Australian Government

Australian Pesticides and Veterinary Medicines Authority

Public Release Summary

on the evaluation of the new active spiromesifen in the product Interrupt 240 SC Miticide

APVMA product number 92500

June 2024

ISSN 1443-1335 (electronic)

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Comments and enquiries regarding copyright:

Assistant Director, Communications
Australian Pesticides and Veterinary Medicines Authority
GPO Box 3262
Sydney NSW 2001 Australia

Telephone: +61 2 6770 2300

Email: communications@apvma.gov.au.

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 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 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 registration of Interrupt 240 SC Miticide 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 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 23 July 2024 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email.

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:

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

Please note: submissions will be published on the APVMA 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 Team – Pesticides
Australian Pesticides and Veterinary Medicines Authority
GPO Box 3262
Sydney NSW 2001

Phone: +61 2 6770 2300
Email: casemanagement@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 Interrupt 240 SC Miticide, and approval of the new active constituent, spiromesifen.

Applicant

Bayer CropScience Pty Ltd.

Purpose of application

Bayer CropScience Pty Ltd has applied to the APVMA for registration of the new product Interrupt 240 SC Miticide, containing 240 g/L, as a suspension concentrate formulation, of the new active constituent spiromesifen.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of the product Interrupt 240 SC Miticide, and approval of the new active constituent spiromesifen.

Proposed claims and use pattern

Interrupt 240 SC Miticide is intended for the control of two-spotted mites (*Tetranychus urticae*) in pome and stone fruit. Proposed application methods are by vertical sprayer, at a rate of 50-60 mL/100 L, applied to the point of run-off to ensure complete coverage of foliage and fruit. No more than one application per season is to be made in each crop, at a maximum rate of 1.6 L/ha per application.

Mode of action

Spiromesifen is a member of the spirocyclic tetronic acid group, whose members include spirodiclofen and spirotetramat, which act as broad-spectrum insecticides/acaricides. Spiromesifen is classified as an insect growth regulator that acts through inhibition of acetyl CoA carboxylase in the lipid synthesis and growth regulation pathways (IRAC Group 23). Spiromesifen is considered to be locally systemic in plants, displaying translaminar movement within leaves which allows it to move through the leaf epidermis and mesophyll to control mites not directly exposed to sprayed surfaces. Mites are affected soon after application with the impact on control becoming evident between 4 and 10 days after application. Spiromesifen will offer a miticide with a new mode of action for use in Australia against two-spotted mites infesting pome and stone fruits.

Overseas registrations

The proposed product is currently registered in over 60 countries, as Oberon 240 SC Miticide, for the control of various mite species in several crops, including for use in pome and / or stone fruit in Iran, India, Japan, Korea, Turkey, Taiwan, Kazakhstan, Georgia, Armenia, Ukraine, Chile, Kyrgyzstan, Indonesia, and Belarus.

Chemistry and manufacture

Active constituent

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

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

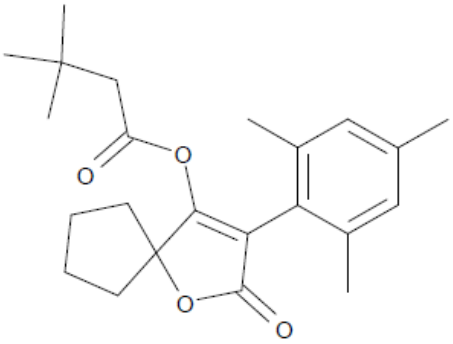
Common name (ISO):	Spiromesifen
IUPAC name:	2-oxo-3-(2,4,6-trimethylphenyl)-1-oxaspiro[4.4]non-3-en-4-yl 3,3-dimethylbutanoate
CAS registry number:	283594-90-1
Molecular formula:	$C_{23}H_{30}O_4$
Molecular weight:	370.49 g mol^{-1}
Structural formula:	

Table 2: Key physicochemical properties of the active constituent spiromesifen

Physical form:	Powder
Colour:	Light-yellow
Odour:	Intensive cheese-like odour
Melting point:	Range: 96.75–99.75°C
Boiling point:	Thermal decomposition starts at 350°C before the boiling point is reached.
Specific gravity/density/bulk density	1.14 g cm^{-3} @ 20°C
Stability:	Thermally stable at ambient temperature under air. Stable on storage for 2 weeks at 54°C, one year at 30ºC, and 6 hours at 65ºC. Spiromesifen does not significantly interact with common metals used for packaging, such as aluminium, copper, brass, plain steel, stainless steel, and tinplate.
Safety properties:	Spiromesifen is not highly flammable, not corrosive, and not explosive, has no significant oxidising properties, and will not self-ignite.
Solubility in water:	0.13 mg L^{-1} @ 20ºC (at pH 4 and pH 9)
Organic solvent solubility:	n-Heptane 23 g L^{-1} Xylene > 250 g L^{-1} Dichloromethane > 250 g L^{-1} 2-Propanol 110 g L^{-1} 1-Octanol 60 g L^{-1} Polyethyleneglycol 400 22 g L^{-1} Acetone > 250 g L^{-1} Ethylacetate > 250 g L^{-1} Acetonitrile > 250 g L^{-1} Dimethylsulfoxide 55 g L^{-1} Methanol 112 g L^{-1}
PH:	A 10 g/ L^{-1} suspension of spiromesifen in distilled water @ 22°C has a pH of 4.7.
Octanol/water partition coefficient (Log K_{ow}/K_{OW}):	4.55
Vapour pressure:	0.0007 mPa @ 20°C for spiromesifen enol
Henry's law constant:	9.3 x 10^{-4} mmHg.m^3.mol^{-1} @ 25°C

UV/VIS absorption spectra:

Condition	Wavelength (nm)	Absorbance	Molar extinction coefficient (L/mol.cm)
Methanol	203	1.352210	37 608
	214	0.812503	22 598
	259	0.100914	2 807
Methanol/buffer solution pH 2	202	1.579130	43 919
	213	0.892259	24 816
	259	0.131052	3 645
Methanol/buffer solution pH 10	218	0.434415	12 082
	259	0.685619	19 069

Formulated product

The product Interrupt 240 SC Miticide will be manufactured in Australia and overseas. Tables 3 and 4 outline some key aspects of the formulation and physicochemical properties of the product.

Table 3: Key aspects of the formulation of the product Interrupt 240 SC Miticide

Distinguishing name:	Interrupt 240 SC Miticide
Formulation type:	Suspension concentrate (SC)
Active constituent concentration/s:	Spiromesifen 240 g/L

Table 4: Physicochemical properties of the product Interrupt 240 SC Miticide

Physical form:	Grey-white liquid suspension
PH:	4.0 – 5.5 (undiluted) (CIPAC MT 75.3)
Density:	1.03 – 1.07 g cm^{-3}
Kinematic viscosity:	At a shear rate of 20 s^{-1}: 3.60 x 10^{-4} m^2/s at 20°C 3.37 x 10^{-4} m^2/s at 40°C at a shear rate of 100 s^{-1}: 1.04 x 10^{-4} m^2/s at 20°C 0.94 x 10^{-4} m^2/s at 40°C
Pourability:	2.32 – 2.56% residue 0.12 – 0.14% rinsed residue
Spontaneity of dispersion:	Minimum 70% (CIPAC MT 160)
Suspensibility:	Minimum 60% (CIPAC MT 184)
Safety properties:	Not flammable, not explosive, no flash point up to the boiling point, no oxidising properties Auto-ignition temperature is 410ºC
Storage stability:	Stable for 2 weeks at 54°C, 3 years at ambient temperature, and 7 days at 0ºC, all in HDPE packaging

Recommendations

The APVMA chemistry section has evaluated the chemistry and manufacturing aspects of the active constituent spiromesifen and associated product Interrupt 240 SC Miticide – including the identification, physicochemical properties, manufacturing process, quality control procedures, 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 3 years when stored under normal conditions.

Based on a review of the chemistry and manufacturing details, the registration of Interrupt 240 SC Miticide, and approval of the active constituent spiromesifen, are supported from a chemistry and manufacturing perspective.

Toxicological assessment

The submitted data package included metabolism, kinetics, and toxicology studies along with the occupational risk assessment report for spiromesifen and the product Oberon 240 SC Miticide prepared by the United States Environmental Protection Agency (US EPA, 2020)[1], the European Food Safety Authority (EFSA, 2012)[2], and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 2016)[3]. Taken together, these reports represent the expert interpretation of the complete toxicity dataset for spiromesifen and formulated product and were considered sufficient.

Evaluation of toxicology

Chemical class

Spiromesifen [3-mesityl-2-oxo-1-oxaspiro [4.4] non-3-en-4-yl 3,3-dimethylbutyrate (IUPAC)] is a contact insecticide-acaricide belonging to the titronic acid class of compounds. The mode of action of spiromesifen is through inhibition of lipid biosynthesis, especially triglycerides and free fatty acids.

Pharmacokinetics

Following the administration of a single oral dose of 2 mg/kg bw of [^{14}C] spiromesifen to rats, absorption was rapid, although incomplete. At a low dose of 2 mg/kg bw, 39% was excreted in urine and 55% in faeces, while at a high dose of 500 mg/kg bw, urinary excretion was 9%, whereas faecal excretion was 90%. Bile duct–cannulated rats treated with 2 mg/kg bw excreted approximately 7% of the administered dose with the bile. At 2 mg/kg bw, at least 48% of the dose was absorbed, while absorption appeared to be much lower at a high dose. Maximum concentrations in blood were reached after 2 hours in males, and one hour in females, after a dose of 2 mg/kg bw, and in 6 hours (both sexes) after a dose of 500 mg/kg bw. Distribution was widespread. The highest tissue concentrations were found in liver, with concentrations in liver higher in males than in females. Spiromesifen is extensively metabolised following absorption, and its metabolites do not accumulate. No parent compound was found in urine or bile.

A sex difference was apparent in excretion profiles. The main metabolite in the excreta of female rats of the low-dose groups was spiromesifen-enol (BSN 0546, M01), whereas the main metabolite in the excreta of the male rats of the low-dose groups was 4-hydroxymethyl- BSN 0546 (M02). The excretion profiles in males and females were not affected by the size of the dose and were not changed by repeated dosing for 14 days.

[1] US EPA (2020). Spiromesifen. Draft Human Health Risk Assessment in Support of Registration Review.

[2] EFSA (2012). Conclusion on the peer review of the pesticide risk assessment of the active substance Spiromesifen. EFSA Journal 2012;10(10):2879.

[3] JMPR (2016). 5.22 SPIROMESIFEN (294). Joint FAO/WHO Meeting on Pesticide Residues.

Dermal absorption of spiromesifen present in the product, Interrupt 240 SC Miticide was 0.04% for the neat formulation (240 g/L) and 10% for the spray dilution (0.144 g/L) in *in-vitro* human skin dermal absorption study.

Acute toxicity (active constituent –spiromesifen)

Spiromesifen was considered to have low acute toxicity via the oral, dermal and inhalation routes of exposure. It is neither a skin nor an eye irritant in rabbits. It is a potential skin sensitiser in guinea pigs.

Acute toxicity (product – Interrupt 240 SC Miticide)

Interrupt 240 SC Miticide was of low acute toxicity via oral, dermal, and inhalational routes. It is neither an eye or a skin irritant, and is not a skin sensitiser in guinea pigs (Buehler test).

