IN-QEK31, IN-QZY47 and IN-TMQ01. For rotational crops used as animal feeds (such as wheat forage, hay and straw), a significant portion of the residue will also be comprised of IN-UNS90. In primary crop metabolism studies, IN-A5760 was only significant in tomatoes, in terms of production and consumption in Australia, and therefore included in the risk assessment definition.

IN-F4106 was also significant in soybean seed; not a proposed use at this time. In rotational crop residue trials, IN-F4106 was a predominant residue in pea matrices (including dry seed). Proposed crops may be rotated with pulses.

IN-UJV12 was generally not a significant metabolite in the metabolism studies, however, it and the other 6 target metabolites occur in various plant commodities at finite levels, and therefore they should be included in the risk assessment definition. The parent should not be included in the risk assessment definition as it is hydrolysed to form IN-QEK31 and IN-F4106 (which are included).

A residue definition that requires an overnight hydrolysis step to form 7 metabolites, for which reference standards may not be readily available, is not considered practicable for an enforcement residue definition. Current OECD guidance[1] for residue definitions states that the enforcement definition should be "*simple (i.e., use of a marker compound, where possible), and suitable for practical, routine monitoring and enforcement of the MRL, at a reasonable cost*".

The available residue trials analysed for the parent fluazaindolizine prior to hydrolysis showed quantifiable residues of parent in all the proposed target crops and that finite MRLs would be required for each.

[1]Organisation for Economic Co-operation and Development, *Guidance document on the definition of residue (as revised in 2009)*, OECD website, 28 July 2009, accessed 2 July 2021.

Given the simplicity of the methods for the parent and the ability to use it as a marker for misuse, it is recommended that the residue definition for plant commodities for enforcement is parent-fluazaindolizine only.

Commodities of animal origin

The primary crops on the label are not used as significant feeds for livestock, with the exception of tomato pomace, and root and tuber vegetables (e.g. cull potatoes), which form a low proportion of the diet. However, there is potential for significant residues in animal feeds from rotational crops. Major metabolites in animal feeds from rotational crops were IN-QZY47, IN-TMQ01, IN-UNS90 and IN-QEK31.

The highest residue of IN-QEK31 in an animal feed was found in rotational wheat straw at 0.44 mg/kg in a European study. Correcting for an assumed dry matter content of 88%, the HR is 0.5 mg/kg on a dry weight basis. In a transfer study, dosing with IN-QEK31 at 19 ppm gave a maximum tissue residue of 0.2 mg/kg in kidney. The estimated maximum IN-QEK31 residue from dosing at 0.5 ppm is 0.005 mg/kg. A higher IN-QEK31 residue of 0.3 mg/kg was observed in milk after dosing at 19 ppm, to give a maximum estimated IN-QEK31 residue of 0.008 mg/kg.

IN-F4106 was a major residue in the goat metabolism study, where animals were dosed with IN-QZY47. The highest residue of IN-QZY47 in an animal feed was 1.43 mg/kg in bean hay. Correcting for an assumed dry matter content of 88% gives a livestock dietary burden of 1.63 ppm, assuming the hay forms 100% of the diet. In the goat metabolism study, dosing with IN-QZY47 at 10 ppm gave a maximum IN-F4106 residue level of 0.15 mg/kg in the liver. The estimated residue in liver from dosing at 1.63 ppm is 0.02 mg/kg.

As IN-TMQ01 was the main component in goat tissues from feeding of this metabolite, it should also be considered for inclusion. However, IN-TMQ01 in tissues was generally at low levels in mg eq/kg (≤0.01 g/kg), except for kidney were it was found at 0.19 mg eq/kg, 87% TRR (after dosing at 10.9 ppm). In field rotational trials, IN-TMQ01 was found at up to 0.67 g/kg in sorghum forage, or 1.91 mg/kg on a dry weight basis, assuming a moisture content of 35% (as indicated by the OECD feed calculator). Feeding of sorghum forage at 70% of total diet would result in a IN-TMQ01 burden of 1.3 ppm, and an estimated maximum IN-TMQ01 residue in kidney of 0.02 mg/kg. As an analytical method for the determination of IN-TMQ01 residues in animal tissues and milk is not available, this metabolite will not be included in the enforcement residue definition for commodities of animal origin at this time.

As parent fluazaindolizine contributes 18% to 85% TRR in goat metabolism studies, it is considered to be a sufficient marker for misuse. The recommended residue definition for enforcement in animal commodities is parent fluazaindolizine. IN-QEK31, IN-F4106 and IN-TMQ01 will be included in the risk assessment definition in addition to the parent compound.

Residues in food and animal feeds

Numerous residue studies conducted on cucurbits, fruiting vegetables (other than cucurbits), and root and tuber vegetables were conducted in North America or Europe. For the proposed enforcement residue definition of parent, the earliest sampling time following application was usually the worst case scenario for residues, due to the increased metabolism at longer PHIs. The cucurbit and other fruiting vegetable trials included application up until harvest. For root and tuber vegetable trials, the last application timing in the

trials for a broadcast spray was 14 days after treatment at planting. MRLs are based on the highest residue of parent from the earliest sampling point onwards.

Cucurbits

The proposed use of fluazaindolizine on cucurbits is a pre-plant drip, prior to transplanting, at 2 kg ai/ha, or for a pre- and post-plant drip at 1 kg ai/ha, with the pre-plant drip immediately before transplanting and the post plant drip occurring 21 days after transplanting. There is also a use involving a post plant drip at 2 kg ai/ha following a pre-plant, or at-planting application of another nematicide. The withholding period for cucurbits is 'Nil'.

The applicant provided full details of residue trials conducted on cucurbits in North America and the EU, in both field and protected situations. Total application rates ranged from 0.75 to 2.2 kg ai/ha (0.4 to 1.1× proposed), at various timings. The trials addressed residues in cucumbers, melons and squash/courgette; the representative crops for Crop Group 011: Fruiting vegetables, Cucurbits (cantaloupe and cucumber and summer squash). Data showed a similar residue potential for each commodity, with the highest parent residues in the three representative crops of 0.1 mg/kg in cucumbers, 0.086 mg/kg in melons and 0.1 mg/kg in squash. These data are suitable for consideration for a cucurbit group MRL.

The combined dataset for field and protected cucurbits, based on the enforcement residue definition of parent compound, is <0.003 (17), 0.003 (5), 0.004 (6), 0.005 (9), 0.006 (5), 0.007 (3), 0.008 (3), 0.009 (2), 0.010 (2), 0.011 (2), 0.012 (2), 0.015, 0.016 (2), 0.018, 0.027, 0.034, 0.047, 0.055, 0.073, 0.086, 0.09 and 0.1 (2) mg/kg.

The OECD MRL calculator recommends an MRL of 0.15 mg/kg (STMR = 0.005 mg/kg, n = 69).

An MRL rounded up to 0.2 mg/kg is recommended for fluazaindolizine on VC 0045 Fruiting vegetables, cucurbits in conjunction with a harvest withholding period of 'Nil', noting that the trials involved application up to harvest.

The combined dataset for field and protected cucurbits based on the risk assessment residue definition is <0.037, 0.037, 0.0379, 0.0409, 0.0420, 0.0427, 0.0428, 0.0444, 0.0447, 0.0459, 0.0466, 0.0469, 0.0478, 0.0491, 0.0496, 0.0501, 0.0536, 0.0541, 0.0545, 0.0550, 0.0580, 0.0583, 0.0608, 0.0614, 0.0625, 0.0641, 0.0642, 0.0678, 0.0683, 0.0686, 0.0694, 0.0719, 0.0730, 0.0744, 0.0758, 0.0773, 0.0803, 0.0814, 0.0889, 0.0896, 0.0978, 0.0987, 0.102, 0.105, 0.108, 0.1124, 0.121, 0.129, 0.129, 0.129, 0.130, 0.132, 0.136, 0.137, 0.147, 0.149, 0.151, 0.153, 0.154, 0.160, 0.168, 0.173, 0.176, 0.178, 0.182, 0.184, 0.192, 0.193 (2), 0.194, 0.202, 0.221, 0.240, 0.247, 0.291 (3), 0.298, 0.309, 0.418, 0.442, 0.614, 0.502 and 1.03 mg/kg. The STMR is 0.10 mg/kg (n = 84).

Fruiting vegetables, other than cucurbits

The proposed use of fluazaindolizine on fruiting vegetables, other than cucurbits is pre-plant drip (before transplanting) at 2 kg ai/ha, or for a pre- and post-plant drip, each at 1 kg ai/ha with the pre-plant drip immediately prior to transplanting, and the post plant drip occurring 21 days post transplanting. There is also a use involving a post plant drip at 2 kg ai/ha, following a pre-plant or at planting application of another nematicide. The withholding period for fruiting vegetables, other than cucurbits is 'Nil'.

The applicant has provided full details of residue trials conducted on fruiting vegetables other than cucurbits in North America and the EU in both field and protected situations. Total application rates ranged from 2 to 2.2 kg ai/ha (1 to 1.1× proposed) at various timings. Data for both representative crops tomatoes and sweet peppers have been provided, including data on small varieties of tomatoes and both bell and non-bell peppers.

