Australian Government

Australian Pesticides and Veterinary Medicines Authority

Public Release Summary

on the evaluation of the new active constituent fluoxapiprolin
in the product Xivana Prime 20 SC Fungicide
APVMA product number 89997
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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 or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

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

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

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of Xivana Prime 20 SC Fungicide should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade, and efficacy and target crop or animal safety. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on 3 May 2022 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

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

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

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

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

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

Written submissions should be addressed to:

Case Management and Administration Unit

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 Xivana Prime 20 SC Fungicide and approval of the new active constituent, fluoxapiprolin.

Applicant

Bayer CropScience Pty Ltd.

Purpose of application

Bayer CropScience Pty Ltd has applied to the APVMA for registration of the new product Xivana Prime 20 SC Fungicide, containing 20 g/L of the new active constituent fluoxapiprolin in a suspension concentrate formulation.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of the product Xivana Prime 20 SC Fungicide, and approval of the new active constituent fluoxapiprolin.

Proposed claims and use pattern

The product is to be applied at 37.5 to 50 mL/100 L in grapevines for the control of downy mildew (*Plasmopara viticola*). No more than 2 applications of Xivana Prime 20 SC Fungicide may be applied to grapevines per growing season with the last application no later than pre-bunch closure.

Mode of action

Fluoxapiprolin is a novel fungicide from the piperidinyl thiazole isoxazoline chemical class. It belongs to the oxysterol binding protein inhibitor mode of action and is active against a wide range of oomycete fungi.

Overseas registrations

Xivana Prime 20 SC Fungicide is currently registered in Armenia, Cambodia and Belarus.

Chemistry and manufacture

Active constituent

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

Fluoxapiprolin is a light beige powder. It is essentially insoluble in water. The vapour pressure (4.5×10-5 Pa at 25°C) and the Henry's law constant (2.4×10-1 Pa·m^3·mol^{-1}) indicates that volatilisation is not expected to be a significant route of dissipation for fluoxapiprolin. There are no flammable, explosive, self-ignition, and/or oxidizing properties of safety concern for fluoxapiprolin.

Table 1: Nomenclature and structural formula of fluoxapiprolin

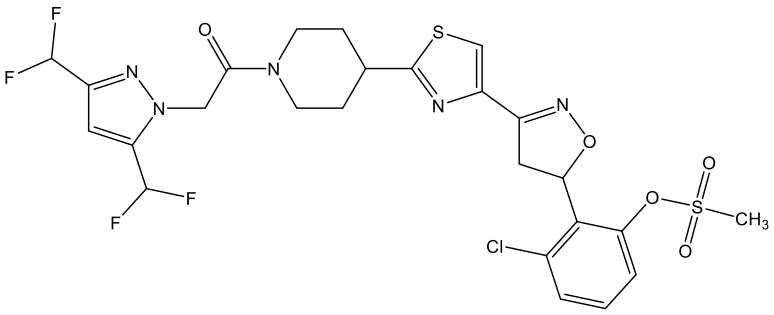
Common name (ISO):	Fluoxapiprolin
IUPAC name:	2-{(5RS)-3-[2-(1-{[3,5-bis(difluoromethyl)-1H-pyrazol-1yl]acetyl}piperidin-4-yl)-1,3-thiazol-4-yl]-4,5-dihydro-1,2-oxazol-5-yl}-3-chlorophenyl methanesulfonate
CAS registry number:	1360819-11-9
Molecular formula:	C25H24ClF4N5O5S2
Molecular weight:	650.1 g/mol
Structural formula:	

Table 2: Key physicochemical properties of fluoxapiprolin

Physical form:	Solid (powder)
Colour:	Light beige
Odour:	Weak (not characteristic)
Melting point:	146.4°C
Boiling point:	Decomposition was observed before boiling
Density:	1.51 g/mL at 20°C
Stability:	In an accelerated model at temperature, <1% change in concentration of the active is observed after 2 weeks storage at 54°C. Technical fluoxapiprolin is expected to be stable during storage under normal conditions for at least 2 years
Safety properties:	Not considered flammable. Not explosive. Not corrosive. No self-ignition observed. Fluoxapiprolin has no oxidation/reduction potential. It does not show any chemical incompatibility with reducing or fire extinguishing agents
Solubility in water:	0.08 mg/L (pH 5.9)
Organic solvent solubility:	Methanol: 1.3 g/L n-Heptane: 0.061 mg/L Toluene: 1.1 g/L Dichloromethane: 143 g/L Acetone: 84 g/L Ethyl acetate: 15 g/L Dimethyl sulfoxide: >270 g/L
PH:	6.4 (24°C, 1% in distilled water, active was not completely dissolved)
Octanol/water partition coefficient (Log K_{ow}/KOW):	Log P_{ow}= 3.4 at pH 4 Log P_{ow}= 3.4 at pH 7 Log P_{ow}= 3.4 at pH 9
Vapour pressure:	3.0×10-5 Pa at 20°C 4.5×10-5 Pa at 25°C 2.9×10-4 Pa at 50°C
Henry's law constant:	2.4×10-1 Pa·m^3·mol^{-1}
UV/VIS absorption spectra:	λmax= 204 nm λmax= 259 nm λmax= 291 nm

Formulated product

The product Xivana Prime 20 SC Fungicide will be manufactured overseas. Tables 3 and 4 outline some key aspects of the formulation and physicochemical properties of the product.

Xivana Prime 20 SC Fungicide will be available in 1 to 110 L HDPE (high density polyethylene) containers.

Table 3: Key aspects of the formulation of Xivana Prime 20 SC Fungicide

Distinguishing name:	Xivana Prime 20 SC Fungicide
Formulation type:	Suspension Concentrate (SC)
Active constituent concentration:	20 g/L fluoxapiprolin

Table 4: Physicochemical properties of Xivana Prime 20 SC Fungicide

Physical form:	White to dark beige odourless suspension
PH:	6.6 at 25°C (1% dilution)
Density:	1.049 g/mL at 20°C
Kinematic viscosity:	378.7×10-6 m²/s at a shear rate of 20 s-1 (20°C) 118.2×10-6 m²/s at a shear rate of 100 s-1 (20°C)
Pourability:	Residue: max. 5% Rinsed residue: 0.27%
Spontaneity of dispersion:	≥60% to ≤105% (CIPAC standard water D)
Suspensibility:	100% (0.06% w/w and 1% w/w in CIPAC standard water D)
Persistent foaming:	0 mL after 10 seconds (0.06% w/w and 1% w/w in CIPAC standard water D)
Wet sieve test:	0.01% residue on a 75 µm sieve
Safety properties:	Not classified as a flammable liquid, explosive, or a corrosive substance
Storage stability:	There were sufficient data to conclude that the product is expected to remain within specifications for at least 2 years when stored under normal conditions

Recommendations

The APVMA Chemistry section has evaluated the chemistry of the active constituent fluoxapiprolin and associated product Xivana Prime 20 SC Fungicide, 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 both the technical active and the formulated product are expected to remain stable for at least 2 years when stored under normal conditions.

Based on a review of the chemistry and manufacturing details, the registration of Xivana Prime 20 SC Fungicide, and approval of the active constituent fluoxapiprolin, are supported from a chemistry perspective.

Toxicological assessment

Fluoxapiprolin was assessed using a full package of toxicological data submitted by the applicant. The data submitted were sufficient to assess the toxicity of fluoxapiprolin.

Evaluation of toxicology

Chemical class

Fluoxapiprolin is a member of the Fungicide Resistance Action Committee (FRAC) Code 49, Group F9, lipid homeostasis and transfer/storage agents, also known as oxysterol binding protein homologue inhibitors. It is a novel fungicide closely related to oxathiapiprolin. Its fungicidal mode of action is via inhibiting fungal oxysterol-binding protein-related protein 1 (ORP1), thereby disrupting sterol transporter activity, the movement of lipids between biological membranes, membrane maintenance, the formation of more complex lipids, and cell signalling processes that are essential for fungal cells to survive.