Repeat-dose toxicity

In repeated-dose oral toxicity studies with spiromesifen in mice, rats and dogs, the most sensitive effect was reduction of plasma cholesterol. This is probably secondary to the inhibition of lipogenesis by spiromesifen. Common findings were effects on body weight, liver (including liver enzyme induction), thyroid, and adrenals. The primary target organs in dietary studies conducted with the rat, mouse, and/or dog were thyroid gland, liver, and adrenal gland.

In a 29-day dietary study in dogs, the NOAEL was 2000 ppm (equal to 72.6 mg/kg bw/d), the highest dose tested.

In a 14-week study in mice, the NOAEL was 20 ppm (equal to 3.2 mg/kg bw/d), based on decreased cholesterol levels in both sexes, and adrenal cytoplasmic eosinophilia in zona fasciculata in one female at 80 ppm (equal to 11.5 mg/kg bw/d).

In a 14-week study in rats, the NOAEL was 100 ppm (equal to 6.3 mg/kg bw/d), based on a slight reduction in body weight gain and water intake in males; an increase in thromboplastin time; increased alkaline phosphatase activity; decreased concentrations of plasma cholesterol and triglycerides; a tendency for higher thyroid hormone values; increased relative kidney weights in males; white jejunal mucosa coverings and cytoplasmic vacuolation of the jejunal mucosa in females; and an increase in incidences of thyroidal follicular cell hypertrophy in females and thyroidal colloidal alterations in males observed at 500 ppm (equal to 32 mg/kg bw/d).

In a 3-month dietary study in dogs, the NOAEL was 2000 ppm (equal to 71 mg/kg bw/d), the highest dose tested. The effects (increased plasma alkaline phosphatase activity, triglyceride levels, and hepatocellular cytoplasmic changes) observed at 250 and 2000 ppm to reflect hepatic enzyme induction. In a second 3-month dietary study in dogs, the NOAEL was 3000 ppm (equal to 101 mg/kg bw/d), based on a 9-fold increase in plasma alkaline phosphatase activity and vomiting at 5000 ppm (equal to 172 mg/kg bw/d).

In a one-year study in dogs, the NOAEL was 400 ppm (equal to 10.8 mg/kg bw per/d) based on decreased body weight in females, decreased T4 (due to increased hepatic T4 elimination), increased alkaline phosphatase activity, hepatic inclusions/vacuoles (hyaline bodies) and a small cell type in adrenocortical

zona fasciculata observed in both sexes at 4000 ppm (equal to 109 mg/kg bw/d). An overall NOAEL for dogs of 400 ppm (equal to 10.8 mg/kg bw/d) can be established based on the 3-month, and one-year dog studies.

In a 28-day inhalation study in rats, no adverse effects were noted, and the NOAEL was 0.081 mg/L equivalent to 21.1 mg/kg bw/d, the highest dose tested.

No adverse systemic effects or local skin reactions were seen in a dermal study with rats exposed to 1,000 mg/kg bw/d (limit dose) over a 4-week period.

Chronic toxicity and carcinogenicity

In an 18-month carcinogenicity study in mice, the NOAEL for chronic toxicity was 20 ppm (equal to 3.3 mg/kg bw/d) based on effects on macroscopic and microscopic effects on adrenal glands. The NOAEL for carcinogenicity was 2000 ppm (equal to 335 mg/kg bw/d), the highest dose tested.

In a one-year toxicity study in rats, the NOAEL was 125 ppm (equal to 6.5 mg/kg bw/d), based on increased T3 levels and thyroidal follicular cell hypertrophy and colloidal alteration in males and a reduction in cholesterol in females at 300 ppm (equal to 16 mg/kg bw/d). In a 2-year carcinogenicity study in rats, the NOAEL for chronic toxicity was 125 ppm (equal to 6.1 mg/kg bw/d) based on effects on white blood cells, a slight increase in opacities in the ocular lens, and decreased plasma cholesterol concentration. The NOAEL for carcinogenicity was 800 ppm (equal to 40 mg/kg bw/d), the highest dose tested.

Based on the available studies in mice and rats it can be concluded that spiromesifen is not carcinogenic.

Reproductive and developmental toxicity

Spiromesifen was not a developmental or reproductive toxicant in a multi-generation study in rats and prenatal developmental toxicity studies in the rat and rabbit.

In a two-generation reproductive toxicity study in rats, the NOAEL for parental toxicity was 120 ppm (equal to 10.2 mg/kg bw/d), based on decreased body weights in F1 males and in F0 and F1 females; decreased relative weights of liver, spleen and kidneys in F0 males; decreased absolute spleen weight in F0 females; decreased absolute brain weight in F1 males; slight effects on the thyroid gland (follicular cell hypertrophy, altered follicular colloid) in males and females of both generations; decreased vacuolation of the adrenal zona glomerulosa cells; and decreased hepatic periportal fat content in F0 females observed at 500 ppm (equal to 47 mg/kg bw/d). The NOAEL for offspring toxicity was 120 ppm (equal to 14.7 mg/kg bw/d), based on decreased body weights (F1, F2, F2b) during lactation and decreased absolute (F1 males, F2 males and females) and increased relative (F1 and F2 males and females) brain weights; decreased absolute spleen and thymus weights (F1 and F2 males and females, F2b males); and decreased absolute thymus weight in F2b females observed at 500 ppm (equal to 56 mg/kg bw/d). The NOAEL for reproductive toxicity was 500 ppm (equal to 47 mg/kg bw/d), the highest dose tested.

In a second two-generation reproductive toxicity study in rats, the NOAEL for parental toxicity was 30 ppm (equal to 3.3 mg/kg bw per/d), based on decreased body weights in F1 males and F1 females and decreased absolute spleen weights in F1 males observed at 120 ppm (equal to 13.2 mg/kg bw/d). The NOAEL for offspring toxicity was 30 ppm (equal to 3.8 mg/kg bw/d, maternal intake), based on decreased

body weights during lactation in male and female F1 and F2 pups and on decreased absolute spleen and thymus weights in male F1 pups observed at 120 ppm (equal to 14.2 mg/kg bw/d). The NOAEL for reproductive toxicity was 500 ppm (equal to 37 mg/kg bw/d), the highest dose tested.

The overall NOAEL for parental toxicity was 30 ppm (equal to 3.3 mg/kg bw/d); for reproductive toxicity, 500 ppm (equal to 47 mg/kg bw/d), the highest dose tested; and for offspring toxicity, 30 ppm (equal to 3.8 mg/kg bw/d).

In a developmental toxicity study in rats, the NOAEL for embryo and foetal toxicity was 70 mg/kg bw/d, based on a marginal decrease in foetal weight and slightly more progressed ossification of phalangeal and single skull bones of equivocal toxicological significance at 500 mg/kg bw/d. No evidence for a teratogenic potential of spiromesifen was identified.

In a developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 5 mg/kg bw/d, based on decreased feed intake and amount of faeces, transient body weight loss and decreased body weight gain at 35 mg/kg bw/d. The NOAEL for embryo and foetal toxicity was 250 mg/kg bw/d, the highest dose tested. There was no evidence of teratogenic potential.

Genotoxicity

Spiromesifen was not genotoxic in an appropriately validated battery of *in vitro* and *in vivo* assays.

Neurotoxicity/immunotoxicity

In an acute neurotoxicity study in rats using gavage doses of spiromesifen of 0, 200, 700, and 2,000 mg/kg bw, there were no test substance-related effects observed at any dose level.

In a 13-week neurotoxicity study in rats using dietary concentrations of spiromesifen of 0, 100, 500, and 2,000 ppm (equal to 0, 6.4, 32, and 123 mg/kg bw per/d for males and 0, 7.9, 38, and 149 mg/kg bw/d for females, respectively), decreased body weight and feed consumption, and behavioural findings were seen at 2,000 ppm (equal to 123 mg/kg/d). In this 13- week repeated dose toxicity study in rat, clinical signs and a neurotoxicity screening gave no indication of any neurotoxic potential for spiromesifen. It was concluded that spiromesifen is not neurotoxic.

No evidence of immunotoxicity was observed in repeat dose toxicity studies in mice and rats (plaque-forming cell assays).

Toxicity of metabolites and/or impurities

The major residues in crops and livestock were spiromesifen, spiromesifen-enol (M01), 4- hydroxymethyl-spiromesifen-enol (M02) and its glucoside, and 4-carboxy-3-hydroxy-spiromesifen- enol (M07). No specific toxicity studies on the metabolites of spiromesifen were available, however, M01, M02, and M07 occur in rats at about 10% of the absorbed dose or higher. The toxicity of the rat metabolites M01, M02 and its glucoside, and M07 is therefore considered to be covered by that of spiromesifen.

Reports related to human toxicity

No specific data have been provided by the applicant. No relevant literature or studies were found based on a literature search conducted by the APVMA.

Health-based guidance values and poisons scheduling

Poisons Standard

Spiromesifen is included in Schedule 5 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) with no exceptions.

Health-based guidance values

Acceptable daily intake

The acceptable daily intake (ADI) for spiromesifen was established at 0.03 mg/kg bw/d, based on a NOAEL of 3.3 mg/kg bw/d. This NOAEL is based on the macroscopic and histopathological effects on the adrenal glands in an 18-month mouse study supported by a NOAEL for parental toxicity of 3.3 mg/kg bw/d, based on decreased body weights in F1 males and F1 females, and decreased absolute spleen weights in F1 males in a two-generation reproductive toxicity study in rats.

Acute reference dose

An acute reference dose (ARfD) was considered unnecessary due to low oral toxicity, and the absence of any neurological effects or developmental toxicity following a single dose.

Recommendations

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

There are no objections on human health grounds to the registration of the product Interrupt 240 SC Miticide containing 240 g/L spiromesifen in a SC formulation when the product is used as directed on the label safety directions.

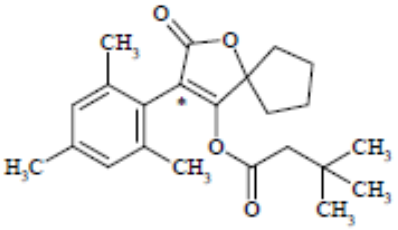
Residues assessment

As part of the residues assessment of spiromesifen, plant and target animal metabolism studies, supervised residue trial data for pome fruit and stone fruit, analytical methodology, fate in storage and processing data, and residues in trade information were considered.