The data showed similar residue potential for parent in tomatoes and peppers. The highest parent residue in peppers was 0.032 mg/kg. While the highest residue in tomatoes was 0.11 mg/kg, the next highest was 0.028 mg/kg, in line with that observed in peppers. The data for the representative crops (tomatoes and peppers) are therefore suitable for the consideration of a combined group MRL for fruiting vegetables, other than cucurbits.

The combined dataset for field and protected fruiting vegetables, other than cucurbits, based on the enforcement residue definition is <0.003 (54), 0.003 (2), 0.004 (2), 0.005 (3), 0.006 (3), 0.007 (2), 0.011, 0.028, 0.031, 0.032 and 0.11 mg/kg.

The OECD MRL calculator recommends an MRL of 0.15 mg/kg (STMR 0.003 mg/kg, n = 71).

An MRL rounded up to 0.2 mg/kg is recommended for fluazaindolizine on VO 0050 Fruiting vegetables, other than cucurbits in conjunction with a withholding period of 'Nil', noting that the trials involved application up to harvest.

The combined dataset for field and protected fruiting vegetables, other than cucurbits based on the risk assessment residue definition is <0.037 (10), 0.037 (4), 0.0385 (2), 0.0388 (2), 0.0393 (5), 0.0394, 0.0409 (2), 0.0421 (3), 0.0423 (2), 0.0430, 0.0453, 0.0464, 0.0487, 0.0499, 0.0501, 0.0504, 0.0529, 0.0547, 0.0562, 0.0583, 0.0584, 0.0594, 0.0600 (2), 0.0606, 0.0626, 0.0682, 0.0689, 0.0698, 0.0707, 0.0711, 0.0718, 0.0741, 0.0808, 0.0824, 0.0836, 0.0837, 0.0843, 0.0849, 0.0850, 0.0904, 0.0991, 0.101, 0.103, 0.110, 0.163, 0.243, 0.568 and 2.31 mg/kg. The STMR is 0.05 mg/kg (n = 71).

Tomato processing

Tomato pomace is used as a feed for livestock in Australia. The highest processing factor for dry tomato pomace was 12× for enforcement and 6× for risk assessment. The median processing factor for dry tomato pomace would be 6.5× for enforcement and 5.5× for risk assessment.

Based on a field tomato HR of 0.11 mg/kg (enforcement definition) in the available residue trials, the HR-P is 1.32 mg/kg. An MRL of 2 mg/kg is appropriate for fluazaindolizine on Tomato pomace, dry.

The STMR in field tomatoes in the available residue trials was 0.003 mg/kg (enforcement definition). The STMR-P for dry tomato pomace for calculation of livestock dietary burden based on the enforcement residue definition is 0.020 mg/kg.

Root and tuber vegetables

The proposed use of fluazaindolizine on root and tuber vegetables is for a pre-plant incorporated, or in-furrow soil treatment at 2 kg ai/ha, or for a pre-plant drip (before transplanting) also at 2 kg ai/ha. There are

also uses for sweet potatoes involving a pre- and post-plant drip, each at 1 kg ai/ha with the pre-plant drip immediately before transplanting, and the post plant drip occurring 21 days after transplanting or for a post plant drip at 2 kg ai/ha, following a pre-plant or at planting application of another nematicide. The harvest withholding period for root and tuber vegetables is 'Not required when used as directed'.

The applicant has provided full details of residue field trials conducted in North America and the EU on potatoes and carrots. Total application rates ranged from 1 to 2.2 kg ai/ha (0.5 to 1.1× proposed) at various application timings. The representative crops for root and tuber vegetables are beetroot, carrot and potato. Noting that the general use on root and tuber vegetables is for a pre-plant incorporated, or in-furrow application, data for potatoes and carrots are considered sufficient. For sweet potatoes, which have a separate use, potatoes are the representative crop.

The data showed a similar residue potential for parent in potatoes and carrots. The highest parent residue in potatoes was 0.19 mg/kg, while the highest residue in carrots was 0.29 mg/kg. The data for the representative crops of potatoes and carrots are therefore suitable for consideration of a combined group MRL for root and tuber vegetables.

The combined dataset for root and tuber vegetables based on the enforcement residue definition is <0.003, 0.003, 0.004, 0.006 (2), 0.007, 0.008 (3), 0.009, 0.01 (2), 0.012, 0.014, 0.016, 0.017 (2), 0.018, 0.022, 0.023, 0.025 (2), 0.028 (2), 0.03, 0.034, 0.044, 0.046, 0.052, 0.054, 0.061, 0.065, 0.068, 0.071, 0.079, 0.14, 0.17, 0.19 and 0.29 mg/kg.

The OECD MRL calculator recommends an MRL of 0.3 mg/kg, the STMR is 0.023 mg/kg (n = 39).

An MRL of 0.3 mg/kg is recommended for fluazaindolizine on VR 0075 Root and tuber vegetables. As the highest residues were recorded at any sampling time, the supported harvest withholding period is 'Not required when used as directed'.

Galangal is included in the proposed label under root and tuber vegetables. Current Codex and APVMA crop group lists galangal in the spices crop group, and not as a root and tuber vegetable. Noting similar crop structures and agronomic practices between galangal and root and tuber vegetables, the proposed pre-plant incorporated, or in-furrow use of fluazaindolizine on galangal is supported. It is recommended that an MRL for HS 0783 'Galangal, rhizomes' be established at the same level as is recommended for root and tuber vegetables (0.3 mg/kg).

The combined dataset for root and tuber vegetables based on the risk assessment residue definition is 0.0473, 0.0542, 0.0594, 0.0636, 0.0668, 0.0748, 0.0786, 0.0832, 0.0896, 0.092, 0.0970, 0.0991, 0.0996, 0.100, 0.101, 0.119, 0.121, 0.125, 0.141, 0.142, 0.143, 0.154, 0.174, 0.178, 0.190, 0.200, 0.202, 0.210, 0.224, 0.252, 0.296, 0.349, 0.380, 0.393, 0.440, 0.456, 0.510, 0.530, 0.593, 0.709, 0.737, 0.792, 1.27, 2.68 and 3.18 mg/kg. The STMR is 0.174 mg/kg (n = 45). The HRs for use in the NESTI calculation were 1.27 mg/kg in potatoes and 3.18 mg/kg in carrots.

Crop rotation

The highest parent fluazaindolizine residue in rotational food commodities after application at 1.3 to 1.7 times the proposed rate was 0.088 mg/kg, in dried peas. An MRL of 0.1 mg/kg would be required for fluazaindolizine for 'All other foods'.

Parent residues in grain crops were: bean mature seed <0.003 and 0.005 mg/kg; maize grain <0.003 (5) mg/kg; oilseed, rape seed <0.003 (2), 0.005, 0.012 and 0.022 mg/kg; pea, dried 0.005, 0.007, 0.042, 0.052 and 0.088 mg/kg; sorghum, grain <0.003 mg/kg; soybean, seed 0.004 and 0.015 mg/kg; wheat, grain <0.003 (8) mg/kg.

The highest parent fluazaindolizine residue in animal feed from cereal, pulse or oilseeds from rotational crop studies was 0.19 mg/kg in pea hay. The OECD feed calculator indicates pea hay consists of 88% dry matter, to give a dry weight residue of 0.22 mg/kg. A primary feed commodities MRL of 0.3 mg/kg would be required to cover residues in animal feeds grown following treatment of a primary crop.

The highest total residues, in accordance with the risk assessment definition in rotational food commodities for dietary exposure assessment were 1.65 mg/kg in a leafy vegetable, 3.1 mg/kg in a root crop and 1.96 mg/kg in a grain crop.

Residues in animal commodities

Considering primary crops from the label, potato culls with a HR of 0.19 mg/kg and tomato pomace with an STMR-P of 0.02 mg/kg (dry weight) can each be fed at up to 10% of the diet. Potato culls with a HR of 0.19 mg/kg and a dry matter content of 20%, corresponds to a burden of 0.095 ppm. The dietary burden for mammalian livestock will be driven by residues in rotational forage crops (HR 0.22 mg/kg), which can form 100% of the diet, to give a maximum burden of 0.22 ppm.

The required mammalian commodity MRLs are estimated below in Table 6 and based on the enforcement definition of parent fluazaindolizine.

Table 6: Required mammalian commodity MRLs – Cattle

Feeding level (ppm)	Milk	Muscle	Liver	Kidney	Fat
	Fluazaindolizine residue (mg/kg)				
2 – feeding study	<0.01	ND	<0.01	0.03	<0.01
0.22 – estimated burden	<0.01	<0.01	<0.01	<0.01	<0.01
Established MRLs	–	–	–	–	
Recommended MRLs	*0.01	*0.01	*0.01 (offal)		

The following MRLs are appropriate for fluazaindolizine:

MO 0105 Edible offal (mammalian) *0.01 mg/kg

MM 0095 Meat (mammalian)	*0.01 mg/kg
ML 0106 Milks	*0.01 mg/kg

The combined HRs for dietary exposure assessment, based on the risk assessment definition, which includes IN-QEK31, IN-F4106 and IN-TMQ01, are:

MO 0105 Edible offal (mammalian)	≤0.092 mg/kg
MM 0095 Meat (mammalian)	≤0.04 mg/kg
ML 0106 Milks	≤0.044 mg/kg

It is noted that all residues in tissues were below the LOQ by 5 days after the last dose at 19 to 20 ppm for both parent and IN-QEK31. However, an ESI is not required as animal commodity MRLs have been recommended at the LOQ.