Pharmacokinetics

In a rat study, fluoxapiprolin was rapidly but poorly absorbed with estimated oral bioavailability of 37% in male rats and 33% in female rats. Absorption of fluoxapiprolin from the gastrointestinal tract occurred with the point of departure from oral dose proportionality at around 82 to 100 mg/kg bw/day. The kinetically derived maximum dose was determined to be in the range of 250 to 300 mg/kg bw/day based on a 3 to 5-fold difference from the expected dose-proportionality of the systemic dose due to the saturation of oral absorption. Plasma kinetics in rats followed a 2-compartment model. In toxicokinetic studies, sex differences in blood plasma concentration (measured as area under the curve, (AUC)) AUC0-∞ were small and independent of the dose. Following low dose exposure, Cmax in females was about 3-fold higher than in males. However, AUC0-24h in high dose females in the dietary exposure combined chronic/carcinogenesis study were 2 to 10-fold higher than those in males. The low-dose plasma elimination t½ was about 25 to 26 hours. Repeated oral dosing was not associated with biologically important changes in plasma kinetics. Fluoxapiprolin was rapidly and widely distributed throughout most organs and tissues, with the highest levels observed in the adrenal gland, ovary, kidney, and liver.

Fluoxapiprolin was extensively metabolised, with a large number of metabolites produced via phenyl and piperidine ring hydroxylation, hydrolysis of the piperidyl and thiazole moieties, defluorination, oxidation, carboxylation, and conjugation with glucuronic acid, cysteine and methylsulfinyl acid. The major metabolites were similar across species. Excretion was rapid and complete, with approximately 80 to 90% excreted in the faeces, and 2 to 6% excreted in the urine within the first 48 hours. No biologically relevant enantiomeric shifting, metabolization, or degradation of fluoxapiprolin occurred in berries or leaves after foliar treatment. The major chemical residue was fluoxapiprolin. Notably the applicant has proposed a residue definition for plants of the sum of fluoxapiprolin parent (sum of isomers), BCS-CC26101, and BCS-DE61185 expressed as the parent compound. BCS-DE61185 (BCS-CS55621-pyrazole-alanine) is the alanine conjugate of the major rat metabolite BCS-CS55621. BCS-CC26101 (BCS-CS55621-pyrazole acetic acid) is a derivative of the major rat metabolite BCS-CS55621 that is found in urine. Accordingly, the current human health risk assessment is sufficient to evaluate the fluoxapiprolin metabolites that have been proposed for incorporation in the plant food residue definition.

Acute toxicity (active constituent)

Fluoxapiprolin is of low toxicity via the oral, dermal, and inhalation routes of exposure. It is slightly irritating to rabbit eyes, but it is neither an irritant to rabbit skin nor a skin sensitiser in the mouse local lymph node assay (LLNA).

Acute toxicity (product)

Xivana Prime 20 SC Fungicide has low acute toxicity via the oral, dermal, and inhalation routes of exposure. It is not irritating to the skin of rabbits; however, it is slightly irritating to the eyes of rabbits and is a potential skin sensitiser based on the results of a mouse LLNA.

Repeat-dose toxicity

In repeat-dose and subchronic toxicity studies, fluoxapiprolin did not induce any adverse effects in rats, mice, or dogs. Oral NOAELs were all established at the highest dose tested, which was 882 mg/kg bw/day in male mice (90-day study), 891 mg/kg bw/day in male rats, and 892 mg/kg bw/day in male dogs. In a short-term dermal study in rats, no adverse effects were noted at the limit dose of 1,000 mg/kg bw/day.

Chronic toxicity and carcinogenicity

Fluoxapiprolin was not carcinogenic in mice at up to, and including, the highest administered dietary dose of 278 mg/kg bw/day in males and 317 mg/kg bw/day in females. The test compound caused transient, dose-related inhibition of bodyweight gain during the first week of treatment in female mice at all doses tested. However, because this was not persistent, and did not cause statistically or biologically significant effects on bodyweight, the finding is considered to be non-adverse. The NOAEL was established at 278 mg/kg bw/day in males and 317 mg/kg bw/day in females, based on the absence of any significant, biologically relevant effects at the highest dose tested.

In a 2-year chronic toxicity and carcinogenicity study in rats, the NOAEL for carcinogenicity and systemic toxicity was established at 288 and 374 mg/kg bw/day in males and females, respectively. This NOAEL was based on the lack of any treatment-related adverse effects at the highest dose tested.

Reproductive and developmental toxicity

In developmental toxicity studies in rabbits and rats, the NOAELs were established at the highest dose tested, 1,000 mg/kg bw/day, based on the absence of treatment-related adverse effects in either species. It should be noted that in rats, there was an increased incidence of incomplete ossification of certain cranial bones, which are considered repairable variations that do not result in permanent loss of either form or function. The incidence of these observations was only increased relative to concurrent controls at the low and mid doses. In addition, it was either within, or marginally above, the range observed among historical control animals. Therefore, these observations were considered possibly treatment-related but non-adverse.

In a 2-generation reproductive toxicity study in rats, fluoxapiprolin had no effects on reproductive performance and the reproductive toxicity NOAEL was established at 262 mg/kg bw/day. Transient changes were observed in food consumption and body weight gain among high dose parental animals. Similarly, transient inhibition of body weight gain was noted in both F1 and F2 pups during the lactation period. These observations were not considered adverse. The NOAELs for systemic toxicity and offspring toxicity were also set at the highest dose tested, equal to 262 mg/kg bw/day (approximately the kinetically derived maximum dose).

Genotoxicity

There was no evidence of genotoxicity when fluoxapiprolin was tested in a battery of *in vitro* and *in vivo* genotoxicity assays.

Neurotoxicity

There was no evidence of neurotoxicity in the fluoxapiprolin database. In an acute neurotoxicity study, the NOAEL for neurotoxicity was 2,000 mg/kg bw (highest dose tested). The NOAEL for general toxicity was 1,000 mg/kg bw based on a slight reduction in bodyweight gain.

Phototoxicity

The phototoxic potential of fluoxapiprolin was tested in an *in vitro* assay using BALB/c 3T3 cells. Under the conditions tested, fluoxapiprolin did not show any phototoxic activity.

Mode of action (toxicology)

Fluoxapiprolin is not a repeat dose, developmental, or reproductive toxicant, it is not genotoxic in a battery of *in vivo* and *in vitro* assays. Fluoxapiprolin is not a human-relevant carcinogen at the expected levels of exposure. Fluoxapiprolin is not neurotoxic and showed no evidence of phototoxicity.

Toxicity of metabolites and/or impurities

A number of investigations were conducted on metabolites or degradates of fluoxapiprolin. For several of the substances, only genotoxicity studies were performed, and these were universally negative. These include:

- BCS-CC26101, which is a rat and dog plasma metabolite of fluoxapiprolin
- BCS-DH17585, which is the sodium salt of BCS-DG91934, a soil metabolite of fluoxapiprolin that may attain concentrations above 0.1 µg/L in groundwater. The metabolite was tested as the sodium salt because BCS-DG91934 is unstable in aqueous solution
- BCS-CZ38260, which is a groundwater metabolite of fluoxapiprolin, and a rat urinary metabolite accounting for <0.1 to 2.0% of the administered dose.

In addition, the groundwater metabolite, 3,5-bis(difluoromethyl)-1H-pyrazole (also known as BCS-CS55621-bis-difluor-methylpyrazol and BCS-BP32808), was assessed in acute oral toxicity, short-term oral toxicity (4-week study in rats with 2-week reversibility period), and a series of genotoxicity assays. Using the up-and-

down procedure, the acute oral LD50 for BCS-BP32808 in rats was estimated at 175 mg/kg bw. In short-term oral toxicity study in rats, the study author set a NOAEL of 2 mg/kg bw/day based on non-specific toxic responses (low bodyweight gain and food intake) or stress-related responses at 5 and 12 mg/kg bw/day, reduced motor activity, and a suspected non-adverse effect on water balance and possibly liver function. In a series of genotoxicity studies, BCS-BP32808 was positive in gene mutation and chromosomal aberration studies *in vitro*, and negative in gene mutation and chromosomal aberration studies *in vivo*.

Health-based guidance values and poisons scheduling

Poisons Standard

Effective 1 February 2022, fluoxapiprolin is included in Appendix B, Part 3 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

Health-based guidance values

Acceptable daily intake

An acceptable daily intake (ADI) for fluoxapiprolin is established at 3 mg/kg bw/day based on the kinetically derived maximum dose of 250 to 300 mg/kg bw/day. Transient changes in body weight gain were observed in repeat dose studies in rats, however these were considered non-adverse. Given that the ADI is based on a toxicokinetic phenomenon associated with saturation of oral absorption and not an overt biologically adverse effect, it is regarded as conservative.

Acute reference dose

An acute reference dose (ARfD) for the general population is not considered necessary for fluoxapiprolin on the basis of its low acute toxicity, the lack of evidence for any acute neurotoxicity, and the absence of any other toxicologically relevant effect that might be attributable to a single dose.