Metabolism

Metabolism studies in target crops (apple, lettuce, tomato, and cotton), confined rotational crops (spinach, turnip, and spring wheat), lactating goats, and laying hens were conducted with spiromesifen labelled with ^{14}C in the 3-dihydrofuranone moiety (Figure 1). Although the studies involved spiromesifen labelled at one position only, the label is centrally positioned in the molecule and should be included in any major metabolites. The JMPR assessed these studies (except for one new apple study) and found them suitable for recommendation of a residue definition.[4]

Figure 1: Position of radiolabel used in plant and target animal metabolism



* Denotes position of ^{14}C- radiolabel

Metabolism in plants

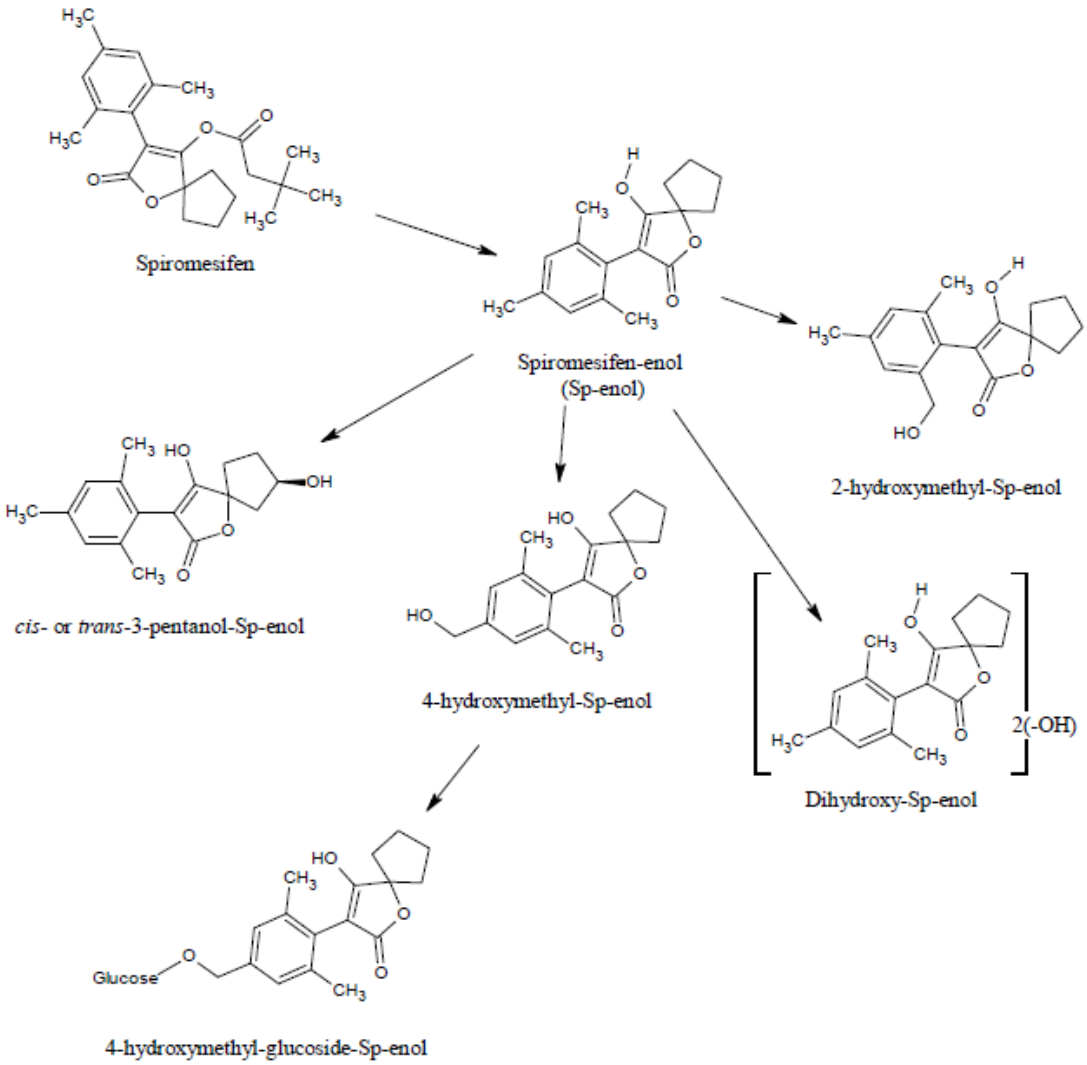
In metabolism studies with apple, tomato, lettuce, and cotton as primary crops, spiromesifen, spiromesifen-enol, and 4-hydroxymethyl-Sp-enol (free and conjugated) consistently accounted for 75 to 100% of the total radioactive residues (TRR) in the harvested food commodities at maturity. Spiromesifen was the predominant residue in apples (97%), tomato fruit (86% TRR), lettuce leaves (58% TRR), and cotton seed (82% TRR in de-linted seed). Spiromesifen-enol was the predominant residue in cotton gin trash (49% TRR), followed by spiromesifen (26% TRR). 4-Hydroxymethyl-Sp-enol was >10% TRR only in lettuce leaves (2.8% + 11.9% as glucoside). Spiromesifen concentrations were at quantifiable levels (0.24–1.7 mg/kg) in all matrices except cotton seed, where the TRR was low (ca. 0.05 mg eq/kg). In crop field trials, spiromesifen was also consistently observed to occur at levels greater than spiromesifen-enol while 4- hydroxymethyl-Sp-enol was not measured.

In confined and field rotational crop studies, spiromesifen and spiromesifen-enol were <LOQ in all crop samples, and 4-hydroxymethyl-Sp-enol (free and conjugated) was the predominant residue (ca. 50% TRR;

[4] Spiromesifen, 2016 Joint Meeting on Pesticide Residues, Food and Agriculture Organisations of the United Nations, accessed September 2023

up to 0.146 mg eq/kg in food crops and 0.607 mg eq/kg in feed crops at a 30-day plant back interval (PBI)). Residues of 4-hydroxymethyl-Sp-enol in wheat grain were still the predominant residues but were <0.005 mg eq/kg at all PBIs. Two additional metabolites occurred as major residues in most commodities in the confined rotational crop study: 3-pentanol-Sp-enol and dihydroxy-Sp-enol. Maximum residues for both compounds were observed at the 30-day PBI and ranged across all matrices from 0.004 to 0.09 mg eq/kg each. Levels of 3-pentanol-Sp-enol and dihydroxy-Sp-enol were generally lower at longer PBIs and were observed at 10 to 40% of the levels of free and conjugated 4-hydroymethyl-Sp-enol.

Figure 2: Proposed metabolic pathway for spiromesifen in primary and rotational crops.



Metabolism in livestock

In the lactating goat metabolism study (dose = 344 ppm in the feed), TRR were higher in kidney (8.9 mg eq/kg) and liver (3.6 mg eq/kg) than in fat (0.47 mg eq/kg), muscle (0.26 mg eq/kg), or milk

(0.11 mg eq/kg). The principal residue in all goat matrices was spiromesifen-enol, making up 29 to 77% of the total residue. The glucose conjugate of spiromesifen-enol was also a major residue in liver (21% TRR), and 4-hydroxymethyl-Sp-enol was a major residue in milk (24% TRR). All other residues were <10% TRR. In the feeding study with lactating cattle (dosing up to 50 ppm in the feed), residues of spiromesifen + spiromesifen-enol were found at quantifiable levels in samples of milk, fat, kidney, and liver from the highest dose group (50 ppm), and in fat and kidney samples from the middle dose group (15 ppm); residues of spiromesifen + spiromesifen-enol were <LOQ in samples of muscle from all dose groups and in all other matrices at the lowest dosing level (5 ppm). Residues of 4-hydroxymethyl-Sp-enol (free and conjugated) were <LOQ in all samples from the feeding study.

In the laying hen metabolism study (dose = 190 ppm in the feed), TRR were highest in liver (1.7 mg eq/kg) and skin (0.32 mg eq/kg), with lower residues in muscle (0.067 mg eq/kg), fat (0.09 mg eq/kg), and egg (0.026 mg eq/kg). Spiromesifen was the only major residue in fat (51% TRR) and a major residue in egg (28% TRR). The spiromesifen-enol metabolite was a major residue in all matrices except fat, ranging from 18% TRR in skin to 44% TRR in egg. The only other major residues were 4-carboxy-3-hydroxy-Sp-enol in liver (20% TRR), unresolved 4-carboxy-3-hydroxy-Sp-enol + oxo-cyclopentyl-Sp-enol (42% TRR) in skin, and 4-carboxy-hydroxy-Sp-enol in liver (16% TRR) and skin (12% TRR).

Analytical methods and storage stability

Full details of various analytical methods for plant and animal commodities have been provided and have been summarised by the 2016 JMPR. Methods used in the submitted pome fruit and stone fruit residue trials and dairy cattle animal transfer study are summarised below.

Plant commodities

In the Australian pome fruit and stone fruit residue trials, the analytical test method ATM-0088 ‘Determination of residues of spiromesifen and spiromesifen-enol in or on plant material by LC-MS/MS’ was used to analyse for residues of spiromesifen and spiromesifen-enol. Samples were extracted by blending in acetonitrile/water and passed through an SPE tube. Internal standards were added and the solution filtered prior to analysis by LC-MS/MS.

The limit of quantitation (LOQ) for spiromesifen and its metabolite spiromesifen-enol was 0.01 mg/kg, each expressed as parent equivalent. This resulted in a total spiromesifen LOQ of 0.02 mg/kg. Recoveries from fortified control samples were generally within acceptable limits. Mean recoveries were within the range 70 – 110%, Relative Standard Deviations (RSDs) were <20%, with the exception of parent spiromesifen in wet apple pomace at the LOQ which gave an RSD of 21%.

Animal commodities

In the dairy cattle transfer study, residues of spiromesifen, spiromesifen-enol, and 4-hdyroxymethyl-Sp-enol were determined by Method 110878. Residues in tissues were extracted with ACN:H2O (4:1, v/v) using accelerated solvent extraction (70°C, 1500 psi, ca. 10,300 KPa); internal standards were added at the completion of the extraction process. Radio-validation data showed extraction efficiencies of 96, 100, and 69% of the total residue (defined as spiromesifen, spiromesifen-enol, and 4-hydroxymethyl-Sp-enol) from

milk, fat, and liver, respectively. Extracts from liver and kidney were cleaned up using a strong cation exchange column and then digested with HCl to hydrolyse conjugated residues. Resulting residues were cleaned up using C-8 solid-phase extraction. Fat and muscle extracts were treated with ammonium hydroxide to hydrolyse spiromesifen to spiromesifen-enol followed by clean up using C-8 solid-phase extraction. Milk samples were not subjected to liquid extraction. Rather, internal standards were added to the milk sample, and residues in milk were isolated using C-8 solid-phase extraction. For all samples, analysis was by HPLC-MS/MS. The LOQ for each analyte was 0.005 mg/kg for milk, 0.01 mg/kg for muscle and fat and 0.05 mg/kg for kidney and liver (the hydrolysis step used in the analysis of tissues in the transfer study quantitatively converts spiromesifen to spiromesifen-enol to give a single analyte). Concurrent recoveries across all analytes and matrices ranged from 84 to 116% with a maximum relative standard deviation of 8.4%.

Storage stability

The applicant has submitted various storage stability studies for spiromesifen and spiromesifen-enol, most of which were evaluated by the 2016 JMPR. The JMPR concluded spiromesifen was stable for to ca. 160 days in mustard greens, maize stover, potato tuber, undelinted cotton seed, and cotton gin trash, between 316 to 376 days in cucumber, tomato fruit and processed commodities, maize grain and forage, and potato processed commodities; and between 679 to 727 days in melon peel, wheat grain, forage, and hay, and turnip root.

The sum of spiromesifen and spiromesifen-enol amounted to ca. 100% of the applied material remaining throughout the storage periods for the various storage stability samples, indicating that in total, those residues are stable for at least ca. 365 days in tomato (fruit and processed commodities), mustard greens, maize (grain and forage), potato (tuber and processed commodities), and cotton (seed and gin trash); and at least ca. 700 days in cucumber, melon peel, French beans, wheat grain, and turnip root.