Poultry

None of the primary crops on the label are significant feeds for poultry. The dietary burden for poultry will be driven by residues in rotational grain crops (HR 0.088 mg/kg in dried pea), which can form 100% of the diet, to give a maximum burden of approximately 0.088 ppm.

In lactating hen metabolism studies involving dosing with parent at 13.1 ppm, the highest total radioactive residue was in liver at 0.732 mg eq/kg. The estimated total residue from dosing at 0.088 ppm is 0.0049 mg eq/kg. Given this is a total residue, it is appropriate to establish poultry commodity MRLs for fluazaindolizine at the LOQ for the analytical method at *0.01 mg/kg.

The following total residues will be used for dietary exposure assessment based on the risk assessment definition which includes IN-QEK31, IN-F4106 and IN-TMQ01:

PE 0112 Eggs	≤0.04 mg/kg
PM 0110 Poultry meat	≤0.04 mg/kg
PO 0111 Poultry, edible offal of	≤0.04 mg/kg

Spray drift

The product should generally be applied through drip irrigation only, and has a restraint to prevent aerial application. However, the general instructions on the label include directions for broadcast application. The label requires a coarse spray droplet size.

In the fluazaindolizine dairy cattle animal transfer study, dosing with fluazaindolizine at 2 ppm gave a maximum parent residue of 0.03 mg/kg in kidney (residues of the metabolites were <LOQ this feeding level). The estimated feeding level (RAL) for residues in kidney to be at the LOQ (0.01 mg/kg) is 0.67 ppm.

The APVMA Spray Drift Risk Assessment Tool indicates that the following label statements are required for protection of international trade for broadcast applications based on a Regulatory Acceptable Level (RAL) of 0.67 ppm:

SPRAY DRIFT RESTRAINTS

Specific definitions for terms used in this section of the label can be found at apvma.gov.au/spraydrift

DO NOT allow bystanders to come into contact with the spray cloud.

DO NOT apply in a manner that may cause an unacceptable impact to native vegetation, agricultural crops, landscaped gardens and aquaculture production, or cause contamination of plant or livestock commodities, outside the application site from spray drift. The advisory buffer zones in the relevant buffer zone table/s below provide guidance but may not be sufficient in all situations. Wherever possible, correctly use application equipment designed to reduce spray drift and apply when the wind direction is away from these sensitive areas.

DO NOT apply unless the wind speed is between 3 and 20 kilometres per hour at the application site during the time of application.

DO NOT apply if there are surface temperature inversion conditions present at the application site during the time of application. These conditions exist most evenings one to two hours before sunset and persist until one to two hours after sunrise.

DO NOT apply by a boom sprayer unless the following requirements are met:

- spray droplets not smaller than a COARSE spray droplet size category
- minimum distances between the application site and downwind sensitive areas (see 'Mandatory buffer zones' section of the following table titled 'Buffer zones for boom sprayers') are observed.

Table 7: Buffer zones for boom sprayers

Application rate	Boom height above the target canopy	Mandatory downwind buffer zones, livestock areas
Up to maximum label rate	0.5 m or lower	100 metres
	1.0 m or lower	350 metres
2000 mL/ha or lower	0.5 m or lower	30 metres
	1.0 m or lower	150 metres

DO NOT apply by a vertical sprayer.

DO NOT apply by aircraft.

Dietary risk assessment

The chronic dietary exposure to fluazaindolizine was estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical, and the mean daily dietary consumption data derived primarily from the 2011–12 National Nutritional and Physical Activity Survey. The NEDI calculation is made in accordance with WHO Guidelines, and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for fluazaindolizine is equivalent to <5% of the ADI. It is concluded that the chronic dietary exposure to fluazaindolizine is acceptable.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived primarily from the 2011–12 National Nutritional and Physical Activity Survey. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. The highest acute dietary intake was estimated at <10% of the ARfD. It is concluded that the acute dietary exposure is acceptable.

Recommendations

The following amendments are required to be made to the APVMA MRL Standard (Table 8).

Table 8: Amendments to the APVMA MRL Standard

Amendments to Table 1			
Compound		**Food**	**MRL (mg/kg)**
Add:			
Fluazaindolizine			
		All other foods	0.1
MO	0105	Edible offal (mammalian)	*0.01
PE	0112	Eggs	*0.01
VC	0045	Fruiting vegetables, cucurbits	0.2
VO	0050	Fruiting vegetables, other than cucurbits	0.2
HS	0783	Galangal, rhizomes	0.3
MM	0095	Meat (mammalian)	*0.01
ML	0106	Milks	*0.01
PM	0110	Poultry meat	*0.01
PO	0111	Poultry, edible offal of	*0.01
VR	0075	Root and tuber vegetables	0.3

Amendments to Table 3	
Compound	**Residue**
ADD:	
Fluazaindolizine	For enforcement for commodities of plant and animal origin: fluazaindolizine. For dietary exposure assessment for commodities of plant origin: Sum of hydrolysis products 2-chloro-5-hydroxybenzenesulfonamide (IN-A5760), 2-chloro-5-methoxybenzenesulfonamide (IN-F4106), 8-chloro-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxylic acid (IN-QEK31), 3-[[(2-chloro-5-methoxyphenyl)sulfonyl]amino]-L-alanine (IN-QZY47), 3-[[(2-chloro-5-methoxyphenyl)sulfonyl]amino]-(2R)-hydroxypropanoic acid (IN-TMQ01), 3-[[(2-chloro-5-hydroxyphenyl)sulfonyl]amino]alanine (IN-UJV12) and 3-[[(2-chloro-5-hydroxyphenyl)sulfonyl]amino]-2-hydroxypropanoic acid (IN-UNS90), expressed as fluazaindolizine. For dietary exposure assessment for commodities of animal origin: Sum of fluazaindolizine, 8-chloro-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxylic acid (IN-QEK31), 2-chloro-5-methoxybenzenesulfonamide (IN-F4106) and 3-[[(2-chloro-5-methoxyphenyl)sulfonyl]amino]-(2R)-hydroxypropanoic acid (IN-TMQ01) expressed as fluazaindolizine

Amendments to Table 4		
Compound	**Animal feed commodity**	**MRL (mg/kg)**
ADD:		
Fluazaindolizine		
	Primary feed commodities	0.3
	Tomato pomace, dry	2

Assessment of overseas trade aspects of residues in food

None of the primary crops on the draft label are major export commodities, however, the proposed uses have the potential to cause detectable residues in the following, or rotational crops that are major export commodities, or significant feeds for livestock, such as cereals, oilseeds and pulses.

Commodities exported and main destinations

Cereals, selected pulses and oilseeds are considered to be major export commodities, as are commodities of animal origin including meat, offal and dairy products. These products may be derived from livestock who were fed feed produced from following crops. Residues in these commodities as a result of the use of Salibro Reklemel active Nematicide may have the potential to unduly prejudice trade.

Exports of Australian cereals, pulses, canola, and cotton are detailed below (Agricultural Commodity Statistics, Australian Bureau of Agriculture and Resource Economics and Sciences, Commonwealth of Australia).

Total exports of barley were estimated at 3,784 kilotonnes in 2019/20, valued at $1.49 billion. Total exports of wheat (including flour) were 9,805 kilotonnes in 2018/19, valued at $3.67 billion. Total exports of oats in 2019/20 were estimated at 145 kilotonnes, valued at $136 million. Exports of sorghum in 2019/20 were estimated at 72 kilotonnes, valued at $34.8 million. Maize exports in 2019/20 were estimated at 41.4 kilotonnes, valued at $21.9 million.

Total oilseed exports in 2019/20 (including canola, cottonseed, linseed, peanuts, safflower, soya bean and sunflower were 1,727 kilotonnes, worth $1.19 billion. Total vegetable oil exports (including canola, cottonseed, linseed, palm, peanut, safflower, soya bean, sunflower and olive) were 224 kilotonnes, at a value of $380 million, in 2019/20. Total oilseed meal exports in 2019/20 were 8.3 kilotonnes at a value of $7.2 million.

Total pulse exports were valued at $1.246 billion, in 2019/20, with the most significant export commodities being chickpeas (370 kilotonnes, $306 million), lupins (230 kilotonnes, $95 million) and field peas (59.9 kilotonnes, $38.6 million).

Table 9: Major destinations for Australian cereal, pulse and oilseed exports

Commodity	Major destinations
Barley	China, Thailand, Japan, Vietnam, Korea, United Arab Emirates, the Philippines, Taiwan
Wheat	The Philippines, Indonesia, Korea, Japan, Vietnam, Malaysia, Iraq, New Zealand, Kuwait, Yemen, Thailand
Sorghum	China, Taiwan, Japan
Cottonseed (including seed, oil, and meal)	Japan, Korea
Canola (including seed, oil and meal)	China, Germany, the Netherlands, Belgium, Japan

The significant export markets for Australian beef, sheep, pig meat and offals are listed in the *APVMA Regulatory Guidelines – Data Guidelines: Agricultural - Overseas trade (Part 5B)*.