Recommendations

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

There are no objections on human health grounds to the registration of the product Xivana Prime 20 SC Fungicide, containing 20 g/L of fluoxapiprolin, when used in accordance with the directions for use (DFU) and adhering to the recommended safety directions.

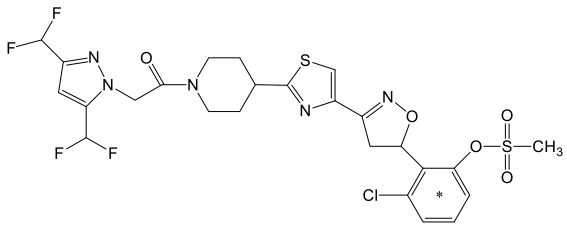
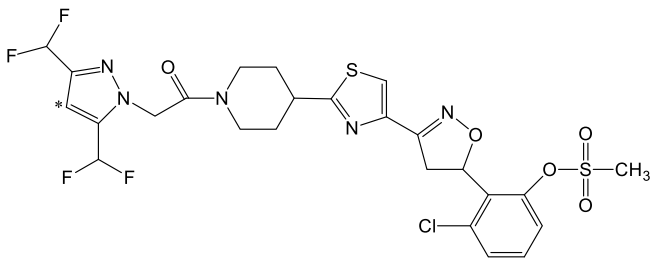
Residues assessment

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

Metabolism

The metabolism and distribution of fluoxapiprolin (BCS-CS55621) was investigated in plants (grapes, lettuce and potatoes and rotational crops) and target animals (lactating goats and laying hens) using fluoxapiprolin labelled in the phenyl (PH) or pyridine (PY) moieties.

Table 5: Phenyl (PH) and pyridine (PY) moieties of fluoxapiprolin

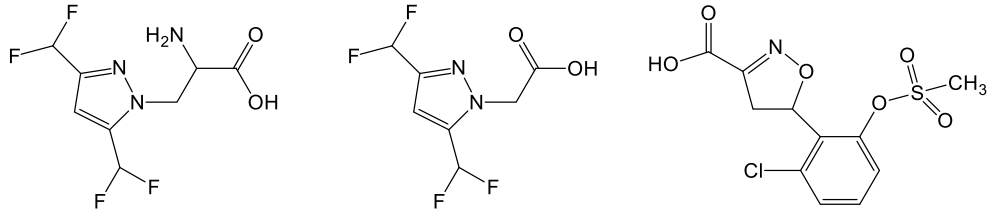
Phenyl-label (PH) [Phenyl-UL-^{14}C]BCS-CS55621	Pyridine-label (PY) [Pyrazole-4-^{14}C]BCS-CS55621
	

Plants

In grapes, 3 applications of labelled fluoxapiprolin were made at BBCH 16, 65, and 85 (total seasonal rate 62 and 59 g a.c./ha for the PH and PY labels respectively). Parent fluoxapiprolin was identified in surface washed fruit accounting for 85 to 92% TRR (0.098 to 0.10 mg/kg), in non-washed fruits at 89 to 90% TRR (0.13 mg/kg), and in leaves at 81 to 91% TRR (6.4 to 9.1 mg/kg).

In lettuce, 3 foliar applications of fluoxapiprolin were made at BBCH 15, 42-43, and 44-45 or 47-48 (total seasonal rate 60 and 59 g a.c./ha for the PH and PY labels respectively). Parent fluoxapiprolin was identified in lettuce matrices accounting for 48 to 74% TRR (0.022 to 0.032 mg/kg) in intermediate lettuce plants and 93 to 95% TRR (0.75 to 0.79 mg/kg) in head lettuce. Other components in lettuce matrices at >10% TRR included BCS-CS55621-pyrazole-alanine (BCS-DE61185) and BCS-CS55621-pyrazole acetic acid (BCS-CC26101) which were observed in intermediate lettuce plants at 20% and 17% TRR (0.009 and 0.008 mg eq./kg, PY label) respectively. BCS-CS55621-phenyl isoxazole acid was observed in intermediate lettuce plants in the phenyl labelled study, at 18% TRR (0.008 mg eq./kg).

Figure 1 Major metabolites of fluoxapiprolin in plant matrices



BCS-CS55621-pyrazole-alanine

BCS-CS55621-pyrazole-acetic acid

BCS-CS55621-phenyl-isoxazole acid

In potatoes, 3 foliar applications of fluoxapiprolin were made at BBCH 13-15, 61, and 93-95 (total seasonal rate 65 and 63 g a.c./ha for the PH and PY labels respectively). Parent fluoxapiprolin was the only significant compound found in tops (leaves and stem) accounting for 90 to 93% TRR (6.7 to 11 mg/kg). BCS-CS55621-pyrazole-alanine and BCS-CS55621-pyrazole acetic acid were observed in tubers at 52% and 41% TRR (0.014 and 0.011 mg eq./kg, PY label) respectively.

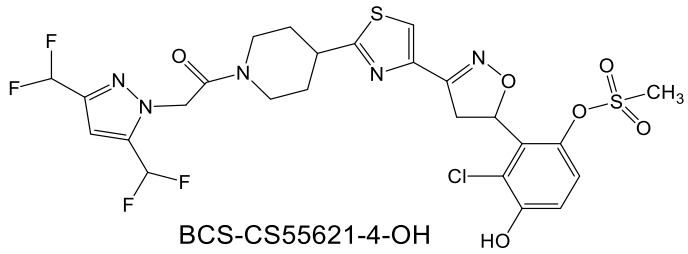
The metabolism of fluoxapiprolin was also investigated in rotational crops (turnips, chard and wheat) after application to soil. No parent was detected in any sample analysed. The phenyl labelled experiment showed low TRRs (<0.01 mg/kg) except in wheat matrices of the first rotation in which BCS-CS55621-phenyl-isoxazole acid was the only identified compound. Higher TRRs were observed in the matrices from the pyrazole labelled experiment. A number of compounds were observed at >10% TRR. Of these compounds, BCS-CS55621-pyrazole-alanine and BCS-CS55621-pyrazole acetic acid were major metabolites across the range of matrices.

Animals

Throughout the study period of the hen metabolism studies (administration at 18 ppm in the feed), the highest concentrations of residues were detected in the liver (0.21 to 0.25 mg eq./kg).

Parent fluoxapiprolin was the major identified component in eggs at 31 to 36% TRR (0.011 to 0.015 mg/kg), muscle at 16% TRR (0.002 mg/kg) and fat at 60 to 64% TRR (0.012 to 0.016 mg/kg). It was also observed in liver at 7.2 to 8.1% TRR (0.015 to 0.020 mg/kg). Of the other metabolites, only the 4-OH metabolite was present at >10% TRR and 0.01 mg eq./kg (16 to 17 % TRR and 0.033 to 0.042 mg eq./kg in liver).

Figure 2: Major metabolite (4-OH) in hen metabolism studies

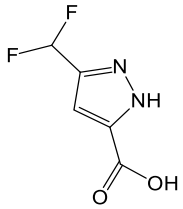


BCS-CS55621-4-OH

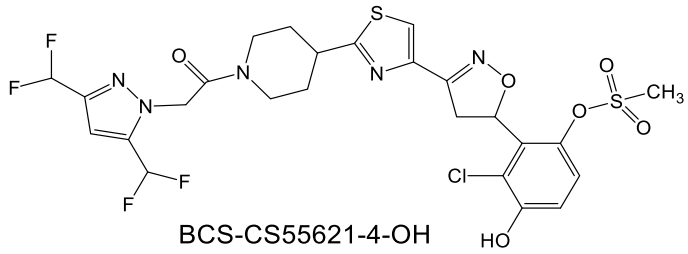
Throughout the study period of the lactating goat metabolism studies (administration at 24 ppm in the feed), the highest concentrations of residues were observed in the liver (0.90 to 0.93 mg eq./kg).

Parent fluoxapiprolin was the major identified component in fat at 59 to 74% TRR (0.008 to 0.009 mg/kg) and liver at 7.8 to 10% TRR (0.073 to 0.089 mg/kg). It was also observed in milk at 5.7 to 12% TRR (0.001 mg/kg) and in kidney at 13 to 18 % TRR (0.007 to 0.010 mg/kg). Of the other metabolites, only the pyrazole-carboxylic metabolite was present at >10% TRR and >0.01 mg eq./kg (34% TRR and 0.026 mg eq./kg in kidney).