An additional storage stability study for dry beans, coffee, and citrus was provided here and showed that there appeared to be a conversion of Spiromesifen to Spiromesifen-enol up to around 80% until 741 days of storage for dry bean samples, and up to around 25% until 755 days of storage for coffee samples. This conversion was not observed for citrus samples up to 728 days. Nevertheless, after a storage period of 24 months under deep-freeze conditions, the total residues of Spiromesifen and Spiromesifen-enol were well recovered from all matrices tested.

In the residue trials submitted, all samples were maintained under freezer conditions (i.e.–18^{o}C) prior to analysis and tested within 157 days of collection. This is acceptable for the purposes of the current application.

Residue definition

Plant commodities

Although spiromesifen was the most predominant residue in primary crops and would be a suitable marker for compliance purposes, its breakdown during storage to spiromesifen-enol necessitates that residues of the spiromesifen-enol metabolite be taken into account in stored analytical samples. The JMPR agreed that

combined residues of spiromesifen and spiromesifen-enol {4-hydroxy-3-(2,4,6- trimethylphenyl)-1-oxaspiro[4.4]non-3-en-2-one}, expressed as parent spiromesifen, are suitable for enforcement purposes in plant commodities. The same definition is recommended here for Australia based on the studies evaluated by the JMPR, the new apple metabolism study, and pome and stone fruit residue trials provided with this application.

In considering residues for dietary risk assessment, crop field trials reported residues of spiromesifen and spiromesifen-enol. However, the trials did not include analysis of free and conjugated 4- hydroxymethyl-Sp-enol. Based on data from the lettuce metabolism study, residues of 4- hydroxymethyl-Sp-enol (free + conjugated) are expected to be at one fourth the concentration of spiromesifen and spiromesifen-enol (combined) in leafy crops (significant residues of 4-hydroxymethyl-Sp-enol are not expected in other crops). A comparison of dietary exposure estimates by the JMPR with and without residues of 4-hydroxymethyl-Sp-enol in leafy crops indicates that exposure to that compound is not negligible. It has been determined that spiromesifen-enol and 4-hydroxymethyl-Sp-enol are no more toxic than spiromesifen, and that for risk assessment, dietary exposure is adequately covered by the ADI for spiromesifen. Therefore, the JMPR determined that combined residues of spiromesifen, Spiromesifen-enol, and free and conjugated 4-hydroxymethyl-Sp-enol {4-hydroxy-3-[4-(hydroxymethyl)-2,6- dimethylphenyl]-1-oxaspiro[4.4]non-3-en-2-one} expressed as spiromesifen, are appropriate for assessing dietary risk from residues in plant commodities.

The proposed crops are pome fruit and stone fruit, therefore, the results of the metabolism studies in apples and tomatoes (as members of fruit category[5]) are directly relevant to the proposed crops. 4-hydroxymethyl-Sp-enol was not significant in the new apple metabolism study (1.7% TRR, 0.012 mg eq/kg + 0.2% TRR, 0.001 mg eq/kg as glucoside), or the tomato fruit metabolism study (0.5% TRR, 0.004 mg equiv/kg + 5.4% TRR, 0.046 mg eq/kg as glucoside).

Although 4-hydroxymethyl-Sp-enol is not expected to be significant in the crops currently proposed for use in Australia, it will be included in the risk assessment residue definition for plant commodities to cover any future registrations and for harmonisation with the JMPR residue definition.

Animal commodities

The spiromesifen-enol metabolite was the predominant residue in all goat and hen matrices except for hen fat. Spiromesifen was the major residue hen fat and was significant in eggs. The JMPR agreed that combined residues of spiromesifen and spiromesifen-enol are suitable markers for compliance with MRLs in livestock commodities. This definition is also recommended for Australia noting also the low estimated livestock dietary burden from the uses on pome fruit and stone fruit considered here.

[5] OECD Test No. 501: Metabolism in Crops, OECD website, accessed August 2023

Residues in food and animal feeds

Pome fruit

The proposed use on pome fruit is for a maximum of one application per season per crop at up to 14.4 g a.c./100 L (to a maximum of 384 g a.c./ha) in conjunction with a 14-day harvest withholding period. The MRL recommendation will be based on available data relevant to this critical GAP.

Six apple trials and 4 pear trials were provided, and these data align with the recommended dataset for pome fruit in APVMA residue guidance.[6]

Total residues of parent plus the enol metabolite in apples and pears at approximately 14 days after one application at 14.2 g a.c./100 L (~1× proposed) were 0.04, 0.04, 0.04, 0.09, 0.12, 0.12, 0.14, 0.16, 0.20 and 0.27 mg/kg. The Organization for Economic Cooperation and Development (OECD) Maximum Residue Limit (MRL) Calculator[7] recommends an MRL of 0.5 mg/kg (STMR = 0.12 mg/kg, n = 10). An MRL of 0.5 mg/kg is recommended for spiromesifen on FP 0009 Pome fruits in conjunction with the proposed 14-day harvest withholding period.

Although the trials did not analyse for 4-hydroxymethyl-Sp-enol (which is included in the plant commodity residue definition for risk assessment), this metabolite is not expected to be significant in fruit, based on the results of the apple and tomato fruit metabolism studies. The total residues of parent plus the enol metabolite will be used in the dietary exposure assessment for pome fruit.

The submitted pome fruit residue trials included treatment regimens involving earlier application timing than the critical use pattern. In trials involving the earliest application at BBCH 71-72 (61–175-day pre harvest interval (PHI)) at the proposed rate, total residues at harvest were <0.02 (7), 0.02 (2) and 0.04 mg/kg. In trials involving application at BBCH 73-74 (54–139-day PHI) at the proposed rate, total residues at harvest were <0.02 (5), 0.02 (4) and 0.05 mg/kg.

In dry apple pomace, total residues of parent plus the enol metabolite approximately 14 days after one application at 28.3 g a.c./100 L (~2× proposed) were 0.41, 0.55, 0.61, 0.64, 1.15 and 1.32 mg/kg. On a dry weight basis, residues were 0.43, 0.59, 0.67, 0.75, 1.31 and 1.5 mg/kg. Scaled for application rate residues were 0.22, 0.30, 0.34, 0.38, 0.66, and 0.75 mg/kg. The OECD MRL calculator recommends an MRL of 1.5 mg/kg (STMR = 0.36 mg/kg, n = 6). An MRL of 1.5 mg/kg is recommended for spiromesifen on AB 0226 Apple pomace, dry.

[6] APVMA guidance on Residue trials to obtain permanent maximum residue limits for crops (Residues), APVMA website, accessed August 2023

[7] Organization for Economic Cooperation and Development (OECD) Maximum Residue Limit (MRL) Calculator

Stone fruit

The proposed use on stone fruit is for a maximum of one application per season per crop at up to 14.4 g a.c./100 L (to a maximum of 384 g a.c./ha) in conjunction with a 14-day harvest withholding period. The MRL recommendation will be based on available data relevant to this critical GAP.

Six peach trials, 3 nectarine trials, one plum trial, and 4 cherry trials were provided, and these data align with the recommended dataset for stone fruit in APVMA residue guidance which states that 6 trials on peaches, 4 trials on nectarines or plums, and 4 trials on cherries should be sufficient to support a permanent use on stone fruit.[8]

Total residues of parent plus the enol metabolite in peaches, nectarine, and plums at approximately 14 days after one application at 14.2 g a.c./100 L (~1× proposed) were 0.05, 0.08, 0.14, 0.16, 0.16, 0.21, 0.23, 0.25, 0.31, and 0.37 mg/kg.

Total residues of parent plus the enol metabolite in cherries at approximately 14 days after one application at 14.2 g a.c./100 L (~1× proposed) were 0.09, 0.12, 0.13 and 0.21 mg/kg.

The results for cherries are similar to other stone fruit. The combined dataset for MRL determination is 0.05, 0.08, 0.09, 0.12, 0.13, 0.14, 0.16, 0.16, 0.21, 0.21, 0.23, 0.25, 0.31, and 0.37 mg/kg. The OECD MRL Calculator recommends an MRL of 0.6 mg/kg (STMR = 0.16 mg/kg, n = 14). An MRL of 0.6 mg/kg is recommended for spiromesifen on FS 0012 Stone fruits in conjunction with the proposed 14-day harvest withholding period.

Although these trials did not analyse for 4-hydroxymethyl-Sp-enol (which is included in the plant commodity residue definition for risk assessment), this metabolite is not expected to be significant in fruit, based on the results of the apple metabolism study.

The submitted stone fruit residue trials included treatment regimens involving an earlier application timing than the critical use pattern. In trials involving the earliest application timing at the proposed rate for peaches and nectarines (BBCH 71-76, 59–78-day post PHI), residues of spiromesifen plus its enol metabolite at harvest were <0.02, 0.03 (2), 0.04, 0.05, 0.06, 0.08 (2) and 0.18 mg/kg. Similarly for cherries after application at BBCH 67-76 (56–58-day PHI), residues of spiromesifen plus its enol metabolite were 0.03 (4) mg/kg.

Crop rotation

A confined rotational crop study has been provided as already discussed. The JMPR had assessed the same confined rotational crop study, in addition to field rotational crop studies which have not been submitted to the APVMA, but not required for the current evaluation as pome fruit and stone fruit are not considered to be rotational crops. The JMPR noted that the results of the environmental fate studies, including rotational crop studies, indicate that spiromesifen and its major metabolites (Spiromesifen-enol and its carboxylated and/or hydroxylated degradation products) are not likely to be persistent in the environment,

[8] APVMA guidance on Residue trials to obtain permanent maximum residue limits for crops (Residues), APVMA website, accessed August 2023

and mineralisation to CO_2 is likely to be significant. The JMPR also noted that in confined and field rotational crop studies, spiromesifen and Spiromesifen-enol were generally < LOQ in all crop samples. One sample of bulb onion and one sample of green onion from a field study contained spiromesifen-enol at 0.033 and 0.039 mg/kg respectively. 4-hydroxymethyl-Sp-enol (free and conjugated) was the predominant residue (ca.50% TRR; up to 0.146 mg/kg in food crops and 0.607 mg/kg in feed crops at a 30-day PBI in the confined study).

No further consideration of rotational crops is required for the current application which is proposing the use of spiromesifen for pome and stone fruit (as those crops are not rotated with other crops).