Overseas registrations and approved label instructions

The applicant indicated that registration of fluazaindolizine products will be sought in United States of America, in addition to other countries including Argentina, Australia, Brazil, Canada, Chile, China, European Union, India, Israel, Japan, Kenya, Korea, Lebanon, Mexico, Morocco, Peru, Saudi Arabia, South Africa, Taiwan, Turkey, and Vietnam.

Comparison of Australian MRLs with Codex and international MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods. Fluazaindolizine has not been considered by Codex, however the applicant has indicated that it has been nominated for review by the Joint Meeting on Pesticide Residues (JMPR). There are currently no overseas MRLs established for fluazaindolizine, although fluazaindolizine MRLs and residue definitions are expected to soon be established in the USA and Canada. Canada has recently published its proposed MRLs and residue definition (parent compound for enforcement) for consultation.[2]

Potential risk to trade

Export of treated produce containing finite (measurable) residues of fluazaindolizine may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country, or, (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country.

The proposed primary crops on the label are not major export commodities, and with the exception of tomato pomace and root and tuber vegetable culls, are not significant feeds for livestock. The risk to trade with respect to primary crops is low.

However, the proposed use has the potential to cause residues in rotational or following crops which are major export commodities, and are significant feeds for livestock, such as cereals, pulses and oilseeds. Given there are currently no overseas MRLs established for fluazaindolizine, this creates a risk to trade should the grain crops be grown in rotation with vegetables treated via the proposed uses by drip irrigation or in-furrow treatment. Parent residues in all rotational grain crops were: bean mature seed <0.003 and 0.005 mg/kg; maize grain <0.003 (5) mg/kg; oilseed rape seed <0.003 (2), 0.005, 0.012 and 0.022 mg/kg; pea

[2] PMRA, Health Canada, *Proposed Maximum Residue Limit PMRL2021-17, Fluazaindolizine*, Health Canada website, 18 June 2021, accessed 2 July 2021.

dried 0.005, 0.007, 0.042, 0.052 and 0.088 mg/kg; sorghum grain <0.003 mg/kg; soybean seed 0.004 and 0.015 mg/kg; wheat grain <0.003 (8) mg/kg.

Animal commodity MRLs have been proposed at the LOQ for the analytical method, based on the enforcement definition of parent, suggesting a low risk to trade for animal commodities. An Export Slaughter Interval is not considered necessary.

Recommendations

Comment is sought on the potential for the proposed uses to prejudice Australian trade.

Work health and safety assessment

Health hazards

Salibro Reklemel active Nematicide was of very low acute oral and inhalation toxicity, and low dermal toxicity. It was a slight eye and skin irritant and was not a skin sensitiser.

Fluazaindolizine was of very low toxicity in a repeat dose dermal toxicity study at a limit dose of 1000 mg/kg bw/day, with no adverse effects on bodyweight, ophthalmology, clinical signs or pathological parameters.

Occupational exposure

Exposure during use

Workers are likely to be exposed to the product primarily from dermal contact during mixing and loading activities. Based on the vapour pressure of fluazaindolizine, inhalational exposure is likely to be very low. Based on the low dermal toxicity, a quantitative assessment of dermal exposure was not considered necessary.

Exposure during re-entry or rehandling

As the product will be applied by direct injection into drip irrigation systems, and/or by pre/plant or in-furrow incorporation, no re-entry statement is required, as exposure during re-entry is expected to be minimal. Based on the low dermal toxicity of fluazaindolizine, no assessment of systemic toxicity for re-entry or rehandling is required.

Public exposure

The product is intended to be used in professional settings only. Exposure via diet is addressed by the establishment of suitable maximum residue limits. Due to the proposed methods of use, no exposure by spray drift was anticipated.

Recommendations

The following first aid instructions, safety directions and precautionary (warning) statements are recommended for the product label:

First aid instructions

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131 126.

Safety directions

May irritate the eyes and skin. Avoid contact with eyes and skin. When preparing the product for use, and using the product, wear gauntlet-length PVC gloves. Wash hands after use. After each day's use, wash gloves.

Precautionary (warning) statements

Nil.

Environmental assessment

Fate and behaviour in the environment

Soil

Degradation via photolysis was found to be insignificant for product located on soil surface. Degradation in soil photolysis produced the main metabolites IN-QEK31[3] and IN-F4106[4], likely due to microbial, aerobic soil degradation. Rapid degradation of IN-QEK31 did occur under soil photolysis conditions. Very little IN QEK31 was found during soil photolysis study, even though dark controls showed the presence of significant amounts. Therefore, IN QEK31, if formed at the soil surface, will likely undergo rapid soil photolysis.

Fluazaindolizine was degraded readily in soil via microbe-mediated transformations. In laboratory studies, degradation tended to follow first order kinetics (n = 13), although biphasic degradation was observed in some soils. Modelled DT_{50} values from laboratory studies ranged from 10 to 241 days.

Degradation occurs via 2 processes. The major pathway involves cleavage of the molecule into 2 portions at the amide linkage, resulting in the formation of IN-QEK31 from the imidazopyridine side and IN-F4106 from the phenyl side. The minor pathway involves demethylation of the methoxy group, which results in IN-REG72[5]. IN REG72 then undergoes cleavage of the molecule at the sulphonamide bridge (similar to the parent compound) resulting in the formation of IN-QEK31 and IN-A5760[6].

Further degradation of IN-QEK31 in soil generates a volatile metabolite, IN-VM862[7]. Eventually both IN-VM862 and IN-A5760 undergo mineralization as well as incorporation into bound residue. Due to the splitting of the molecule into two portions, all metabolites (except for IN-REG72) are observed only in one of the 2 radiolabels.

Significant mineralization was observed in virtually all soils and from both rings, which indicates that this compound will not persist in the environment. IN-VM862 is a volatile metabolite, and is readily lost while concentrating soil extracts. IN-VM862 volatilises from the soil. Laboratory soil metabolism studies are available for all major soil metabolites, all of which demonstrated a degree of persistence. The geometric mean soil DT_{50} values for IN-F4106, IN-QEK31, IN-REG72, IN-VM862 and IN-A5760 were 293, 89, 134, 387 and 149 days, respectively.

Under anaerobic conditions, the degradation pathway remains unchained, but is considerably slowed.

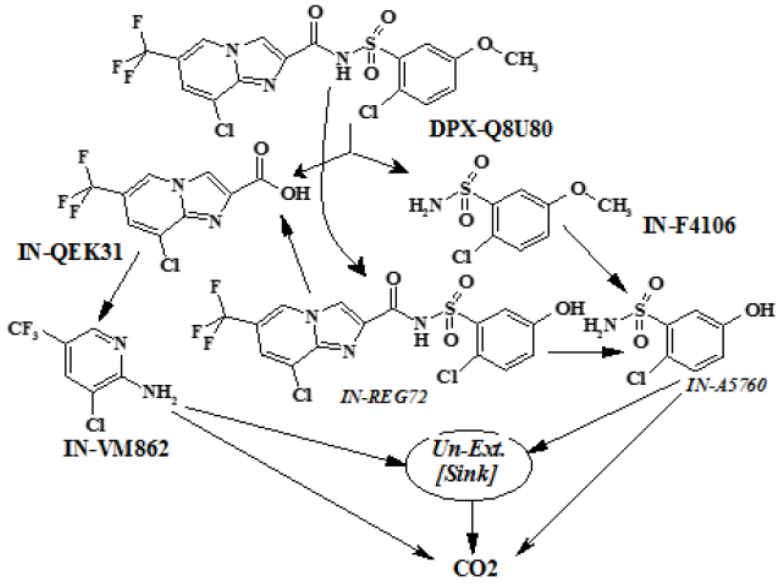
Ten field studies were conducted with the formulated SC product between 2013 and 2016 in the United States, Canada and Europe. The majority of the studies were undertaken in North America and consisted of one or 2 applications. DT_{50} values were determined to range from 7.6 to 234 days, and followed first order and biphasic kinetics. The European studies (n = 3) showed DT_{50} values ranging from 12 to 121 days, all

[3] 8-chloro-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxylic acid
[4] 2-chloro-5-methoxybenzenesulfonamide
[5] 8-chloro-N-[(2-chloro-5-hydroxyphenyl)sulfonyl]-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide
[6] 2-chloro-5-hydroxybenzenesulfonamide
[7] 3-chloro-5-(trifluoromethyl)pyridin-2-amine

following biphasic kinetics. From the field studies, the geometric mean DT_{50} value was 50 days. There were no statistically significant differences between laboratory and field results, and the final regulatory DT_{50} soil half-life value is the geometric mean of the combined data set at 48 days.

Standard batch equilibrium test results were available for 5 soils from an adsorption/desorption study. The soils tested had a range of 0.56% to 2.6% organic carbon. Sorption strength was well correlated with the organic carbon levels of the soil. Regression derived K_F values for 1% and 5% soil organic carbon were calculated to be 1.3 and 5.6 mL/g, respectively. Fluazaindolizine is expected to be mobile in soils based on these results, and sorption is non-linear with an average 1/n 0.85. Freundlich equations were developed for the main soil metabolites. Average K_F values of 1.5, 1.2, 2.3, 2.8 and 1.1 mL/g were derived for IN-F4106, IN-QEK31, IN-REG72, IN-VM862 and IN-A5760, respectively.