Figure 3: Major metabolites (pyrazole-carboxylic acid and 4-OH) in lactating goat metabolism studies



BCS-CS55621-pyrazole-carboxylic acid



BCS-CS55621-4-OH

Analytical methods and storage stability

In the submitted Australian trials, residues of fluoxapiprolin were determined in grapes using analytical method ATM-0081: “Determination of residues of BCS-CS55621 in or on plant material by LC MS/MS”.

Parent fluoxapiprolin residues were extracted from each sample with water: acetonitrile and with shaking. A volume of the extract was then filtered using a PTFE syringe filter. An aliquot of the filtered extract was then placed in an auto-sampler vial and internal standard and water; acetonitrile added before residues of fluoxapiprolin were determined by LC-MS/MS. The limit of quantitation (LOQ) for fluoxapiprolin was determined as 0.01 mg/kg.

In the European grape trials, residues of fluoxapiprolin and its metabolites BCS-CC26101, BCS-BP32808, BCS-DE61185, BCS-DE72760 and BCS-DE72761 were determined according to the analytical method 01554: “Analytical Method 01554 for the determination of BCS-CS55621 and its metabolites BCS-CC26101, BCS-BP32808, BCS-DE61185, BCS-DE72760 and BCS-DE72761 in plant by HPLC-MS/MS”.

Parent fluoxapiprolin and its metabolites BCS-CC26101, BCS-BP32808, BCS-DE61185, BCS-DE72760 and BCS-DE72761 were extracted with a mixture of acetonitrile/water. After addition of internal standards, the extract was diluted either in aqueous or organic solvent to obtain 2 final extracts. The analytical determination was performed by HPLC using C18 and HILIC columns, and tandem mass spectrometry with electrospray ionisation for detection. For all compounds, the quantification was realised by internal standardisation using stable labelled internal standards in pure solvent. The LOQ was determined as 0.01 mg/kg for fluoxapiprolin and its metabolites (BCS-CC26101, BCS-BP32808, BCSDE61185, BCS-DE72760 and BCS-DE72761) all calculated as BCS-CS55621.

Analytical method 01628 was described for the determination of residues of fluoxapiprolin in/on poultry (egg, skin with fat) and bovine (liver, milk). In this method, homogenised samples were extracted 3 times with acetonitrile/water. The solids were separated by centrifugation prior to LC-MS/MS determination. The LOQ was 0.01 mg/kg. A successful independent laboratory validation was conducted.

Residue definition

Overall, the metabolic pathway is consistent between the 3 crops of grapes, lettuce, and potatoes, with the primary component being parent. The only other components observed at >10% TRR in the primary crop metabolism studies were BCS-CS55621-pyrazole-alanine (BCS-DE61185) and BCS-CS55621-pyrazole acetic acid (BCS-CC26101). These were also the dominant components in matrices in the confined rotational study. Therefore, apart from parent, BCS-CS55621-pyrazole-alanine and BCS-CS55621-pyrazole acetic acid, there are no other obvious candidates for a residue definition encompassing all 3 primary crops or rotational crops.

A number of suitable analytical methods have been validated to determine residues of parent fluoxapiprolin and metabolites in plant and processed commodities.

Fluoxapiprolin and the metabolites BCS-DE61185 and BCS-CC26101 were considered toxicologically equivalent.

Based on the available information, parent fluoxapiprolin is considered to be the appropriate residue definition for commodities of plant origin for enforcement, while the sum of parent fluoxapiprolin, BCS-CC26101 and BCS-DE61185, expressed as fluoxapiprolin, is considered to be the appropriate residue definition for commodities of plant origin for dietary risk assessment.

A suitable analytical method is available to determine residues of parent fluoxapiprolin, but not its metabolites, in animal commodities.

Based on the available information, parent fluoxapiprolin, which was a significant component in goat and hen tissues, milk, and eggs is considered to be the appropriate residue definition for commodities of animal origin, for both enforcement and dietary risk assessment purposes.

Residues in food and animal feeds

Australian and European GLP residues trial data for grapes were submitted. The Australian residue trials addressed the proposed GAP. The European residue trials did not address the proposed Australian GAP, however, the processing components of those studies were considered relevant.

Grapes

In 8 trials conducted between 2017–19 in Australia, the highest residues observed in wine and table grapes at 63 to 96 DALA, after 2 applications of an SC formulation of fluoxapiprolin at a concentration of approximately 0.8 or 1 g a.i./100L and a 7 to 17 day RTI, and for 7 of the trials after conversion to expected residues at 1× the maximum proposed application concentration (1 g a.i./100L), were, in rank order:

<0.013 (2), 0.013, 0.03, 0.038, 0.05 and 0.075 (2) mg/kg (STMR= 0.034 mg/kg, n=8).

Based on this data, the OECD calculator estimated an MRL of 0.15 mg/kg with the proviso “High uncertainty of MRL estimate due to small dataset”.

A fluoxapiprolin MRL of 0.15 mg/kg for FB 0269 Grapes is considered appropriate to cover residues in grapes arising from the proposed use, in conjunction with the proposed harvest WHP of “Not required when used as directed”, with the critical comment of ‘DO NOT apply the last application later than pre-bunch closure’ and the grazing WHP of “DO NOT graze livestock in treated vineyards”.

Juice

4 processing trials conducted in Germany indicated that fluoxapiprolin residues do not concentrate in juice (all processing factors <1), so it is not necessary to establish a separate MRL.

Wine

4 processing trials conducted in Germany indicated that fluoxapiprolin residues do not concentrate in wine (all processing factors <1), so it is not necessary to establish a separate MRL.

It is noted that based on the scaled HR in grapes (0.075 mg/kg), and the highest processing factor in the German processing trials (0.063×), residues in wine are expected to be <0.01 mg/kg.

In one non-GLP trial conducted in Australia in 2020–21, no residues were observed in wine prepared from grapes harvested after 2 applications of fluoxapiprolin up to pre-bunch closure (EL-32), the last proposed application timing, and at either 1× or 2× the proposed concentration.

Dried grapes

The highest processing factor in 2 Italian trials was 3.54×. Based on the scaled HR in grapes in the Australian trials (0.075 mg/kg), the highest estimated residue value (HR-P) in raisins is 0.27 mg/kg. An MRL of 0.5 mg/kg is recommended for fluoxapiprolin on DF 0269 Dried grapes (=currants, raisins and sultanas).

Grape pomace

The highest wet grape pomace processing factor in 4 German trials was 7.6×. Based on the scaled HR in grapes (0.075 mg/kg), the highest estimated residue value (HR-P) in wet grape pomace is 0.57 mg/kg. The highest estimated residue value (HR-P) in dry grape pomace is therefore 3.8 mg/kg.

An MRL of 5 mg/kg is recommended for fluoxapiprolin in AB 0269 Grape pomace, dry.

Crop rotation

A field rotational study conducted in France, Spain, and Italy was submitted in addition to the previously discussed, confined rotational studies. This study was conducted to determine the magnitude of residues of parent fluoxapiprolin and its metabolites BCS-CC26101, BCS-BP32808, BCS-DE61185, BCS-DE72761 and BCS-DE72760 in or on rotated field crops (succeeding crops), and residues of parent and its metabolites BCS-CY96288, BCS-CU97237, BCSDA63612, BCS-CC26101 and BCS-CZ38260 in soil, following one spray application with BCSCS55621 SC 020, (20 g/L BCSCS55621) to bare soil followed by sowing or planting of the rotational crops (carrot, lettuce and barley).

No quantifiable residues of parent fluoxapiprolin or the metabolites BCS-CC26101, BCS-BP32808, BCS-DE72760 or BCS-DE72761 were found in any matrix of carrot (leaf, root), lettuce (head), or barley (green material, grain or straw) at 3 plant-back intervals designed to simulate crop failure, a second use of the same plot in a single season, or to simulate a re-use of the same plot in the following season. Residues of BCS-DE61185 (0.012 to 0.020 mg/kg) were only observed in lettuce head grown at the first plant-back interval (21 to 48 DAT) in 2 of the 3 trials.

The proposed use of fluoxapiprolin is grapes, which are not considered to be a rotational crop. It is therefore unnecessary to consider residues with respect to crop rotation for this application.

Residues in animal commodities

No mammalian or poultry transfer studies for fluoxapiprolin were submitted with the current application. Residues may be found in grape pomace, which may contribute up to 20% of the diet for beef cattle and 20% of the diet for dairy cattle, and 20% of the diet for turkeys.

Cattle

The estimated maximum dietary burden of fluoxapiprolin for beef and dairy cattle resulting from the proposed use on grapes (consumption of grape pomace) is calculated to be 0.15 ppm.