Residues in animal commodities

The draft label has a grazing restraint for treated orchards. Apple pomace is a feed for both beef and dairy cattle in Australia. The maximum livestock dietary burdens are summarised below using the OECD Feed Calculator:

Table 5: Estimation of livestock dietary burden for beef cattle

Commodity	CC	Residue (mg/kg)	Basis	DM (%)	Residue dw (mg/kg)	AU Diet content (%)	AU Residue Contribution (ppm)
Apple pomace, wet	AB	0.36	STMR	100	0.4	20	0.07
Total						20	0.07

Table 6: Estimation of livestock dietary burden for dairy cattle

Commodity	CC	Residue (mg/kg)	Basis	DM (%)	Residue dw (mg/kg)	AU Diet content (%)	AU Residue Contribution (ppm)
Apple pomace, wet	AB	0.36	STMR	100	0.4	10	0.04
Total						10	0.04

The maximum livestock dietary burden is estimated to be 0.07 ppm for beef cattle and 0.04 ppm for dairy cattle. Estimated residues in tissues and milk and required MRLs as a result of feeding on apple pomace are summarised below:

Table 7: Estimated residues in cattle milk and tissues and required MRLs

Feeding level (ppm)	Milk	Muscle	Liver	Kidney	Fat
	Spiromesifen + sp-enol residue (mg/kg)				
5 (feeding study)	0.0165 (50 ppm)	<0.01	<0.05	<0.05	<0.01

Feeding level (ppm)	Milk	Muscle	Liver	Kidney	Fat
	Spiromesifen + sp-enol residue (mg/kg)				
0.07 – beef, estimated burden	–	<0.01	<0.05	<0.05	<0.01
0.04 – dairy, estimated burden	<0.005	–	–	–	–
Established MRLs	–	–		–	–
Recommended MRLs	*0.005	*0.01 (fat)		*0.05 (offal)	

Poultry

Apple pomace is not considered to be a feed for poultry. Poultry commodity MRLs will be established at the LOQ of the analytical method.

Fat solubility

The Log P_{ow} for spiromesifen is 4.55 (ambient temperature) suggesting some fat solubility. In the feeding study, total residues of spiromesifen and spiromesifen-enol were ca. 11-fold greater in fat than in muscle and ca. 22-fold greater in cream than in skim milk. On that basis, the JMPR concluded that the residue is fat soluble. The meat (mammalian) and poultry meat MRLs will be established in the fat, but residues are not expected to occur as a result of the proposed use given the low livestock dietary burden.

Dietary risk assessment

The chronic dietary exposure to spiromesifen is 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 spiromesifen is equivalent to <10% of the ADI. It is concluded that the chronic dietary exposure to spiromesifen 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. An acute reference dose is considered to be unnecessary for spiromesifen. A NESTI calculation is not required.

Recommendations

The following amendments are required to be made to the APVMA MRL Standard (Table 4).

Table 8: Amendments to the APVMA MRL Standard

Amendments to Table 1		
Compound	**Food**	**MRL (mg/kg)**
Add:		
Spiromesifen		
MO 0105	Edible offal (mammalian)	*0.05
PE 0112	Eggs	*0.01
MM 0095	Meat (mammalian) [in the fat]	*0.01
ML 0106	Milks	*0.005
FP 0009	Pome fruits	0.5
PM 0110	Poultry meat [in the fat]	*0.01
PO 0111	Poultry, edible offal of	*0.05
FS 0012	Stone fruits	0.6

Amendments to Table 3	
Compound	**Residue**
Add:	
Spiromesifen	Commodities of plant and animal origin for enforcement: sum of spiromesifen and 4-hydroxy-3-(2,4,6-trimethylphenyl)-1-oxaspiro[4.4]non-3-en-2-one (spiromesifen- enol), expressed as spiromesifen. Commodities of plant origin for dietary exposure assessment: sum of spiromesifen, 4-hydroxy-3-(2,4,6-trimethylphenyl)-1-oxaspiro[4.4]non-3-en-2-one (spiromesifen-enol), and 4- hydroxy-3-[4-(hydroxymethyl)-2,6-dimethylphenyl]-1-oxaspiro[4.4]non-3-en-2-one (4-hydroxymethyl-spiromesifen-enol) (free and conjugated), all expressed as spiromesifen. Commodities of animal origin for dietary exposure assessment: sum of spiromesifen and 4-hydroxy-3-(2,4,6-trimethylphenyl)-1-oxaspiro[4.4]non-3-en-2-one (spiromesifen-enol), expressed as spiromesifen.

Amendments to Table 4		
Compound	**Animal feed commodity**	**MRL (mg/kg)**
Add:		
Spiromesifen		
AB 0226	Apple pomace, dry	1.5

Assessment of overseas trade aspects of residues in food

Pome fruit and stone fruit are considered to be major export commodities, as are commodities of animal origin, such as meat, offal and dairy products, which may be derived from livestock fed feeds produced from treated apple pomace.[9] Residues in these commodities resulting from the use of Interrupt 240 SC Miticide may have the potential to unduly prejudice trade. As quantifiable residues of spiromesifen are not expected to occur in animal commodities they do not require further consideration with respect to trade at this time.

Commodities exported and main destinations

In 2021 Australia exported 2,147 t of fresh apples valued at $5.9 million. Major export markets were Papua New Guinea (PNG), Italy, Hong Kong, Thailand, and India. In 2021 Australia exported 8,229 t of fresh pears valued at $13.5 million. Major export markets were New Zealand, Canada, Singapore, Indonesia, and the United States of America (USA).[10]

In 2021 Australia exported 414 t of fresh apricots, valued at $2.4 million. Major export markets were the United Arab Emirates (UAE), Kuwait, Saudi Arabia, Qatar, and Oman. In 2021 Australia exported 13,187 t of fresh nectarines/peaches valued at $59.3 million. Major export markets were China, Singapore, UAE, Hong Kong, and Malaysia. In 2021 Australia exported 7,383 t of fresh plums valued at $30.4 million. Major export markets were China, Singapore, UAE, Hong Kong and Malaysia. In 2021 Australia exported 4,715 t of fresh cherries valued at $82.4 million. Major export markets were Hong Kong, China, Vietnam, Singapore, and Taiwan.[11]

Overseas registrations and approved label instructions

The applicant indicated that spiromesifen products are registered in a number of countries for various uses. Spiromesifen is registered in Iran, India, Japan, Korea, Turkey, Taiwan, Kazakhstan, Georgia, Armenia, Ukraine, Chile, Kyrgyzstan, Indonesia, and Belarus for uses in pome and/or stone fruit.

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. Spiromesifen has been considered by Codex but no Codex MRLs have been established for pome or stone fruit. The following relevant international MRLs have been established for spiromesifen (Table 9).

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[9] APVMA Regulatory Guidelines – Data Guidelines: Agricultural - Overseas trade (Part 5B)

[10] Australian Horticulture Statistics Handbook, 2020/21, Hort Innovation, accessed February 2023

[11] Australian Horticulture Statistics Handbook, 2020/21, Hort Innovation, accessed February 2023

Table 9: Proposed Australian and current international MRLs for spiromesifen

Commodity	Tolerance for residues arising from the use of spiromesifen (mg/kg)								
	Australia	China[12]	Codex[13]	EU[14]	Hong Kong[15]	Japan[16]	Korea[17]	Taiwan[18]	USA[19]
Residue definition	Spiromesifen + sp-enol (proposed)	Sum of spiromesifen and its metabolite 4-Hydroxy-3-mesityl-1 -oxaspiro(4.4) non-3-en-2-one (= sp-enol), expressed as spiromesifen	Sum of spiromesifen and 4-hydroxy-3-(2,4,6-trimethylphenyl)-1-oxaspiro[4.4]no n-3-en-2-one (= sp-enol), expressed as spiromesifen	Spiromesifen	Sum of spiromesifen and 4-hydroxy-3-(2,4,6-trimethylphenyl)-1-oxaspiro[4.4]no n-3-en-2-one (= sp-enol), expressed as spiromesifen	sum of spiromesifen and metabolite M1 (4-hydroxy-3-mesityl-1-oxaspiro[4.4]no n-3-en-2-one = sp-enol), expressed as spiromesifen	-	-	Sum of spiromesifen [2-oxo-3-(2,4,6-trimethylphenyl)-1-oxaspiro[4.4]non-3-en-4-yl 3,3-dimethylbutanoat e] and 4-hydroxy-3-(2,4,6-trimethylphenyl)-1-

[12] United States Department of Agriculture, Foreign Agricultural Service, Translation of Maximum Residue Limits for Pesticides in Foods. Beijing, China - People's Republic of, USDA website 24 August 2021, accessed March 2023.

[13] Food and Agriculture Organisation of the United Nations, *Codex Alimentarius, International Food Standards*, FAO website, accessed March 2023.

[14] European Commission, *EU Pesticide residue(s) and maximum residue levels (mg/kg)*, European Commission website, accessed March 2023.

[15] Centre for Food Safety, Hong Kong Pesticide MRL Database, The Government of the Hong Kong Special Administrative Region, accessed March 2023

[16] Japanese Food Chemistry Research Foundation, *Table of MRLs for Agricultural Chemicals*, JFCRPF website, accessed March 2023.

[17] Ministry of Food and Drug Safety, Korea, MRLs in Pesticides, accessed March 2023.

[18] Laws & Regulations Database of the Republic of China (Taiwan), Standards for Pesticide Residue Limits in Foods, accessed March 2023.

[19] Electronic Code of Federal Regulations, *USA Electronic Code of Federal Regulations*, eCFR website, accessed March 2023.

Commodity	Tolerance for residues arising from the use of spiromesifen (mg/kg)								
	Australia	China[12]	Codex[13]	EU[14]	Hong Kong[15]	Japan[16]	Korea[17]	Taiwan[18]	USA[19]
									oxaspiro[4.4]non-3-en-2-one (sp-enol)
Pome fruit	0.5 (proposed)	–	–	0.02*	2 (apple) 2 (pear)	2 (apple, pear, Japanese pear)	2 (persimmon) 0.5 (pear) 1 (apple) 0.3 (balsam pear)	2 (apple) 2 (loquat) 2 (pear) 2 (thorn apple) 2 (wax apple)	–
Stone fruit	0.6 (proposed)	–	–	0.02*	0.2 (peach)	0.2 (peach) 1 (nectarine) 5 (apricot) 0.7 (Japanese plum, including prune) 5 (mume plum) 5 (cherry)	1.5 (Korean plum) 2 (peach) 1 (apricot) 0.5 (plum) 0.7 (cherry)	2 (apricot) 2 (ground cherry) 2 (peach) 2 (plum) 2 (prune)	–

Potential risk to trade

Export of treated produce containing finite (measurable) residues of spiromesifen 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.

Quantifiable residues may occur in pome and stone fruit from the proposed use pattern which may pose a risk to trade in pome and stone fruit. At present, Codex MRLs in pome and stone fruit are not established. MRLs in certain pome and stone fruit commodities are established in Hong Kong, Japan, Korea, and Taiwan.

The applicant has proposed to manage any potential risks to trade in pome fruit and stone fruit by inclusion of the following export advice on the label:

EXPORT OF TREATED PRODUCE

Growers should note that suitable MRLs or import tolerances may not be established in all markets for produce treated with Interrupt 240 SC. If you are growing produce for export, please check with Bayer Crop Science for the latest information on MRLs and import tolerances BEFORE using Interrupt 240 SC.

Recommendations

Comment is sought from the relevant industry groups on the potential for the proposed uses of Interrupt 240 SC Miticide on pome fruit and stone fruit to prejudice Australian trade.

Work health and safety assessment

Health hazards

Interrupt 240 SC Miticide was of low acute toxicity via oral, dermal, and inhalational routes. It is neither an eye nor a skin irritant. It is not a skin sensitiser in guinea pigs (Buehler test).

Occupational exposure

Exposure during use

Interrupt 240 SC Miticide containing 240 g/L spiromesifen in a SC formulation is intended for the control of two spotted mite in pome and stone fruit. Interrupt 240 SC Miticide is intended for professional use and will be applied by air blast equipment. Interrupt 240 SC Miticide is to be applied to the point of run-off at the first sign of mite movement, at a maximum rate of 1.6 L/ha per application. Interrupt 240 SC Miticide will be applied a maximum of once per season in each crop.