Figure 2: Proposed degradation pathway for fluazaindolizine in aqueous systems



Water and sediment

Based on the studies conducted in aquatic systems, fluazaindolizine is stable to hydrolysis and no meaningful degradation is likely at any pH due to hydrolytic reactions.

Photochemically, fluazaindolizine and its metabolites will degrade rapidly in water. Low molecular weight fragments were observed following a 2-week study. Half-lives in pH 4 and pH 9 systems under continuous irradiation were <1 day based on SFO kinetics (DT_{50} 0.63 days, 0.56 days and 0.43 days in pH 4, pH 9 and natural water, respectively).

Fluazaindolizine did not significantly mineralize during a 60 day study in 2 natural water systems. All test systems showed <10% mineralization over 60 days, and there was a minimal decline in the concentration of the parent compound. A DT_{50} of >1000 days was calculated for both water systems. These results indicate metabolism in water/sediment systems is due to microbial degradation within sediment.

Degradation in the water/sediment systems was relatively fast. In 2 systems, dissipation from the water phase, and degradation within the whole system followed first order kinetics. Within the water phase, the DT_{50} was 19 to 48 days, while for the total system, the DT_{50} was 21 to 51 days. In a third paddy water system, degradation in the sediment phase followed first order kinetics (DT_{50} 86 days), while dissipation in the water phase was biphasic with a modelling DT_{50} of 9.4 days. The maximum fluazaindolizine found in the sediment was 53% AR after 15 days. The major metabolites in the aquatic systems were IN-REG72 (max 87% in system: 51% in water, 41% in sediment), IN-QEK31 (max 47% in system, 44% in sediment), and IN-A5760 (max 21% in system, 20% in sediment).

In an anaerobic water/sediment study the sandy and silty-loam systems showed a total system DT_{50} of 22 and 11 days, respectively. Degradation was determined to occur almost exclusively in the sediment.

Fluazaindolizine was shown to be not readily biodegradable in a standard test.

Air

Fluazaindolizine is predicted to have an atmospheric half-life of 1.4 days based on 12 hours of sunlight per day. Fluazaindolizine has a low vapour pressure and low Henry's law constant, and is not expected to partition significantly to the air compartment. It is therefore unlikely to be transported long or short distances in air.

Effects and associated risks to non-target species

Terrestrial vertebrates

Fluazaindolizine has moderate toxicity to mammals (geomean LD_{50} 1056 mg ac/kg bw, *Rattus norvegius*) and low toxicity to birds (lowest LD_{50} >2000 mg ac/kg bw, *Anas platyrhynchos*). In reproductive toxicity testing, offspring toxicity was observed in mammals at doses as low as 94 mg ac/kg bw/d (NOEL 32 mg ac/kg bw, *Rattus norvegicus*), and reduced offspring survival in birds was observed at doses as low as 102 mg ac/kg bw/d (NOEL 51 mg ac/kg bw/d, *Colinus virginianus*). Available data indicate that soil and plant metabolites are less toxic to mammals than the parent substance.

The acute and reproductive risks to terrestrial vertebrates following dietary exposure of contaminated food items were assessed using a tiered approach. The screening level assessment considered that the indicator species (small granivorous mammal and small granivorous bird for a 'bare soil' scenario) feed on food items directly contaminated in the treatment area at the time of application. Risks to mammals and birds were determined to be acceptable at the screening level. No protection statements are therefore required for terrestrial vertebrates.

Aquatic species

Fluazaindolizine has low toxicity to fish (lowest LC_{50} >26 mg ac/L, *Cyprinodon variegatus*; LC_{50} >99 mg ac/L, *Oncorhynchus mykiss*), aquatic invertebrates (lowest EC_{50} >10 mg ac/L, *Crassostrea virginica*; EC_{50} >120 mg ac/L, *Daphnia magna*), and in sediment dwellers (EC_{50} >110 mg ac/L, *Chironomus riparius*), and moderate toxicity to algae (geomean E_rC_{50} 47 mg ac/L, *Pseudokirchneriella subcapitata*) and aquatic

plants (geomean E_rC_{50} 32 mg ac/L, *Lemna gibba*). The SC formulation enhanced toxicity to aquatic invertebrates (EC_{50} 43 mg ac/L for SC formulation, *Daphnia magna*), but did not influence toxicity to fish, algae or aquatic plants.

Following long-term exposure to fluazaindolizine, possible effects on the hatching of fish were observed at concentrations as low as 12 mg ac/L (NOEC 5.8 mg ac/L, *Cyprinodon variegatus*). Reduced growth and reproduction of aquatic invertebrates were observed at concentrations as low as 2.3 mg ac/L (NOEC of 1.2 mg ac/L, *Daphnia magna*), while no adverse effects were observed in sediment dwellers at the maximum concentrations tested (NOEC 35 mg ac/L, NOEC 37 mg ac/kg dry sediment, *Chironomus riparius*).

No chronic data were available on mysid shrimp, which are often the most sensitive species tested. For the purpose of risk assessment, an NOEC value of 0.30 mg ac/L was estimated based on acute mysid LC_{50} >30 mg ac/L and acute-to-chronic ratio of 100 based on daphnid toxicity data (>120/1.2).

The soil metabolites IN-F4106, IN-QEK31, IN-REG72 and IN-VM862 were demonstrated to have low toxicity to aquatic species, while IN-VM862 had moderately toxicity in aquatic invertebrates (EC_{50} 13 mg/L, *Daphnia magna*) and algae (E_rC_{50} 22 mg/L, *Pseudokirchneriella subcapitata*).

The acute and chronic risks to aquatic species were assessed using a tiered approach. Although the product is not applied to water, a screening level risk assessment assumed the worst-case scenario of a direct overspray of shallow aquatic habitat in order to identify those substances and associated uses that do not pose a risk to aquatic species. Acceptable risks could be concluded at the screening level for all aquatic species except aquatic invertebrates, due to the potential toxicity of fluazaindolizine in sensitive aquatic invertebrates.

A spray drift assessment was conducted according to APVMA's approach to spray drift management. It considered the lowest RAC of 300 µg ac/L (chronic toxicity to aquatic invertebrates), a maximum application rate of 4,000 L/ha (2,000 g ac/ha), and COARSE spray quality using ground boom sprayer equipment. The assessment determined that buffer zones are not required for the protection of aquatic species.

A runoff assessment considered the lowest RAC of 300 µg ac/L (chronic toxicity to aquatic invertebrates), and assumed a runoff event occurs 3 days after application. The Tier 1 (screening) level of assessment is a worst-case scenario where the slope is fixed at 8%, which is considered protective of 95% of agricultural activities in Australia. The rainfall value is set at 8 mm, which results in the maximum receiving water concentration using the standard water body of 1 ha and 15 cm initial depth when the clay dominated Queensland soil profile is used; the catchment is 10 ha. Further, for this worst-case scenario, a fallow/bare soil runoff profile was assessed. Runoff risks were determined to be acceptable at the first level of assessment; however, the product must not be applied when a runoff event can be expected soon after application (i.e. due to storms or irrigation).

Bees

Fluazaindolizine and its representative SC formulation have low toxicity to adult bees by contact exposure (LD_{50} >200 µg ac/bee, two species tested) and oral exposure (LD_{50} >19 µg ac/bee for technical active, LD_{50} 132 µg ac/bee for SC formulation, *Apis mellifera*), and moderate toxicity to bee larvae (LD_{50} 22 µg ac/larva, *Apis mellifera*). Following long-term dietary exposure, no adverse effects were observed in adult bees at the

highest tested dose (NOEL 4.8 µg ac/bee/d, *Apis mellifera*). Increased mortality of bee larvae was observed at doses as low as 0.75 µg ac/bee/d (NOEL 0.38 µg ac/bee/d, *Apis mellifera*).

The soil metabolite IN-F4106 has low toxicity to adult bees by contact exposure (LD_{50} >100 µg/bee, 2 species tested), moderate toxicity to adult bees by oral exposure (lowest LD_{50} 16 µg/bee, *Apis mellifera*), and moderate toxicity to bee larvae (LD_{50} 13 µg/bee, *Apis mellifera*).

The soil metabolite IN-QEK31 has low toxicity to adult bees by contact exposure (LD_{50} >100 µg/bee, 2 species tested) and oral exposure (LD_{50} >100 µg/bee, two species tested), and low toxicity to bee larvae (LD_{50} >100 µg/bee, *Apis mellifera*).

Two semi-field studies conducted in flowering *Phacelia tanacetifolia,* with a representative SC formulation applied in furrow or as drip solution at 1,000 g ac/ha showed no effect on honey bee colonies after bee flight. No effects were noted on the mortality of adult honey bees or pupae, flight intensity, behaviour, colony size (number of worker bees), number of brood cells, brood index, compensation index and termination rate of the individually marked cells with eggs, young or old larvae. Additionally, no residues of fluazaindolizine or its soil/plant metabolites (IN-F4106, IN-QEK31, IN-QZY47 and IN-TMQ01) were detected at or above the limit of quantification (0.005 mg/kg) in any of the nectar and pollen samples.