No feeding study was submitted showing residues of fluoxapiprolin in milk or tissues following administration to mammals. In the absence of a feeding study, the results of the submitted lactating goat metabolism studies (highest observed TRRs after feeding at 24 ppm), were considered to predict residues in milk and tissues.

The estimated maximum residues in milk and tissues after feeding at the calculated maximum dietary burden of 0.15 ppm (beef and dairy cattle), after extrapolation from the observed maximum residues after feeding dairy cattle for 5 days at 24 ppm, are as follows in Table 6.

Table 6: Maximum estimated dietary burden of fluoxapiprolin for beef and dairy cattle

Feeding level (ppm)	Milk	Muscle	Liver	Kidney	Fat
	TRR residue (mg/kg)				
24.23 (Pyrazole labelled lactating goat metabolism study)		0.008		0.076	0.015
23.86 (Phenyl labelled lactating goat metabolism study)	0.012		0.928		
0.15 – Beef and dairy cattle, estimated burden	0.00008	0.00005	0.006	0.0005	0.00009
Recommended MRLs	*0.01	–		*0.01 (offal)	*0.01 (meat [in the fat])

Quantifiable residues of fluoxapiprolin are not expected to occur in mammalian animal commodities as a result of the proposed use. It is appropriate to establish animal commodity MRLs at the LOQ of fluoxapiprolin in the analytical method. The following MRLs are recommended:

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

MM 0095 Meat (mammalian) [in the fat]: *0.01 mg/kg

ML 0106 Milks: *0.01 mg/kg.

Poultry

The estimated maximum dietary burden of fluoxapiprolin for turkeys resulting from the proposed use on grapes (consumption of grape pomace) was calculated to be 0.15 ppm.

No feeding study was submitted showing residues of fluoxapiprolin in eggs or tissues following administration to poultry. In the absence of a feeding study, the results of the submitted laying hen metabolism studies (highest observed TRRs after feeding at 18 ppm), were considered to predict residues in eggs and tissues.

The estimated maximum residues in eggs and tissues after feeding at the calculated maximum dietary burden of 0.15 ppm (turkeys only), after extrapolation from the observed maximum residues after feeding laying hens for 14 days at 18 ppm, are as follows in Table 7.

Table 7: Maximum estimated dietary burden of fluoxapiprolin for poultry

Feeding level (ppm)	Egg	Muscle	Fat	Liver
	TRR residue (mg/kg)			
18 (Pyrazole labelled laying hen metabolism study)	0.042	0.010	0.027	0.250
0.15 – Turkeys, estimated burden	0.0004	0.00008	0.0002	0.002
Recommended MRLs	*0.01		*0.01 (meat [in the fat])	*0.01 (offal)

Quantifiable residues of fluoxapiprolin are not expected to occur in poultry animal commodities as a result of the proposed use. It is appropriate to establish poultry commodity MRLs at the LOQs of fluoxapiprolin in the analytical method. The following MRLs are recommended:

PE 0112 Eggs: *0.01 mg/kg

PM 0110 Poultry meat [in the fat]: *0.01 mg/kg

PO 0111 Poultry, Edible offal of: *0.01 mg/kg

Bioaccumulation potential

The log K_{ow} value for fluoxapiprolin is 3.4 (mean) at 25°C and pH 4, pH 7 and pH 9, indicating moderate fat solubility and potential for bioaccumulation.

The lactating goat metabolism studies showed that fluoxapiprolin TRRs were higher in fat (0.011 and 0.015 mg eq./kg) than muscle (0.004 and 0.008 mg eq./kg), although both were lower than in offal (liver and kidney).

The hen metabolism studies showed slightly higher TRRs in fat (0.018 and 0.027 mg eq./kg) compared to muscle (0.005 and 0.010 mg eq./kg), and much lower than observed in liver.

MRLs for mammalian and poultry meat will be recommended as ‘in the fat’.

Spray drift

Animal commodity MRLs for fluoxapiprolin in overseas markets are not currently established. It is therefore considered that residues should be below the LOQ of 0.01 mg/kg in animal tissues in order to mitigate any risk to international trade of animal tissues.

No mammalian transfer studies have been submitted with the current application. In the phenyl-labelled lactating goat metabolism study, dosing with fluoxapiprolin at 24 ppm gave a highest TRR of 0.93 mg/kg in liver. For residues of fluoxapiprolin to be at the LOQ (0.01 mg/kg), the maximum feeding level or Regulatory Acceptable Level (RAL) is 0.26 ppm.

If this Regulatory Acceptable Level for fluoxapiprolin, and the proposed spray drift parameters are used in the APVMA Spray Drift Risk Assessment Tool (SDRAT), no buffer zones are required for livestock areas and the protection of international trade.

Dietary risk assessment

The chronic dietary exposure to fluoxapiprolin 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 Guidelines1, and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for fluoxapiprolin is equivalent to <1% of the ADI. It is concluded that the chronic dietary exposure of fluoxapiprolin 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 ARfD for fluoxapiprolin was considered unnecessary by the APVMA, therefore an acute exposure assessment is not required.

[1] WHO (2008). Consultations and workshops: Dietary Exposure Assessment of Chemicals in Food: Report of a joint FAO/WHO Consultation, Annapolis, Maryland, USA, 2–6 May 2005.

Recommendations

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

Table 8: Amendments to the APVMA MRL Standard

Amendments to Table 1			
Compound		**Food**	**MRL (mg/kg)**
Add:			
Fluoxapiprolin			
DF	0269	Dried grapes (=currants, raisins and sultanas)	0.5
MO	0105	Edible offal (mammalian)	*0.01
PE	0112	Eggs	*0.01
FB	0269	Grapes	0.15
MM	0095	Meat (mammalian) [in the fat]	*0.01
ML	0106	Milks	*0.01
PM	0110	Poultry meat [in the fat]	*0.01
PO	0111	Poultry, Edible offal, of	*0.01

Amendments to Table 3	
Compound	**Residue**
Add:	
Fluoxapiprolin	Commodities of plant origin for enforcement: Fluoxapiprolin Commodities of plant origin for dietary exposure assessment: Sum of fluoxapiprolin, [3,5-bis(difluoromethyl)-1H-pyrazol-1-yl]acetic acid (BCS-CC26101) and 3-[3,5-bis(difluoromethyl)-1H-pyrazol-1-yl]alanine (BCS-DE61185), expressed as fluoxapiprolin Commodities of animal origin: Fluoxapiprolin

Amendments to Table 4			
Compound		**Animal feed commodity**	**MRL (mg/kg)**
Add:			
Fluoxapiprolin			
AB	0269	Grape pomace, dry	5

Assessment of overseas trade aspects of residues in food

Commodities exported and main destinations

Grapes (including dried grapes) and wine are considered to be major export commodities[2], as are commodities of animal origin (such as meat, offal or dairy products) which may be derived from livestock fed feeds produced from treated grapes. Residues in these commodities resulting from the use of Xivana Prime 20 SC Fungicide may have the potential to unduly prejudice trade.

Australian exports of table and dried grapes totalled 120.7 kt ($460.7 million) in 2020–21. The major export markets for fresh table grapes in that period included China, Indonesia, Hong Kong, Japan, and the Philippines.[3]

Australian exports of wine totalled 744 ML ($2,900 million) in 2019–20. The major export markets for wine in the year ending June 2020 included China, United States, United Kingdom, Canada, Hong Kong, Singapore, New Zealand, Netherlands, Japan, and Denmark.[4]

Overseas registrations and approved label instructions

Xivana Prime 20 SC Fungicide is currently registered in Armenia, Cambodia and Belarus.

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. Fluoxapiprolin has not been considered by Codex.

The Applicant has indicated that as Xivana Prime 20 SC Fungicide contains a new active constituent and registration activities for the active and accompanying products are ongoing. MRLs in relevant overseas countries have therefore not been set.

Potential risk to trade

Export of treated produce containing finite (measurable) residues of fluoxapiprolin may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing

[2] Australian Pesticides and Veterinary Medicines Authority, *APVMA Regulatory Guidelines – Data Guidelines: Agricultural – Overseas trade (Part 5B)*, APVMA website, 20 July 2020.

[3] Hort Innovation, *Australian Horticulture Statistics Handbook 2020–21 – Fruit*, Hort Innovation website.

[4] Australian Bureau of Agricultural and Resource Economics and Sciences, *Agricultural commodities and trade data 2020*, DAWE website.

country, or, (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country.

Grapes and dried grapes

A finite MRL (0.15 mg/kg) is proposed for grapes. Finite residues (HR = 0.075, STMR = 0.034 mg/kg) of fluoxapiprolin may be expected in exported grapes. There is a potential risk to trade as no export markets for fresh grapes have established MRLs.