This occupational risk assessment is based upon both acute exposure to the product and repeat exposure to the active constituent. Workers/users of products may be exposed repeatedly to the product from dermal and/or inhalation routes during mixing, loading and application (M/L/A) and dermal exposure during post-application activities. Minor or accidental ocular exposure may also occur.

Given the low toxicity of spiromesifen following short-term exposures, and taking into consideration the predominant route of exposure, a repeat dose, dermal exposure study is considered appropriate for risk assessment. A 28-day repeat, semi-occlusive dermal exposure study concluded no systemic effects at the limit dose of 1000 mg/kg bw/d spiromesifen. Furthermore, in the absence of any reproductive, developmental, genotoxic, carcinogenic, or neurotoxic effects observed in repeat dose oral studies conducted with spiromesifen, a quantitative risk assessment was considered not necessary.

The rational for this conclusion is that there is no known scenario that may result in unacceptable occupational exposure, when compared with the above limit dose. Consequently, no mitigation measures are required to manage the low risk resulting from repeated systemic occupational exposure while handling the product.

Exposure during re-entry or rehandling

Post-application exposure to the product may occur from dermal contact with foliage when workers undertaking activities associated with orchard maintenance. On the same basis as above, no mitigation measure is required to manage the systemic exposure risk resulting from spiromesifen residues for workers performing re-entry activities in treated orchards. As there are no acute risks associated with exposure to the spray, a re-entry statement is not required on the product label.

Public exposure

The product is intended for professional use and is not expected to be handled by members of the public.

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; New Zealand 0800 764 766.

Safety directions

Wash hands after use.

Precautionary (warning) statements

Restraints/restrictions

DO NOT apply by aircraft.
DO NOT apply by a boom sprayer.
DO NOT allow bystanders to come into contact with the spray cloud.

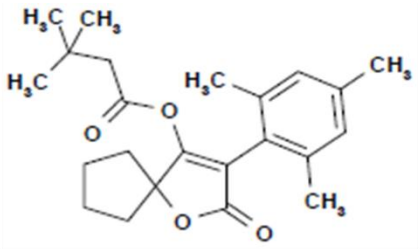
Re-entry or re-handling statement

A re-entry statement is not required on the product label.

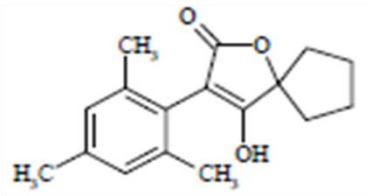
Environmental assessment

Fate and behaviour in the environment

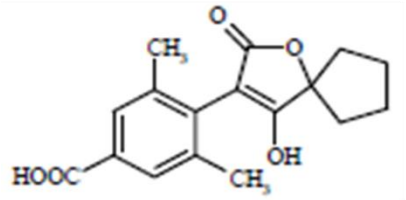
Figure 3: Proposed route of aerobic degradation in soil.



Spiromesifen



Spiromesifen-enol
Metabolite M01



Spiromesifen-4-carboxy
Metabolite M09

Soil

Spiromesifen is hydrolysed to form the major soil metabolite spiromesifen-enol (M01; maximum of 85% AR after 14 days), which oxidises to the major metabolite spiromesifen-4-carboxy (M09; maximum of 14.1% AR after 90 days). These metabolites have aerobic soil half-lives ranging from 8.8-102 days for M01 (geomean model DT_{50} 22 days) and 1.7-224 days for M09 (geomean model DT_{50} 26 days).

Spiromesifen was not susceptible to photolysis in soil, but photolysis may contribute to loss of spiromesifen-enol (metabolite M01) in light-exposed soil. The aerobic soil metabolism half-life of spiromesifen ranged from 2.6 to 18 days (6 soils; geomean model DT_{50} 5.3 days).

Freundlich sorption values of spiromesifen were obtained from 6 soils. There was no correlation between sorption and organic carbon content, and sorption was largely independent of concentration (1/n = 0.96). K_F values ranged from 66.1-1536 L/kg (mean 440 L/kg) and corresponding K_{FOC} values ranged from 2212-

38120 L/kg (mean 12177 L/kg). In addition, mobility was determined in 4 soils using thin layer chromatography. These results confirmed the high sorption potential with K_{OC} values of 45296-106195 L/kg.

Sorption of the metabolite M01 was tested in 4 soils. This metabolite was mobile, with K_F values ranging from 0.031-0.067 L/kg and an average 1/n of 0.82. The low mobility of spiromesifen and potential mobility of M01 were confirmed by the results of laboratory column leaching studies. Mobility of metabolite M09 was measured in only one soil, from which this metabolite is expected to be mobile (K_{OC} 3.0 L/kg).

Field soil dissipation studies (bare soil) of spiromesifen were provided from 4 sites located in the USA with 2 to 3 consecutive applications at each site. Dissipation was described by single first order kinetics; model DT_{50} values ranged from 1.9-6.8 days (geometric mean DT_{50} 3.5 days). Residues of spiromesifen were essentially restricted to the top 15 cm. Metabolite M01 was the major metabolite observed in all field studies, and was also mobile (see above), being found down to the 60-75 cm soil layer at one site.

Water

Spiromesifen hydrolysed primarily to the metabolite M01 and was less stable as pH increased (DT_{50} values of 53, 25 and 4.3 days at pH 4, 7 and 9, respectively). The photolytic half-life of spiromesifen in water was calculated to be 1.7 days; metabolite M01 was stable with respect to photolysis in water.

When spiromesifen was applied to a water column in water-sediment studies (2 systems) it dissipated from the water rapidly, partitioning to sediment with a DT_{50} of 0.31-0.38 days (geometric mean 0.35 days). Degradation in sediment occurred with single first order sediment DT_{50}s of 6.5-9.3 days (geomean model DT_{50} 7.8 days), and whole system model DT_{50}s of 4.1-7.8 days (geomean model DT_{50} 5.7 days). The only major metabolite identified in water and sediment was M01 (maximum in water 89.7% AR after 63 days; maximum in sediment of 38% after 90 days). Mineralization was practically negligible and unextractable residue in the sediment was 3-16% AR after 120 days.

When applied to sediment and followed by flooding, spiromesifen was more persistent with a DT_{50} of 82 days. There was limited movement from sediment to the water column. Conversion to M01 was slower with up to 16.6% M01 in the water phase at the end of the study and residues of this metabolite not reaching a plateau after 28 days.

Air

Standard modelling was undertaken to predict the atmospheric half-life of spiromesifen through reaction with hydroxyl radicals. Based on a global, annual average 24-hour concentration of 1.5×10^6 OH-radicals/cm^3, reaction with hydroxyl radicals and a 12-hour day, the atmospheric DT_{50} was calculated to be 1.7 hours (0.07 days).

Effects and associated risks to non-target species

Terrestrial vertebrates

Spiromesifen has low toxicity to mammals (LD_{50} >2500 mg a.c./kg bw, *Rattus norvegicus*) and birds (LD_{50} >2000 mg a.c./kg bw, *Colinus virginianus*). In short-term dietary testing with birds with continual exposure over 5 days spiromesifen did not exhibit toxicity, with the lowest LD_{50} of >1165 mg a.c./kg bw/d (*Colinus virginianus*) based on highest tested feed concentration. Long-term dietary administration in birds showed effects on parental bodyweight and some reproductive parameters at concentrations as low as 681 ppm diet (NOEC 229 mg a.c./kg diet, NOEL 23 mg a.c./kg bw/d). In mammals, a 2-generation reproductive toxicity study with *Rattus norvegicus* resulted in a NOEL of 3.3 mg a.c./kg bw/d, based on decreased body weights in F1 males and F1 females and decreased absolute spleen weights in F1 males at 120 ppm (13.2 mg/kg bw/d).

Risks of Interrupt 240 SC Miticide to terrestrial vertebrates were determined to be acceptable assuming direct dietary exposure within the treatment area at the maximum seasonal rate (1.6 L/ha or 384 g a.c./ha) on foliated crops; therefore, no protection statements are required for terrestrial vertebrates.

The octanol-water partition coefficient for spiromesifen (log K_{OW} of 4.6) indicates a potential for bioaccumulation. A food chain assessment indicated that any accumulated residues in earthworms or fish will not reach levels harmful to predators under the proposed conditions of use.

Aquatic species

Spiromesifen has high toxicity to fish (lowest LC_{50} 0.016 mg a.c./L, *Oncorhynchus mykiss*; 5 species tested). At the limit of solubility, spiromesifen has low to moderate toxicity to aquatic invertebrates (lowest EC_{50} >0.026 mg a.c./L, 3 species tested), algae (lowest E_rC_{50} >0.071 mg a.c./L, 4 species tested) and aquatic plants (E_rC_{50} >0.10 mg a.c./L, *Lemna gibba*), and low toxicity to sediment dwellers (lowest LC_{50} >64 mg a.c./kg dry sediment, 2 species tested). The SC formulation did not enhance toxicity to aquatic species; a definitive toxicity value could be established for *Daphnia magna* indicating moderate toxicity (EC_{50} 16 mg a.c./L). The M01 and M09 metabolites were less toxic than the parent substance, spiromesifen. A protection statement is required on the Interrupt 240 SC Miticide label on the basis of spiromesifen's high toxicity to fish.

Following long-term exposure to spiromesifen, effects on swim-up and growth of fish fry were observed at concentrations as low as 0.0078 mg a.c./L (NOEC 0.0047 mg a.c./L, *Oncorhynchus mykiss*) and reduced reproduction of aquatic invertebrates was observed at concentrations as low as 0.00045 mg a.c./L (NOEC 0.00025 mg a.c./L, *Daphnia magna*). Emergence of sediment dwellers (*Chironomus riparius*) was inhibited in a dose-dependent manner in both water-spiked (EC_{10} 0.020 mg a.c./L) and sediment-spiked (EC_{10} 0.47 mg a.c./kg dry sediment) tests.

The BCF for fish is 543, but spiromesifen declines rapidly in water and depuration from fish is also rapid. The potential to bio-accumulate is therefore low.

Spray drift risks to aquatic species were determined to be acceptable provided a mandatory downwind buffer zone of 75 metres is observed for the protection of natural aquatic areas. Runoff risks of spiromesifen to

aquatic species were determined to be acceptable under a reasonable worst-case scenario; however, general runoff restraints are required to mitigate the risk of a runoff event soon after application (i.e. due to heavy storms or irrigation).

Bees

Spiromesifen has low toxicity to adult bees (*Apis mellifera*) by contact exposure (LD_{50} >200 µg a.c./bee) and oral exposure (LD_{50} 792 µg a.c./bee), and moderate toxicity to bee larvae (LD_{50} 3.1 µg a.c./bee). The SC formulation was moderately toxic to adult bees by oral exposure (LD_{50} 60 µg a.c./bee), although its toxicity remained low by contact exposure (LD_{50} >200 µg a.c./bee).

Following long-term dietary exposure, increased mortality of adult bees and bee larvae was observed at doses as low as 35 and 0.60 µg a.c./bee/d, respectively (NOEDD 18 and 0.30 µg a.c./bee/d, respectively). The metabolite M01 was more toxic to adult bees and bee larvae than the parent substance (LDD_{10} 0.12 and 0.078 µg a.c./bee/day, respectively).