Although fluazaindolizine is not systemic in plants, the screening level risk assessment assumed that it is systemically transported to nectar and pollen following soil application. Contact exposure of soil drench and in-furrow applications is considered to be negligible. Acceptable risks to bees were concluded at the screening level, and no protection statements are therefore required for bees.

Other non-target arthropods

A representative SC formulation of fluazaindolizine had low toxicity to the indicator species of predatory arthropods (LR_{50} >1,000 g ac/ha, *Typhlodromus pyri*) or parasitic arthropods (LR_{50} >1000 g ac/ha, *Aphidius rhopalosiphi*) in Tier 1 (glass plate) laboratory toxicity tests. Extended laboratory tests with ground dwelling species also demonstrated low toxicity to predatory spiders (ER_{50} >1,000 g ac/ha, *Pardosa* sp) and parasitic rove beetles (ER_{50} >1,000 g ac/ha, *Aleochara bilineata*).

A screening level risk assessment utilises Tier 1 toxicity data, and assumes the non-target arthropods are exposed to fresh-dried residues within the treatment area immediately after application. Acceptable risks to the indicator species could be concluded at the screening level. The product can therefore be considered compatible with integrated pest management programs utilising beneficial arthropods.

Soil organisms

Following long-term exposure to fluazaindolizine or its representative SC formulation, the reproduction rates of soil macro-organisms such as earthworms and springtails were inhibited in a dose-dependent manner (EC_{10} 275 mg ac/kg dry soil, *Folsomia candida*; NOEC 206 mg ac/kg dry soil, *Eisenia fetida*). No adverse effects were observed on soil mites (NOEC 1000 mg ac/kg, *Hypoaspis aculeifer*).

Soil macro-organisms were more sensitive to the soil metabolites IN-A5760 (lowest NOEC 3.0 mg/kg dry soil, *Eisenia fetida*), IN-F4106 (lowest NOEC 12 mg/kg, *Folsomia candida*), IN-QEK31 (lowest NOEC

50 mg/kg dry soil, *Eisenia fetida*), IN-REG72 (lowest NOEC 50 mg/kg dry soil, *Hypoaspis aculeifer*), and IN-VM862 (lowest NOEC 12 mg/kg dry soil, *Folsomia candida*).

Fluazaindolizine at exaggerated soil concentrations (NOEC 77 mg ac/kg dry soil) did not adversely affect soil processes such as nitrogen transformation or respiration, while its soil metabolites did not impact soil processes even when tested at higher rates.

A screening level risk assessment assumes a worst-case scenario of direct application to soil of 5 cm depth in order to identify those substances and associated uses that do not pose a risk to soil organisms. Acceptable risks could be concluded at the screening level, and no protection statements are therefore required for soil organisms.

Non-target terrestrial plants

When tested as either the technical active constituent or the representative SC formulation, fluazaindolizine has negligible effects on seedling emergence, growth and vegetative vigour of non-target terrestrial plants. Both pre- and post-emergent exposure of 10 crop species resulted in ER_{25} and ER_{50} values greater than 2,000 g ac/ha.

Due to the lack of phytotoxicity in 10 species from 2 test systems and with 2 test items, use of fluazaindolizine as proposed is not expected to result in off target damage to terrestrial plants, and risks are considered to be acceptable without the need for downwind buffer zones or other protection measures.

Recommendations

Based on assessment of environmental data, it was determined that the use of Salibro Reklemel active Nematicide, when used according to instruction, would not be likely to have an unintended effect that is harmful to animals, plants, or things or to the environment.

Standard label runoff restraints are advised to avoid a runoff even occurring soon after application (i.e. due to storms or irrigation).

Efficacy and safety assessment

Proposed product use pattern

Salibro Reklemel active Nematicide is proposed for the control of root-knot nematodes (*Meloidogyne* spp.) in cucurbits, fruiting vegetables and root and tuber vegetables. The product is to be applied to soil by mechanical or irrigation incorporation, as an in-furrow treatment or through trickle tape, made at pre-plant (up to 3 days prior), planting or post-planting (one day after except for sweet potatoes). The proposed maximum amount to be applied to a crop is 4 L/ha (2 kg ai/ha) per year, as a single application or as 2 applications of 2 L/ha.

Efficacy and target crop/animal safety

Efficacy and crop safety was assessed in 45 Australian field trials, conducted in Western Australia, Queensland, South Australia, Tasmania and New South Wales, between 2014 and 2020. Assessments were made in several representative crops from each major crop grouping listed on the label: cucurbits, fruiting vegetables and root and tuber vegetables. Salibro was applied at pre-plant, at planting or transplant and at post-planting in accordance with the proposed label directions. Proposed Salibro label rates were tested for efficacy at either 4 L/ha or two applications of 2 L/ha at 14 or 21 days and twice label rates for crop safety. The product was applied in water volumes similar to grower practices.

The trials used appropriate trial design, scientific methodology and assessment parameters, with 4 or 5 replicates, industry standards and untreated controls. Results were analysed using standard statistical procedures (ANOVA and LSD).

Naturally occurring nematode infestations were relied on in all trials. Nematodes were identified to genus level in all trials and to species level in some. Nematode infection was reported using rating scales such as Zeck's scale of 0 to 10, or scales of 0 to 5 or 0 to 1, nematode per cent gall ratings per plant. Assessments included crop yields and changes in pest density. Galling assessments, 60 to 120 days after planting, were also calculated in some trials. Efficacy was determined by assessing reductions in plant damage such as nematode root galling severity on plant roots and/or declines in marketable yields of fruit as a result of treatment differences.

Efficacy

The majority of trials demonstrated efficacy or control of root-knot nematode by a reduction in damage caused by root-knot such as a lower incidence or severity of root-knot galls or an increase in yield in the representative crops when compared to the untreated control crops. Numerical reductions in nematode severity or plant yields were recorded in some trials for all nematicide treatments but the differences were not always significant. Difficulties are routinely encountered in nematode field trials due to the patchy nature of nematode infestations and the movement of nematodes in and out of plant material and trial sites.

Cucurbits

Twelve trials were presented in support of the claim of efficacy and safety in cucurbits against root-knot nematode. Trials were conducted in representative crops of cucurbits (field and protected): cucumber, pumpkin, rockmelon, watermelon and zucchini. Salibro was tested at rates of 1, 1.5, 2 and 4 L/ha as a single application and as two applications of 1 + 1, 2 + 1, 2 + 2, 4 + 1 and 4 + 4 L/ha or 2 + 1 + 1 L/ha as 3 applications at 14 to 28-day intervals via trickle irrigation. The product was applied 1 to 4 days pre-planting, at planting, or 1 day after planting.

The cucurbit trials demonstrated that Salibro was effective in reducing root-knot nematode severity at the proposed label rates of 4 L/ha as a single application or two applications of 2 L/ha. The timing of the applications or soil type did not alter efficacy and Salibro was as effective as the industry standards.

Fruiting vegetables

Twelve trials were presented in support of the claim of efficacy and safety in fruiting vegetables against root-knot nematode. Trials were conducted in representative crops of fruiting vegetables (field grown): capsicum and tomato. Salibro was tested at rates of 1, 1.5, 2 and 4 L/ha as a single application and as 2 applications of 1 + 0.5, 1 + 1, 2 + 1, 2 + 2, 4 + 1, 4 + 2 and 4 + 4 L/ha or 2 + 1 + 1 L/ha as 3 applications at 14 to 28-day intervals via trickle or drench irrigation. The product was applied 1 to 2 days pre-planting, at planting, or 1 day after planting.

The fruiting vegetable trials demonstrated that Salibro was effective in reducing root-knot nematode severity at the proposed label rates of 4 L/ha as a single application or 2 applications of 2 L/ha. The timing of the applications or soil type did not alter efficacy and Salibro was as effective as the industry standards.

Root and tuber vegetables

Twenty-one trials were presented in support of the claim of efficacy and safety in root and tuber vegetables against root-knot nematode. Trials were conducted in representative crops of root and tuber vegetables: carrot, potato and sweet potato. Salibro was tested at rates of 2,3, 4 and 8 L/ha as a single application and as two applications of 2 + 2 L/ha via surface irrigation or in-furrow. The product was applied one day pre-planting or at planting.

The root and tuber vegetable trials demonstrated that Salibro was effective in reducing root-knot nematode severity at the proposed label rates of 4 L/ha as a single application or two applications of 2 L/ha. The timing of the applications or soil type did not alter efficacy and Salibro was as effective as the industry standards.

Crop safety

Detailed assessments of phytotoxicity were made during all of the above efficacy trials. No phytotoxic symptoms were observed in any of the Salibro treatments, when applied at up to double the proposed label rate (i.e. 4,000 g ai/ha). Timing and method of application of Salibro did not impact crop safety. These data confirmed crop safety for the range of crops listed on the proposed label.

Resistance management

Fluazaindolizine is a new sulfonamide non-systemic nematicide, active against root-knot nematodes, reniform nematodes, dagger nematodes and some root lesion nematodes. The mode of action is not fully elucidated and is classed as a Group N-UN Unknown by the Insecticide Resistance Action Committee (IRAC), but the product inhibits nematode mobility following contact via soil pore water.

Although resistance to nematicides in nematode field populations has not been documented (IRAC 2018), repeated exclusive use of any product may potentially lead to a reduction in control. Rotation with a nematicide with a different mode of action is recommended.