Given residues concentrated on processing to raisins, there will be a similar risk to trade in dried grapes, with a proposed MRL of 0.5 mg/kg, as no export markets have established MRLs.

Wine

Based on the scaled HR in grapes (0.075 mg/kg), and the highest processing factor in the German processing trials (0.063×), residues in wine are expected to be <0.01 mg/kg.

In one non-GLP trial conducted in Australia in 2020–21, no residues were observed in wine prepared from grapes harvested after 2 applications of fluoxapiprolin up to pre-bunch closure (EL-32), the last proposed application timing, and at either 1× or 2× the proposed concentration.

The risk to trade in wine is considered to be low, as quantifiable residues are not expected.

Animal commodities

MRLs for animal commodities are proposed at the LOQ (0.01 mg/kg), so the risk to trade in animal commodities is considered to be low.

The Applicant has proposed the following risk mitigation statement which is considered appropriate and acceptable:

EXPORT OF TREATED PRODUCE

Growers should note that suitable MRLs or import tolerances may not exist in all markets for produce treated with Xivana Prime 20 SC Fungicide. If you are growing produce for export, please check with Bayer Crop Science for the latest information on MRLs and import tolerances and for advice on any potential trade issues and their management.

Grapes for wine intended for export: For the latest information consult with Bayer Crop Science, your winery or the Australian Wine Research Institute (AWRI) before using Xivana Prime 20 SC Fungicide in grapes which may be used to make wine for export.

Work health and safety assessment

Xivana Prime 20 SC Fungicide is proposed for the control of downy mildew on grapevines, to which it will be applied via ground spray (airblast or handheld/backpack sprayer) at a dilution rate of 37.5 to 50 mL product/100 L water. At the maximum anticipated spray volume of 1,500 L spray mix/ha, the application rate would be 750 mL product or 15 g fluoxapiprolin/ha. The product is to be applied up to twice per season with an interval of 10 to 21 days between applications. Therefore, the pattern of occupational exposure is expected to be discontinuous, seasonal, and short-term in duration.

Health hazards

Xivana Prime 20 SC Fungicide has low acute toxicity via oral, dermal, and inhalational routes of exposure. It is not irritating to the skin of rabbits but is slightly irritating to the eyes and is a potential skin sensitiser based on the results of a mouse LLNA.

In dermal absorption investigations using human skin *in vitro*, dermal penetration was estimated at approximately 0.20% from undiluted SC 20 g/L formulation, rising to 1.29% from a 1/100 dilution and 3.08% from a ½,000 dilution.

Occupational exposure

Exposure during use

With an adequate short-term dermal toxicity study showing no adverse effects at the limit dose of 1,000 mg/kg bw/day, quantitative risk assessment may be unnecessary. The application rate and frequency of use also indicate that exposure to fluoxapiprolin through its use in grapes is likely to be very low. No worker exposure studies for Xivana Prime 20 SC Fungicide were submitted for assessment. To confirm the anticipated low risk estimates from using the product, and in the absence of studies, the US EPA Occupational Pesticide Handler Exposure Calculator (OPHEC) was used to estimate worker exposure during mixing, loading and application and the US EPA Occupational Pesticide Re-Entry Exposure Calculator (OPREC) was used to estimate exposure during re-entry.

OPHEC exposure and risk estimates for Xivana Prime 20 SC Fungicide were all several orders of magnitude higher than the desired MOE of 100, confirming that quantitative risk estimation is unnecessary in this circumstance.

Exposure during re-entry or rehandling

Results from the US EPA OPREC calculator indicate that the MOEs on day zero are all several orders of magnitude higher than the target MOE of 100, hence no re-entry restrictions are required to mitigate risks due to systemic exposure to fluoxapiprolin. However, as the product is a skin sensitiser, it is recommended that skin contact with wet foliage be avoided. A re-entry statement is recommended for the product label.

Public exposure

Xivana Prime 20 SC Fungicide is not intended for use by the general public or in areas accessible by the general public. Therefore, public exposure is not expected.

No specific measures are required to protect the public or bystanders from risks posed by the use of the product Xivana Prime 20 SC Fungicide. However, since the product is a skin sensitiser, the following statement is recommended for the restraint section of the product label:

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

Recommendations

The following first aid instructions, safety directions, re-entry statement and restraints are recommended for the product label.

First aid instructions

First aid is not generally required. If in doubt, contact a Poisons Information Centre (phone Australia 13 11 26) or a doctor.

Safety directions

May irritate the eyes. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. When opening the container and preparing the product for use, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length chemical resistant gloves. Wash hands after use. After each day's use, wash gloves and contaminated clothing.

Re-entry statement

There are not expected to be re-entry risks associated with dermal contact with crops treated with Xivana Prime 20 SC Fungicide after the spray has dried. However, as the product is a skin sensitiser, the following re-entry statement is recommended:

DO NOT enter treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

Restraints

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

Environmental assessment

Fate and behaviour in the environment

Soil

In soil photolysis testing, degradation from irradiated samples was similar to those from dark control samples and it is assumed photodegradation on soils will not be a significant removal mechanism for fluoxapiprolin in the environment.

The route and rate of degradation of fluoxapiprolin were studied in 6 aerobic laboratory soils (pH 5.6 to 7.5, OC% 0.7 to 4.7%), with 3 radiolabel positions (phenyl, pyrazole, thiazolyl). Fluoxapiprolin was moderately persistent with model DT_{50} values of 36 to 81 days (geomean 47 days, combined radiolabel results). Consistent over all studies and labels, fluoxapiprolin hydroxylated to form BCS-CY96288 (max 7.6% AR). Pyrazole label studies show that, presumably from both fluoxapiprolin and BCS-CY96288, cleavage of the amide bond leads to BCS-CC26101 (max 24% AR) with subsequent metabolism of the acetic acid moiety to form BCS-BP32808 (max 22% AR). Hydroxylation and oxidation of the difluoromethyl group results in BCS-CZ38260 (max 8.8% AR). The metabolites that form with the phenyl and thiazolyl label are, after amide cleavage, the piperidine moiety BCS-DC21250 (max 17% AR) and a further oxidated lactam BCS-DA63612 (max 14%). Only in Californian soil, further degradation of the piperidine ring leads to BCS-DG91934 (max 8.6%).

After 120 to 125 days, mineralisation of fluoxapiprolin was significant (11 to 33% AR), and bound residues accounted for up to 21 to 38% AR. The proposed degradation pathway of fluoxapiprolin in soil is shown in Figure 4.

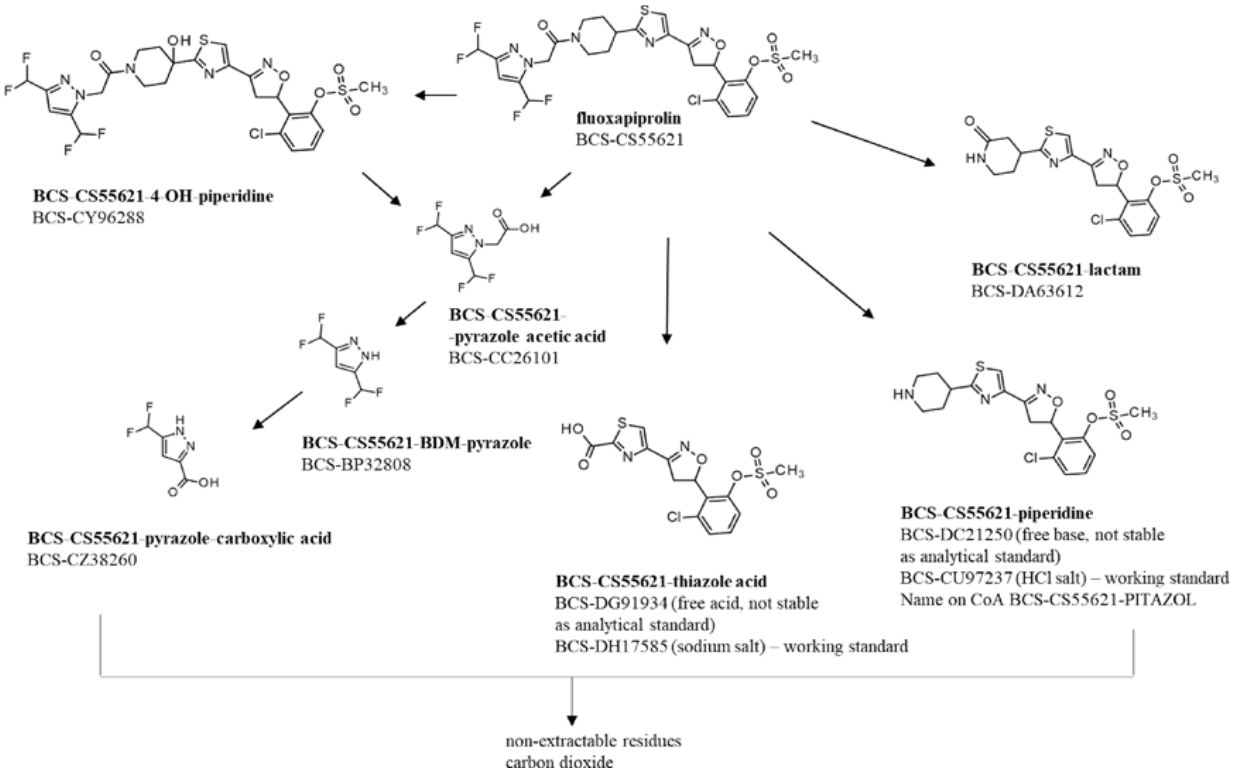
The anaerobic degradation of fluoxapiprolin was examined with 2 radiolabel positions in one soil type. Aerobic metabolism was allowed to take place for 14 days before anaerobic conditions were introduced. Near-maximum concentrations of metabolite BCS-CY96288 occur in soils around day zero after soil flooding and are continually maintained under anaerobic conditions over 120 days, as are levels of carbon dioxide (1.6% AR). The metabolite BCS-CC26101, formed under aerobic conditions disappears under the anaerobic conditions slowly (25% at day zero after flooding to 2% at day 90 after flooding), indicating that under the anaerobic conditions, its degradation speed is reduced when compared to aerobic conditions. The metabolite BCS-CZ38260 formed at levels similar to the aerobic soil study (9.3% at day 29 after flooding).