There are no data for potential residue levels in pollen and nectar of pome or stone fruits, but measurements of metabolite M01 in pollen and nectar from field studies with sweet corn, strawberry and cotton indicate it can be present, although at levels lower than the parent compound. When peak residues are adjusted for the proposed maximum application rate, representative levels of M01 in pollen and nectar are calculated to be 2.5 and 3.8 mg/kg respectively. A colony-level assessment based on these predicted levels indicates a potential risk to adult bees and larvae through oral exposure. Accordingly, it is considered that the product must not be applied when crops are in flower. Additional protection measures are also required to mitigate dietary exposure of bees.

Other non-target arthropods

Assessments of contact toxicity of fresh dried residues of a representative SC formulation of spiromesifen on glass plates were made for the predatory mite (*Typhlodromus pyri*) and the parasitic wasp (*Aphidius rhopalosiphi*) with respective LR_{50} values of 68 and 9.8 g a.c./ha. *Aphidius rhopalosiphi* was further tested in a more realistic test system and toxicity was found to be mitigated (LR_{50} and ER_{50} >864 g a.c./ha). Tests of contact toxicity of a representative SC formulation for the rove beetle (*Aleochara bilineata*) resulted in an ER_{50} >626 g a.c./ ha. The most sensitive non-target arthropod tested in glass plate studies was the ladybird *Coccinella septempunctata* which had an LR_{50} of 41 g a.c./ha.

On the basis of these data, it is considered that the product may not be compatible with integrated pest management (IPM) programs using beneficial arthropods.

Soil organisms

Toxicity results for spiromesifen to earthworms were corrected by a factor of 2 to account for the log K_{ow} of 4.6 for this substance. The acute corrected LC_{50} to earthworms (*Eisenia fetida*) was >500 mg a.c./kg dry soil. In a 56-day chronic test, there was no effect on adult mortality or reproduction at the highest tested rate, and the NOEC was 4.3 mg a.c./kg dry soil. Toxicity of the metabolites M01 and M09 to springtails (*Folsomia candida)* was similar with NOECs for both metabolites of 32 mg/kg dry soil.

For soil microorganisms no adverse effects on carbon or nitrogen transformation were found at spiromesifen concentrations up to 3.0 mg a.c./kg dry soil; the NOECs for M01 and M09 were 1.1 mg/kg dry soil and 3.2 mg/kg dry soil respectively.

Risks of use of the product to soil organisms were therefore determined to be acceptable, and no protection statements are required.

Non-target terrestrial plants

Effects of spiromesifen on seedling emergence and vegetative vigour were assessed at a single application rate of 909 g a.c./ha for 10 standard test plant species. Three species (onion, ryegrass, and turnip) showed >25% effects in the seedling emergence study, while 2 species (ryegrass and turnip) showed >25% effects in the vegetative vigour study.

These 3 species were subsequently tested in further dose/response studies. Effects were greater in the seedling emergence study, with ryegrass (*Lolium perenne*) being the most sensitive (ER_{25} 21 g a.c./ha and ER_{50} 53 g a.c./ha). In the vegetative vigour study, the most sensitive ER_{25} was 195 g a.c./ha for turnip (*Brassica rapa*; EC_{50} 623 g a.c./ha) and the most sensitive ER_{50} was 605 g a.c./ha (EC_{25} 213 g a.c./ha) for ryegrass.

The regulatory acceptable level (RAL) for non-target terrestrial vegetation areas was determined to be 5.3 g a.c./ha. Mandatory buffer zones of up to 20 metres for vertical sprayers are required to mitigate these risks.

Recommendations

In considering the environmental safety of the proposed use of Interrupt 240 SC Miticide, the APVMA had regard to the toxicity of the active constituent and its residues, including degradation products, in relation to relevant organisms and ecosystems. Available information indicates that spiromesifen is not a PBT (persistent, bioaccumulative or toxic) substance or POP (persistent organic pollutant). In addition, spiromesifen provides no indication of activity as an endocrine-disrupting agent. Based on the outcome of the risk assessment, the APVMA can be satisfied that the proposed use of the product meets the environmental safety criteria when used according to the label directions.

Efficacy and safety assessment

Proposed product use pattern

Spiromesifen was first registered overseas in 2004 as the product 'Oberon 240 SC Miticide' (240 g/L spiromesifen). It is approved for use in over 60 countries for the control of various mites and insects in a range of crops.

Spiromesifen is a tetramic acid derivative belonging to the mode of action Group 23 (IRAC 2023). It is a growth inhibitor acting on acetyl coenzyme A carboxylase, the enzyme that catalyses the first step in fatty acid biosynthesis. According to the applicant, translaminar movement of spiromesifen allows the active to move through the leaf epidermis and mesophyll to control mites not directly exposed to sprayed surfaces.

In Australia, 'Oberon 240 SC Miticide' will be marketed under the name 'Interrupt 240 SC Miticide' for the control of two-spotted mites (*Tetranychus urticae*) in pome and stone fruits. Proposed application methods are by vertical sprayer, at a rate of 50–60 mL/100 L, applied to the point of run-off to ensure complete coverage of foliage and fruit. No more than one application per season is to be made in each crop, at a maximum rate of 1.6 L/ha per application.

Efficacy and target crop/animal safety

Data from 15 Australian field trials were submitted to support the efficacy and crop safety of Interrupt 240 SC Miticide for the control of two-spotted mites in pome and stone fruit. All trials were conducted in commercial orchards in major pome and stone fruit growing areas of Queensland (8), Victoria (4) and Western Australia (3) over 3 seasons (2020–22). Trials aimed to demonstrate efficacy against two-spotted mite and crop safety in several varieties of apple (6 trials, 4 varieties), nectarine (4 trials and 4 varieties), peach (4 trials and 3 varieties) and pear (one trial and one variety). Additional crop safety data for several other varieties of pome and stone fruit (including cherry and plum) was submitted as part of the Residues assessment (see Crop Safety section below).

Trials used a randomised complete block design, with at least 4 replicates. Plots were typically a single tree, but multiple trees were used in dense plantings such as trellised pome or stone fruit. The proposed product was applied at rates ranging from 20 to 120 mL/100 L (4.8 g a.c. to 28.8 g a.c./100 L). In several trials, 2 applications of Interrupt were applied, at approximately 26 days apart. All trials included an untreated control and at least one industry standard miticide for comparison, containing the actives bifenazate, abamectin, or abamectin + chlorantraniliprole. Standard treatments were selected based on those used commercially in the respective region of the trial. Standard treatments were applied at registered rates and according to the respective label directions for use. The addition of an adjuvant (Hasten) to the proposed product was also tested in one trial.

All treatments were applied as foliar sprays to near the point of run-off using handheld spray lances or guns delivering a medium or larger spray droplet. Water volumes used in apples and stone fruit were 1,000–3,000 L/ha, while in pears it was 1,700–3,500 L/ha.

Efficacy

Due to insufficient pest populations in 3 trials, efficacy was assessed in 12 out of the 15 trials. Efficacy assessments for two-spotted mite control were made via leaf collection and counting. At each assessment timing, 20–25 leaves were randomly collected from trees. In most trials the number of mite eggs, motile nymphs, and motile adults on each leaf were counted and recorded.

Leaf damage (percentage area with silvering/discolouration due to mite feeding) was assessed in some trials on the same leaves collected from each plot for the mite counts, with data presented as the mean area damaged per leaf. Predatory mites were also counted where present in trials.

Across all trials, Interrupt applied once at 50–60 mL/100 L provided comparable control of two-spotted mites to a commercial standard containing the active bifenazate and improved control compared to a commercial standard containing abamectin + chlorantraniliprole. In 4 trials, Interrupt applied at 40 mL/100 L and above gave excellent control of two-spotted mite numbers after one application. In 5 trials, an application rate of 50 mL/100 L and above provide good control of two-spotted mites after one application but the 40 mL/100 L rate did not provide sufficient control in these trials. In 2 trials, where a high or medium persistent population of two-spotted mites developed, a rate of 60 mL/100 L provided good control after one application. The trial results support a proposed label rate of 50–60 mL/100 L for the control of two-spotted mites in pome and stone fruit.

No effect on predatory mites were observed in 8 out of 11 trials where they were included in the assessment. In the remaining 3 trials, reductions in the beneficial species populations coincided with reductions in the two-spotted mite populations. Therefore, differences were likely a result of reduced food source availability.

Crop safety

Crop safety was estimated as a percent of phytotoxicity on the whole plot at each post-spray assessment. Foliage and fruit were examined for any signs of phytotoxicity on each occasion and scored using a standard rating system of 0–100.

No phytotoxicity was observed in any trial. In addition to these 15 crop safety trials, further evidence of safety of Interrupt 240 SC Miticide to pome and stone fruit can be derived from 24 residues trials submitted with this application, where no symptoms of phytotoxicity were observed when the product was applied at up to x2 the maximum proposed label rate. Together, crop safety was satisfied in the following pome and stone fruit varieties:

- Apples: ruby pink, pink lady, red delicious, royal gala, alivan gala, granny smith, envy
- Pears: williams, packham, buerre bosc, corella
- Cherries: regina, lapins
- Peaches: tatura 204, red haven, O’Henry, angel, ivory queen, golden queen
- Nectarines: April jewel, bright pearl, August fire, majestic pearl, grand blight, autumn bright, carene
- Plums: angelino

Resistance management

Spiromesifen belongs to the ketoenols chemical class and IRAC Group 23 (IRAC 2023). It is a tetramic acid derivative and represents a new class of miticide chemistry with a unique mode of action and no known cross-resistance with any of the presently registered miticides in Australia. Therefore, Interrupt is expected to provide pome and stone fruit growers with a useful control agent, with a different mode of action, for rotation in mite resistance management programs. The draft label includes a standard insecticide resistance statement. To mitigate risks of resistance developing, application of Interrupt will be restricted to one spray per crop and season, and no more than 1.6 L/ha per application.

Recommendations

Trial data demonstrated that Interrupt 240 SC Miticide will be effective in controlling two-spotted mite infestations in pome and stone fruit crops when applied at the proposed label rates of 50–60 mL/100 L, as a single application. The product was safe to use at the proposed label rates in all varieties of pome and stone fruits tested.

There are no objections on efficacy or target-crop safety grounds to the registration of the product Interrupt 240 SC Miticide, containing 240 g/L spiromesifen, when used as directed.

Spray drift assessment

Regulatory Acceptable Levels (RALs) were established using the APVMA Spray Drift Assessment Tool (SDRAT), or Spray Drift Management Tool (SDMT), by each risk area, to calculate the appropriate spray drift buffer zones for Interrupt 240 SC Miticide.

Human health

Based on the absence of systemic toxicity in the 28-day rat dermal toxicity study at the limit dose, a buffer zone to mitigate any potential bystander exposure is not considered necessary.

Residues and trade

Based on a RAL of 5 ppm, mandatory no-spray zones are not required for protection of livestock areas for international trade. The applicants proposed label statements regarding spray drift are acceptable with respect to trade.

Environment

Based on an aquatic RAL of 0.25 µg a.c./L (from the *Daphnia magna* NOEC of 0.25 µg a.c./L and an assessment factor of 1), a mandatory downwind buffer zone of 75 metres was determined for the protection of natural aquatic areas.