Recommendations

Trial data support that Salibro will be effective in reducing root-knot nematode severity when applied at the proposed label rates of 4 L/ha, as a single application or as two applications of 2 L/ha. The timing of the applications did not alter efficacy and Salibro was as effective as the industry standards. The product was safe to use at the proposed label rate in all the crops tested and at twice the label rate of 4 + 4 or 8 L/ha.

There are no objections on efficacy or target-crop safety grounds to the registration of the product Salibro Reklemel active Nematicide, containing 500 g/L fluazaindolizine.

Labelling requirements

CAUTION
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING

CORTEVA™ agriscience

Salibro®

Reklemel® active

NEMATICIDE

ACTIVE CONSTITUENT: 500 g/L FLUAZAINDOLIZINE

GROUP	N-UN	NEMATICIDE

For the control of nematodes in Cucurbits, Fruiting vegetables, Root and Tuber vegetables as per the Directions for Use

CONTENTS: 1 L to 200 L

Production Agriscience (Australia) Pty Ltd
ACN 616 181 769
67 Albert Avenue CHATSWOOD NSW 2067
www.corteva.com.au
CUSTOMER SERVICE TOLL FREE 1-800 700 096

DIRECTIONS FOR USE

RESTRAINTS

DO NOT use in hydroponic systems.

DO NOT directly soak or drench bare transplant roots during the planting process.

DO NOT apply if heavy rains or storms are forecast within 3 days.

DO NOT irrigate to the point of water runoff from the treatment area for at least 3 days after application.

DO NOT apply to sweet potatoes later than 21 days after planting

DO NOT apply by a vertical sprayer.

DO NOT apply by aircraft.

SPRAY DRIFT RESTRAINTS

Specific definitions for terms used in this section of the label can be found at apvma.gov.au/spraydrift.

DO NOT allow bystanders to come into contact with the spray cloud.

DO NOT apply in a manner that may cause an unacceptable impact to native vegetation, agricultural crops, landscaped gardens and aquaculture production, or cause contamination of plant or livestock commodities, outside the application site from spray drift. Wherever possible, correctly use application equipment designed to reduce spray drift and apply when the wind direction is away from these sensitive areas.

DO NOT apply unless the wind speed is between three and 20 kilometres per hour at the application site during the time of application.

DO NOT apply if there are hazardous surface temperature inversion conditions present at the application site during the time of application. Surface temperature inversion conditions exist most evenings one to two hours before sunset and persist until one to two hours after sunrise.

DO NOT apply by a boom sprayer unless the following requirements are met:

- spray droplets not smaller than a COARSE spray droplet size category

- minimum distances between the application site and downwind sensitive areas (see 'Mandatory buffer zones' section of the following table titled 'Buffer zones for boom sprayers') are observed.

Buffer zones for boom sprayers

Application rate	Boom height above the target canopy	Mandatory downwind buffer zones				
		Bystander areas	Natural aquatic areas	Pollinator areas	Vegetation areas	Livestock areas
Up to maximum label rate	0.5 m or lower	0 metres	0 metres	0 metres	0 metres	100 metres
	1.0 m or lower	0 metres	0 metres	0 metres	0 metres	350 metres
2000 mL/ha or lower	0.5 m or lower	0 metres	0 metres	0 metres	0 metres	30 metres
	1.0 m or lower	0 metres	0 metres	0 metres	0 metres	150 metres

For use in all States where appropriate for the crop and/or disease.

VEGETABLE CROPS

CROP	PEST	APPLICATION METHOD	APPLICATION TIMING	RATE	CRITICAL COMMENTS
ALL CROPS: Salibro rates should only be applied to the portion of the field/greenhouse that requires protection from nematode infestation. For example, if the inter-row accounts for 30% of the area the use rate over the full hectare will be 2 or 4 litres per ha x 70%. To calculate the treated area measure the length of the row, by the width. For example, a 200 m long by 1 m wide bed is 200 m^2 or 0.02 ha. With an application rate of 2 or 4 L/ha x 0.02 ha either 40 or 80 mL (respectively) will be required to treat the selected area. **DO NOT** apply more than 4 L/ha per year. Refer to the application section of the label for guidance on application methods.					
Cucurbits (field and protected crops): including Bitter melon, Cantaloupe, Chokos, Cucumber, Gherkin, Gourds, Marrow, Melons, Pumpkins, Rockmelon, Squash, Summer Watermelon, Winter squash, Zucchini	Root Knot Nematode (*Meloidogyne* spp.)	At establishment drip/trickle irrigation	Apply up to three (3) days before planting to one (1) day after planting	4 L/ha	
		Soil applied and incorporated by irrigation or mechanical incorporation	Apply up to three (3) days before transplanting		
		Pre- & post plant drip irrigation	Apply 2 L/ha up to three (3) days before planting to one (1) day after planting. For extended control apply a second application, 14 - 28 days after transplanting	2 L/ha + 2 L/ha	Refer to pre-plant application for a suitable method of application
		Post-plant drip (following a pre-plant or at plant application of another effective nematicide)	-	2 or 4 L/ha	Use the low rate where the prior nematicide treatment(s) has provided effective control and extended residual control (i.e. “top-up”) is required. Use the higher rate where nematicide pressure is high.

CROP	PEST	APPLICATION METHOD	APPLICATION TIMING	RATE	CRITICAL COMMENTS
Fruiting vegetables (field and protected crops): including Bush tomato, Capsicum (Pepper), Cherry tomato, Chilli, Eggplant, Ground cherries, Okra, Sunberry, Tomatillo, Tomato	Root Knot Nematode (*Meloidogyne* spp.)	At establishment drip/trickle irrigation	Apply up to three (3) days before planting to one (1) day after planting	4 L/ha	
		Soil applied and incorporated by irrigation or mechanical incorporation	Apply up to three (3) days before transplanting		
		Pre- & post plant drip irrigation	Apply 2 L/ha up to three (3) days before planting to one (1) day after planting. For extended control apply a second application, 14 - 28 days after transplanting	2 L/ha + 2 L/ha	Refer to pre-plant application for a suitable method of application
		Post-plant drip (following a pre-plant or at plant application of another effective nematicide)	-	2 or 4 L/ha	Use the low rate where the prior nematicide treatment(s) has provided effective control and extended residual control (i.e. “top-up”) is required. Use the higher rate where nematicide pressure is high.

CROP	PEST	APPLICATION METHOD	APPLICATION TIMING	RATE	CRITICAL COMMENTS
Root and Tuber vegetables: including Arrowroot, Beetroot, Carrot, Cassava, Celeriac, Galangal, Ginseng, Horseradish, Parsnip, Potato, Radish, Swede, Taro, Turnip Garden, Yams	Root Knot Nematode (*Meloidogyne* spp.)	Pre-plant incorporated or in-furrow soil treatment	Apply up to three (3) days before planting	4 L/ha	Refer to the Application section for detailed instructions.

CROP	PEST	APPLICATION METHOD	APPLCATION TIMING	RATE	CRITICAL COMMENTS
Sweet Potato	Root Knot Nematode (*Meloidogyne* spp.)	At establishment drip/trickle irrigation	Apply three (3) days before planting to three (3) days after planting	4 L/ha	
		Soil applied and incorporated by irrigation or mechanical incorporation	Apply up to three (3) days before transplanting		
		Pre- & post plant drip irrigation	Apply 2 L/ha three (3) days before planting to three (3) days after planting. For extended control apply a second application, 14 - 21 days after transplanting	2 L/ha + 2 L/ha	Refer to pre-plant application for a suitable method of application
		Post-plant drip (following a pre-plant or at plant application of another effective nematicide)	Apply up to 21 days after transplanting	2 or 4 L/ha	Use the low rate where the prior nematicide treatment(s) has provided effective control and extended residual control (i.e. “top-up”) is required. Use the higher rate where nematicide pressure is high.

WITHHOLDING PERIODS
Harvest:
CUCURBITS, FRUITING VEGETABLES: NIL.
ROOT AND TUBER VEGETABLES: NOT REQUIRED WHEN USED AS DIRECTED.

TRADE ADVICE
EXPORT OF TREATED PRODUCE
Growers should note that suitable Maximum Residue Levels (MRLs) or import tolerances may not be established in all markets for produce treated with Salibro. If you are growing produce for export, please check with Corteva Agriscience for the latest information on MRLs and export tolerances before using this product.

GENERAL INSTRUCTIONS
Salibro is a sulfonamide nematicide, in the form of suspension concentrate and is to be diluted with water. Salibro works by contact with nematodes in the soil pore water, and is not considered systemic in plants by soil application. Intrinsic sensitivities differ to Salibro, with plant parasitic nematodes being of higher sensitivity than other groups of the soil nematode community.

The physico-chemical properties of Salibro lend it to be well balanced in terms of the soil mobility and residual properties in the soil root zone. As such it is compatible with a number of grower application methods; such as drip irrigation, bed sprays, in furrow application or incorporation before planting. Thus, agronomically, it has a fit for use in nematode control in a range of crops.