Field studies were provided for 6 European sites (3 in northern Europe, 3 in southern Europe). Degradation tended to follow biphasic kinetics but could be described by SFO kinetics at 2 sites. Degradation was faster in the southern sites with DT_{50} values ranging 30 to 123 days, compared to the northern sites with DT_{50} values ranging from 119 to 209 days. The geometric mean DT_{50} was 99 days. Leaching through the field soil profiles was not observed with residues essentially retained in the top 10 cm soil layer at all sites.

Standard batch equilibrium test results were available for 4 soils. In addition, sorption was measured as a Kd only (single test concentration) in 4 additional soils. From this study, representative Kf values were calculated from the Kd and applying 1/n 0.90. The soils tested had a range of 0.7 to 5.7% organic carbon. Sorption strength was not correlated with organic carbon levels of the soil. Kf values ranged 61 to 229 L/kg

(mean 143 L/kg, 1/n 0.90) indicating fluoxapiprolin will have limited mobility in soil. Several soil metabolites were tested in standard batch equilibrium studies in 4 test soils. BCS-CC26101 and BCS-BP32808 had very high mobility (KF <1 L/kg in all soils). BCS-DC21250 (KF 70 to 187 L/kg) and BCS-DA63612 (KF 26 to 60 L/kg) were slightly mobile.

Figure 4: Fluoxapiprolin – proposed degradation pathway in soil



Water

Fluoxapiprolin was stable to hydrolysis at environmentally relevant water temperatures. Under continuous irradiation, the DT_{50} from photolysis was 39 days. Nine to 14 degradation products formed in low amounts. No degradation products >10% AR were observed.

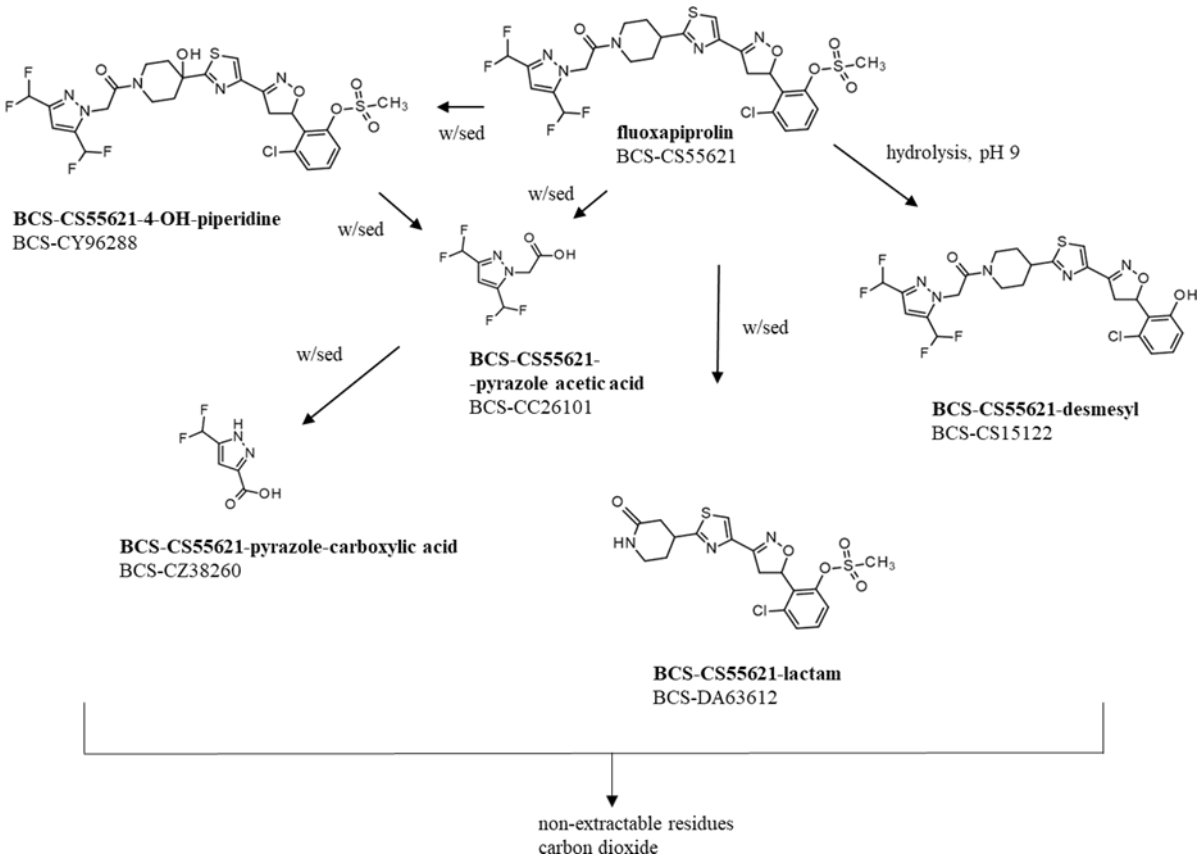
Mineralisation in surface water was considered in a suspended sediment test (one system, 2 concentrations of 8 and 40 µg/L). At the higher concentration, fluoxapiprolin was more persistent with a model DT_{50} of 41 days (FOMC DT_{90} 136 days) compared to 2.8 days (SFO) at the lower concentration. Half-lives were based on combined residues from the water layer and extracted from suspended sediment.

In 2 water/sediment systems, fluoxapiprolin hydroxylated to form BCS-CY96288 (max 1.3% in water, 9.2% in sediment). Pyrazole label studies show that both fluoxapiprolin and BCS-CY96288 undergo cleavage of the amide bond leading to BCS-CC26101 (max 32% in water, 14% in sediment), with subsequent metabolism to cleave off the acetic acid moiety, hydroxylation, and oxidation of the difluoromethyl group to result in BCS-CZ38260 (max 15% water, 3.6% in sediment). The metabolite that forms with the phenyl label is, after amide cleavage and further oxidation, the lactam BCS-DA63612 (max 1.9% in water, 16% in sediment). After

100 days, mineralisation was variable (0.4 to 38% AR) and bound residues accounted for 14 to 39% AR. The proposed degradation pathway from the water/sediment studies is shown in Figure 5.

Fluoxapiprolin is not ready biodegradable.

Figure 5: Fluoxapiprolin – proposed degradation pathway in aquatic systems



Air

Fluoxapiprolin is predicted to have an atmospheric DT_{50} of 0.14 days (reaction with hydroxyl radicals) based on 12 hours of sunlight per day. Fluoxapiprolin has a vapour pressure of 4.5 × 10-5 Pa at 25°C, indicating it is only very slightly volatile and not expected to partition to the atmosphere. The major soil metabolite, BCS-BP32808, has a vapour pressure of 1.2 Pa at 25°C and is considered volatile. However, it is not expected to persist in the atmosphere with a calculated atmospheric DT_{50} of 0.28 days.