Based on the pollinator RAL of 0.000013 g a.c./ha (from the *Apis mellifera* chronic larval oral LDD_{10} of 0.078 µg a.c./larva for the spiromesifen metabolite M01 (spiromesifen-enol) and a conversion factor of LOC 0.4/ExpE2.4 * 1000, the product must not be applied when crops are in flower, and additional protection measures are required to mitigate dietary exposure of bees.

Based on the vegetation RAL of 5.3 g a.c./ha (from the *Lolium perenne* pre-emergence ER_{50} of 53 g a.c./ha and an assessment factor of 10), a mandatory downwind buffer zone of 20 metres is required for protection of vegetation areas.

Table 10: Summary of RALs for Interrupt 240 SC Miticide

Sensitive area	Regulatory acceptable level	
	Level of active	Units
Bystander	–	g/ha
Livestock	5	ppm
Aquatic	0.25	µg/L
Pollinator	0.000013	g/ha

Sensitive area	Regulatory acceptable level	
	Level of active	Units
Vegetation	5.3	g/ha

Buffer zones calculated by the SDRAT or SDMT, using the above RALs, were incorporated into the Interrupt 240 SC Miticide label spray drift instructions (see *Labelling requirements*).

Labelling requirements

CAUTION

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

Interrupt ® 240 SC Miticide

ACTIVE CONSTITUENT: 240 g/L SPIROMESIFEN

For the control of two-spotted mites in pome and stone fruit as per the DIRECTIONS FOR USE Table

DIRECTIONS FOR USE

RESTRAINTS

DO NOT apply by aircraft.
DO NOT apply by ground boom.
DO NOT apply if heavy rains or storms are forecast within 3 days.
DO NOT irrigate to the point of runoff for at least 3 days after application.

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 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 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.

Vertical sprayers

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

- The spray is not directed above the target canopy.
- The outside of the sprayer is turned off when turning at the end of rows and when spraying the outer row on each side of the application site.
- For dilute water rates up to the maximum listed for each type of canopy specified, minimum distances between the application site and downwind sensitive areas are observed (see ‘Mandatory downwind buffer zones’ section of the following table titled ‘Buffer zones for vertical sprayers’).

Buffer zones for vertical sprayers

Application rate	Type of target canopy and dilute water rate	Mandatory downwind buffer zones				
		Bystander areas	Natural aquatic areas	Pollinator areas	Vegetation areas	Livestock areas
50 mL/100L	Up to 2 metres height, foliated, maximum spray volume 1000 L/ha	0 m	25 m	0 m	5 m	0 m
	Taller than 2 metres, foliated, maximum spray volume 3200 L/ha	0 m	75 m	0 m	20 m	0 m
Up to 60 mL/100L	Up to 2 metres height, foliated, maximum spray volume 1000 L/ha	0 m	30 m	0 m	5 m	0 m
	Taller than 2 metres, foliated, maximum spray volume 2667 L/ha	0 m	75 m	0 m	20 m	0 m

CROP	PEST	RATE	WHP	CRITICAL COMMENTS
Pome fruit, stone fruit	Two-spotted mite (*Tetranychus urticae*)	**Dilute spraying** 50–60 mL/100L **Concentrate spraying** Refer to application section	14 days	Monitor the orchards and commence applications once local thresholds are reached. Apply Interrupt to the point of run-off. Complete coverage of all foliage and fruit is essential – refer 'Application' section in GENERAL INSTRUCTIONS. Use the higher rate under conditions of high or persistent pest pressure. **Do not apply more than one application per season in each crop. Do not apply more than 1.6 L/ha per application.** Further treatments, if required, should be made with alternate mode-of-action miticides. **Resistance management** This use may be subject to a CropLife resistance management strategy. Refer to www.croplife.org.au for more information.

NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL UNLESS AUTHORISED UNDER APPROPRIATE LEGISLATION.

WITHHOLDING PERIOD (WHP)
Harvest (H): Pome and stone fruit: DO NOT HARVEST FOR 14 DAYS AFTER APPLICATION
Grazing (G): DO NOT GRAZE TREATED ORCHARD

EXPORT OF TREATED PRODUCE
Growers should note that suitable MRLs or import tolerances may not be established in all markets for produce treated with Interrupt 240 SC. If you are growing produce for export, please check with Bayer Crop Science for the latest information on MRLs and import tolerances BEFORE using Interrupt 240 SC.

GENERAL INSTRUCTIONS

Mixing
Shake the container well before using. Partially fill the spray tank with clean water (do not use hard/saline water or water with suspended solids) and add the required volume of product whilst agitating, then top up to the desired level with water. Interrupt 240 SC should be agitated constantly before and during application and applied as soon as possible after mixing.

Application
Dilute spraying

- Use a sprayer designed to apply high volumes of water up to the point of run-off and matched to the crop being sprayed.
- Set up and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient water to cover the crop, including fruit, to the point of run-off. Avoid excessive run-off.
- The required spray volume may be determined by applying different test volumes, using different settings on the sprayer, from industry guidelines or expert advice.
- Add the amount of product specified in the Directions for Use table for each 100 L of water. Spray to the point of run-off.
- The required dilute spray volume will change and the sprayer set up and operation may also need to be changed, as the crop grows.

Concentrate spraying

- Use a sprayer designed and set up for concentrate spraying (that is a sprayer which applies spray volumes less than those required to reach the point of run-off) and matched to the crop being sprayed.
- Set up and operate the sprayer to achieve even coverage throughout the crop canopy using your chosen spray volume.
- Determine an appropriate dilute spray volume (See *Dilute spraying* above) for the crop canopy. This is needed to calculate the concentrate mixing rate.
- The mixing rate for concentrate spraying can then be calculated in the following way:

Example only

1. Dilute spray volume as determined above: For example 1500 L/ha.
2. Your chosen concentrate spray volume: For example 750 L/ha.
3. The concentration factor in this example is 2X (i.e. 1500 L ÷ 750 L = 2).
4. If the dilute label rate is 60 mL/100 L, then the concentrate rate becomes 2 x 60, which is 120 mL/ 100 L of concentrate spray.

- The chosen spray volume, amount of product per 100 L of water, and the sprayer set up and operation may need to be changed as the crop grows.
- Do not use at a concentration factor greater than 2X (e.g. at a rate higher than 120 mL/ 100 L where a dilute spraying rate of 60 mL/ 100 L is specified).
- For further information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow industry best practice.

COMPATIBILITY

For the latest compatibility recommendations contact the Bayer Crop Science Technical Information Line 1800 804 479 or your local Bayer Crop Science representative.

INSECTICIDE RESISTANCE WARNING

GROUP	23	INSECTICIDE

For insecticide resistance management, Interrupt 240 SC Miticide is a Group 23 insecticide.

Some naturally occurring insect biotypes resistant to Interrupt 240 SC and other Group 23 insecticides may exist through normal genetic variability in any insect population. The resistant individuals can eventually dominate the insect population if Interrupt 240 SC or other Group 23 insecticides are used repeatedly. The effectiveness of Interrupt 240 SC on resistant individuals could be significantly reduced. Since occurrence of resistant individuals is difficult to detect prior to use, Bayer CropScience Pty Ltd accepts no liability for any losses that may result from the failure of Interrupt 240 SC to control resistant mites.

Interrupt 240 SC may be subject to specific resistance management strategies. For further information contact your local supplier, Bayer Crop Science representative or local agricultural department agronomist.

INTEGRATED PEST MANAGEMENT

May be toxic to beneficial arthropods. May not be compatible with integrated pest management (IPM) programs utilising beneficial arthropods. Minimise spray drift to reduce harmful effects on beneficial arthropods in non-crop areas.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product or used containers.

PROTECTION OF HONEY BEES AND OTHER INSECT POLLINATORS

Spiromesifen has a systemic action. Harmful to bees, including bee brood. DO NOT apply while bees are actively foraging. DO NOT allow spray drift to flowering weeds or flowering crops in the vicinity of the treatment area. Before spraying, notify beekeepers to move hives to a safe location with an untreated source of nectar and pollen, if there is potential for managed hives to be affected by the spray or spray drift.

STORAGE AND DISPOSAL

Store in the closed, original container in a cool, secure, well-ventilated area. Do not store for prolonged periods in direct sunlight.

(all containers excluding SCHUTZ/re-useable/ returnable containers)

Triple-rinse container before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling break, crush or puncture and deliver empty container to an approved waste management facility. If an approved facility is not available, bury the empty container 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. Do not re-use empty container for any other purpose.

(SCHUTZ/re-useable/returnable containers)

If tamper evident seals are broken prior to initial use then the integrity of the contents cannot be assured. Empty container by pumping through the dry-break connection system. Do not attempt to unscrew the valve or breach the locked filling point. Do not contaminate the container with water or other foreign material. Ensure that the coupler, pump, meter and hoses are disconnected, triple rinsed with clean water and drained after each use. Contact point of purchase to arrange return or collection of empty containers. This container remains the property of Bayer CropScience Pty Ltd.

SAFETY DIRECTIONS

Wash hands after use.

FIRST AID

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

SAFETY DATA SHEET

Additional information is listed in the Safety Data Sheet, which can be obtained from www.crop.bayer.com.au.

EXCLUSION OF LIABILITY

This product must be used strictly as directed, and in accordance with all instructions appearing on the label and in other reference material. So far as it is lawfully able to do so, Bayer CropScience Pty Ltd accepts no liability or responsibility for loss or damage arising from failure to follow such directions and instructions.

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APVMA Approval No.: 92500/135730

Bayer CropScience Pty Ltd
A.B.N. 87 000 226 022
Level 4, 109 Burwood Rd
Hawthorn, Vic. 3122
Phone: 03 9248 6888
Technical Enquiries: 1800 804 479
www.crop.bayer.com.au

Acronyms and abbreviations

Shortened term	Full term
ac	active constituent
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ARfD	Acute Reference Dose
bw	bodyweight
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
dw	dry weight
E_bC_{50}	Concentration at which the biomass of 50% of the test population is impacted
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
F_0	Original parent generation
g	gram
GAP	Good Agricultural Practice
geomean	geometric mean is a mean or average which indicates a central tendency of a finite set of real numbers by using the product of their values
ha	hectare
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
in vitro	Outside the living body and in an artificial environment
in vivo	Inside the living body of a plant or animal
IPM	Integrated Pest Management
IRAC	Insecticide Resistance Action Committee
ISO	International Organisation for Standardization
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
K_F	Freundlich sorption value

Shortened term	Full term
K_{FOC}	Fraction of organic carbon
K_{OC}	Organic carbon partitioning coefficient
kg	kilogram
K_{OC}	Organic carbon partitioning coefficient
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
LR_{50}	Rate of chemical that kills 50% of the test population of organisms
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
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
n	number of samples
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short-Term Intake
ng	nanogram
NOAEL	No Observed Adverse Effect Level
NOEC/NOEL	No Observable Effect Concentration/Level
NOEDD	No Observed Effect Dietary Dose
PPE	Personal Protective Equipment
ppm	parts per million
RAL	Regulatory Acceptable Level
s	second
SC	Suspension Concentrate
SDMT	Spray Drift Management Tool
SDRAT	Spray Drift Risk Assessment Tool

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
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 registry 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
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
Toxicology	The study of the nature and effects of poisons

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