NEMATODE PRESSURE AND MANAGEMENT
A variety of nematode population pressures can exist in field conditions. The visible efficacy of a single product will depend upon the effectiveness of the product and the accuracy of application of the product into the treated root zone area, and the level of nematode population. Under extremely high nematode pressure no single product will provide high-level nematode control, and in these circumstances a range of nematode management measures should be undertaken by the grower to reduce the nematode pressure, such as use of rotations, fallow periods, resistant or tolerant varieties, chemical and biological nematode control agents.

INTEGRATED PEST MANAGEMENT
Salibro has a favourable profile for non-target organisms making it an ideal product for use in integrated pest management (IPM) systems. In particular, Salibro has been shown to be highly compatible with a broad range of naturally occurring or introduced biological control agents, such as beneficial fungi and nematodes, bacteria and other important non-target organisms that inhabit the soil rhizosphere (such as worms) and help sustain crop and soil health.

Consider the following recommended management practices to sustainably control or suppress plant parasitic nematode populations:

- Take soil samples regularly to determine the plant parasitic nematode species present and population density from the previous crop.
- Consider using nematode resistant or tolerant crop varieties.
- Consider cultural methods to reduce nematode populations, e.g., fallow periods, rotations, or soil amendments.
- Consider a combination of effective products in a nematode management program – pre-planting and in the crop; e.g., approved fumigants, nematicides, and other products that protect crop roots. This may be critical under high pest pressure situations where no single product may provide sufficient control.
- To minimise the possibility of enhanced microbial degradation from occurring, avoid long-term repeated applications of the same product or group of compounds in the same field. If any reduction in product performance is noted, it is important to contact the local company representative.

MIXING INSTRUCTIONS (In-furrow or broadcast application)
Ensure the spraying equipment is clean and properly calibrated prior to application. Spray equipment must be clean and free of previous pesticide deposits before applying this product.

Fill spray tank ¼ to ½ full of water. Add Salibro mixes directly to the spray tank during filling.

Once dispersed, the material must be kept in suspension at all times by continuous agitation. Use mechanical or hydraulic means, **DO NOT** use air agitation.

If spray solution is left standing, ensure thorough re-agitation of the spray mix until fully resuspended. **DO NOT** allow spray mix to sit overnight.

Surfactant/Wetting Agents
Use of a surfactant/wetting agent is not required.

APPLICATION BY TRICKLE OR DRIP IRRIGATION
Any drip system used must be properly designed, free of leaks, and operated in a manner that provides uniform application of water in the targeted root zone area across the field.

This product acts by contact action with plant parasitic nematodes in soil pore water. This product must be applied uniformly across the root zone or poor performance may result. Drip tape or emitters must be located within or directly adjacent to the root zone that requires protection from nematodes.

Apply in sufficient water and of sufficient duration to apply the labelled rate evenly to the entire treated area. In most situations, this product should be applied in the second quarter or middle third of the drip cycle. The delivery system should be fully charged with water, and at required operating pressure, then sufficient water should be applied to the soil root zone to ensure it is moist, and then this product is applied, and then a further amount of water is applied to distribute the product in the soil and ensure the drip system is thoroughly flushed through.

The minimum injection period is the time that it takes water to move from the injection point to the furthest emitter in the irrigation zone (line). If this time is not known, it can be calculated by measuring the time for a soluble dye to move from the injection point to the farthest emitter. A longer injection time may improve uniformity throughout the zone, but needs to allow for at least an equal period of flush and move the product through the soil. If you have any questions about calibration, you should contact service specialists, equipment manufacturers, or other specialists.

When the application is finished, allow the entire irrigation and injector system to be thoroughly flushed clean before stopping the system.

IN-FURROW AT-PLANT APPLICATION
Where permitted by crop specific use directions apply in-furrow during planting operations. Direct applications into the open furrow and cover with soil.

BROADCAST APPLICATION FOLLOWED BY INCORPORATION
Apply using conventional application equipment. Prepare the spray mix by adding the product to the spray tank with a minimum of 150 L/ha of water to obtain a uniform application. Maintain sufficient agitation during mixing and application to ensure a homogeneous spray solution. Uniformly apply the spray mix over the whole field. Immediately after application, mechanically incorporate to a depth of 10 - 15 cm with incorporation equipment to ensure even distribution.

If irrigation is used to water the application, use a sufficient amount of water to move the applied product at least 5 cm deep in the soil. However, **DO NOT** apply irrigation water such that the water moves off the field.

COMPATIBILITY
Salibro is physically compatible with most commonly used fungicide and insecticide products. To confirm compatibility, perform a compatibility test or jar test prior to mixing in a spray tank. Using a clear glass jar with lid, premix a small quantity of a desired tank mix and observe possible adverse changes (settling out, flocculation, etc.). Mix the ingredients in the same order and proportions as they will be used in the spray tank. The mixture is compatible if the materials mix readily when the jar is inverted several times. The mixture should remain stable after standing for 30 minutes, or, if separation occurs, should readily mix if agitated. An incompatible mixture is indicated by separation into distinct layers that do not readily remix when agitated and/or the presence of flakes, precipitates, gels, or heavy oily film in the jar.

The crop safety of all potential tank-mix partners with Salibro has not been tested on all crops. Before applying any tank-mix with a partner not specified on this label, apply to a small portion of the crop to be treated to ensure an adverse response will not occur.

The tank-mixing sequence recommended is: water soluble bags, dry flowable or water dispersible granules, wettable powders, water based suspension concentrates (e.g. Salibro), water soluble concentrates, oil based suspension concentrates, emulsifiable concentrates, adjuvants surfactants, soluble fertilisers and drift retardants.

PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS
The data that is currently available indicates no problems in the sequential applications in rotation regimes with other commonly-used agricultural products. Crop cultivars can differ in their response and certain environmental conditions may also be influential. It is not possible to test all sequential applications in product rotation regimes. So, prior to using the product alone or in sequential applications in grower's product rotation regimes on a new variety or on a wide area, test the products in a small area to ensure that an adverse crop response will not occur.

IMPORTANT: Not all crops within a crop group, and not all varieties, cultivars or hybrids of crops, have been individually tested for crop safety. To test for crop safety, apply the product in accordance with the label instructions to a small area of the target crop to ensure that a phytotoxic response will not occur, especially where the application is a new use of the product by the applicator.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
DO NOT contaminate wetlands or watercourses with this product or used containers.

STORAGE AND DISPOSAL
Store in the closed, original container in a cool, well-ventilated area. **DO NOT** store for prolonged periods in direct sunlight.

This container can be recycled if it is clean, dry, free of visible residues and has the ***drum****MUSTER* logo visible. Triple or pressure rinse container for disposal. Dispose of rinsate by adding to the spray tank. Do not dispose of undiluted chemicals on site. Wash outside of the container and cap. Store cleaned containers in a sheltered place with cap removed. It will then be acceptable for recycling at any ***drum****MUSTER* collection or similar container management site. The cap should not be replaced but taken separately. If not recycling, break, crush, or puncture and deliver empty packaging to an approved waste management facility. If an approved waste management facility is not available, bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose, clear of waterways, desirable vegetation and tree roots, in compliance with relevant local, state or territory government regulations. **DO NOT** burn empty containers or product.

SAFETY DIRECTIONS
May irritate the eyes and skin. Avoid contact with eyes and skin.

When preparing the product for use and using the product, wear gauntlet-length PVC gloves. Wash hands after use. After each day's use, wash gloves.

FIRST AID INSTRUCTIONS
If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26.

SAFETY DATA SHEET
Additional information is listed on the Safety Data Sheet for SALIBRO REKLEMEL ACTIVE NEMATICIDE which is available from Corteva Agriscience on request. Call Customer Service Toll Free on 1-800 700 096 or visit www.corteva.com.au.

Acronyms and abbreviations

Shortened term	Full term
ac	active constituent
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ANOVA	Analysis of variance
ARfD	Acute Reference Dose
bw	bodyweight
d	day(s)
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EC_{50}	concentration at which 50% of the test population are immobilised
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
ER_{25}	effective rate, 25th percentile
ER_{50}	effective rate, median
ESI	Export Slaughter Interval
F_0	original parent generation
g	gram
GAP	Good Agricultural Practice
h	hour
ha	hectare
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
ip	intraperitoneal
IPM	Integrated Pest Management
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
ISO	International Organization for Standardization

Shortened term	Full term
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
kg	kilogram
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection—level at which residues can be detected
Log K_{OW}	Log to base 10 of octanol water partitioning co-efficient, synonym P_{OW}
LOQ	Limit of Quantitation—level at which residues can be quantified
LSD	Least significant difference
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NOEC/NOEL	No Observable Effect Concentration Level
NOAEL	No Observed Adverse Effect Level
Pa	Pascal
ph	Acidity or alkalinity of a solution
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
RAL	Regulatory acceptable level
s	second
SC	Suspension Concentrate
SFO	Single First Order

Shortened term	Full term
STMR	Supervised Trial Median Residue
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TRR	Total radioactive residue
µg	microgram
WHO	World Health Organisation
WHP	Withholding Period

Glossary

Term	Description
Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration
CAS number	Unique numerical identifier assigned by the Chemical Abstracts Service (CAS) to every chemical substance
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Henry's law constant	A gas law that states that the amount of dissolved gas in a liquid is proportional to its partial pressure above the liquid
IUPAC name	International Union of Pure and Applied Chemistry naming scheme for organic compounds
Leaching	Removal of a compound by use of a solvent
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

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