Effects and associated risks to non-target species

Terrestrial vertebrates

Following gavage administration, fluoxapiprolin had low toxicity to mammals (LD50 >2,000 mg a.c./kg bw, *Rattus norvegicus*) and birds (LD50 >2,000 mg a.c./kg bw, 2 species tested). Fluoxapiprolin also had low toxicity to birds following short-term dietary exposure (LC50 >1067 mg a.c./kg bw/day, 2 species tested).

Following long-term dietary administration in reproduction studies, there were no effects observed at the highest dosage tested in mammals (NOEL 262 mg a.c./kg bw/d, *Rattus norvegicus*) or birds (lowest NOEL 80 mg a.c./kg bw/d, *Colinus virginianus*).

The major soil metabolite BCS-BP32808 is moderately toxic to mammals (LD50 175 mg/kg bw, *Rattus norvegicus*); however, this metabolite was not identified in plant or mammalian metabolism studies and is therefore not considered relevant to wild mammals. BCS-BP32808 was identified as a metabolite in birds; therefore, its risks are considered acceptable based on the outcomes of the risk assessment of the parent substance fluoxapiprolin.

Risks of fluoxapiprolin to terrestrial vertebrates were determined to be acceptable, assuming non-target species feed exclusively on oversprayed food items at the maximum seasonal rate within the treatment area. No protection measures are therefore required for terrestrial vertebrates.

Aquatic species

At its limit of solubility, fluoxapiprolin has low toxicity to fish (LC50 >1.0 mg a.c./L, 2 species tested), aquatic invertebrates (EC50 >0.84 mg a.c./L, 2 species tested), sediment-dwellers (EC50 >1.0 mg a.c./L, *Chironomus riparius*), algae (ErC50 >0.72 mg a.c./L, 4 species tested), and aquatic plants (ErC50 >1.0 mg a.c./L, *Lemna gibba*). Testing with the formulation did not indicate any increase in toxicity to aquatic species.

Following long-term exposure to fluoxapiprolin, no adverse effects were observed in fish (NOEC 0.91 mg a.c./L, *Pimephales promelas*) or sediment dwellers (NOEC 1.0 mg a.c./L, *Chironomus riparius*) up to its limit of solubility. However, adverse reproductive effects were observed in aquatic invertebrates at water concentrations as low as 0.10 mg a.c./L (NOEC 0.032 mg a.c./L, *Daphnia magna*), and reduced development rate was observed in sediment dwellers at sediment concentrations as low as 103 mg a.c./kg dry sediment (NOEC 57 mg a.c./kg dry sediment, *Chironomus riparius*).

Toxicity data for several metabolites are available for aquatic invertebrates (*Daphnia magna*) and algae (*Pseudokirchneriella subcapitata*). Where end-points could be defined, the EC50 results were always >1 mg/L.

Risks of fluoxapiprolin to aquatic species were determined to be acceptable assuming the worst-case scenario of a direct overspray of shallow aquatic habitat at the maximum seasonal rate. No protection measures are therefore required for aquatic species.

Bees

Fluoxapiprolin has low toxicity to adult bees by contact exposure (LD50 >200 µg a.c./bee, 2 species tested) and oral exposure (LD50 >218 µg a.c./bee, 2 species tested), and low toxicity to bee larvae (LD50 >100 µg a.c./bee, *Apis mellifera*). A representative fluoxapiprolin SC formulation did not influence contact toxicity; however, increased mortality was observed through oral exposure (LD50 42 µg/bee; *Apis mellifera*). Four plant metabolites, BCS-CC26101, BCS-DE61185, BCS-DE72760 and BCS-DE72761, were tested for acute contact and oral toxicity to bees (*Apis mellifera*) with LD50 values remaining above highest tested rates of 50 to 100 µg/bee.

Following long-term dietary exposure of adult bees, no adverse effects of technical fluoxapiprolin was observed (NOEDD 42 µg a.c./bee/day, *Apis mellifera*), while the representative fluoxapiprolin SC formulation caused up to 59% corrected mortality at 24 µg a.c./bee/day (NOEDD 14 µg a.c./bee/day, *Apis mellifera*). Similarly, no adverse effects of technical fluoxapiprolin was observed in bee larvae (NOED 74 µg a.c./bee/day, *Apis mellifera*), while the representative fluoxapiprolin SC formulation caused reduced emergence at doses as low as 40 µg a.c./bee/day (NOED 20 µg a.c./bee/day, *Apis mellifera*).

Risks of fluoxapiprolin were determined to be acceptable assuming the worst-case scenario of a direct overspray of blooming plants frequented by bees. No protection measures are therefore required for bees.

Other non-target arthropods

In Tier 1 (glass plate) toxicity tests at environmentally relevant rates, fresh-dried residues of a representative fluoxapiprolin SC formulation had low toxicity to indicator species of predatory mites (LR50 >60 g a.c./ha, ER50 >60 g a.c./ha, *Typhlodromus pyri*) and a parasitic wasp (LR50 >60 g a.c./ha, ER50 59 g a.c./ha, *Aphidius rhopalosiphi*).

Risks of fluoxapiprolin to beneficial arthropods were determined to be acceptable assuming the worst-case scenario of contact exposure to fresh-dried residues within the treatment area immediately after the last application at the maximum seasonal rate. Use of the product is therefore considered to be compatible with integrated pest management programs utilising beneficial arthropods and no protection statements are required.

Soil organisms

Fluoxapiprolin has low toxicity to soil macro-organisms such as earthworms (LC50corr >500 mg a.c./kg dry soil, *Eisenia fetida*). Following long-term exposure, there were no adverse effects on growth or reproductive endpoints on 3 species of soil macro-organisms at exaggerated soil concentrations (lowest NOECcorr 9.6 mg a.c./kg dry soil, *Eisenia fetida*). Similarly, no adverse effects were observed on soil processes, such as nitrogen and carbon mineralisation, at the highest tested soil concentrations (NOEC 0.27 mg a.c./kg dry soil). There was no enhanced toxicity from the representative fluoxapiprolin SC formulation.

The soil metabolite BCS-BP32808 adversely affected reproduction rate of 3 species of soil macro-organisms in a dose-dependent manner (lowest EC10 8.1 mg/kg dry soil, *Folsomia candida*). Soil processes were not affected at the highest test concentration (NOEC 0.093 mg/kg dry soil). The remaining major soil metabolites BCS-CC26101, BCS-DC21250 and BCS-DA63612, and minor soil metabolites BCS-DG91934, BCS-CY96288, and BCS-CZ38260 did not adversely affect soil organisms at the highest concentrations tested.

Risks of fluoxapiprolin to soil organisms were determined to be acceptable, assuming the worst-case scenario of a direct overspray of soil without interception at the maximum seasonal rate. Risks of all metabolites to soil organisms were predicted to be lower than the parent substance. No protection measures are therefore required for soil organisms.

Non-target terrestrial plants

In Tier 1 testing of 10 crop species at the limit rate of 150 g a.c./ha, onion was the most sensitive species following pre-emergent exposure with 13% reduction of shoot dry weight (ER25 >150 g a.c./ha, *Allium cepa*). No effects exceeding 10% was observed in the remaining 9 species following pre-emergent exposure (ER10 >150 g a.c./ha) or in all 10 species following post-emergent exposure (ER10 >150 g a.c./ha).

Risks of fluoxapiprolin to non-target terrestrial plants were determined to be acceptable, assuming the worst-case scenario of a direct exposure to the treatment at the maximum rate. No protection measures are therefore required for non-target terrestrial plants.

Recommendations

In considering the environmental safety of the proposed use of Xivana Prime 20 SC Fungicide, the APVMA had regard to the toxicity of the active constituent and its residues, including metabolites and degradation products, in relation to relevant organisms and ecosystems. Based on the outcome of the risk assessment, the proposed use of Xivana Prime 20 SC Fungicide is supported from an environmental safety perspective.

Efficacy and safety assessment

Proposed product use pattern

Xivana Prime 20 SC Fungicide is a member of the oxysterol binding protein homologue inhibition group of fungicides intended for the control of downy mildew (*Plasmopara viticola*) in grapevines.

The product is to be applied at 37.5 to 50 mL/100 L sprayed to the point of runoff by dilute spraying, or at up to 3× concentrate spraying. Applications may be made at 10 to 21-day intervals. No more than 2 applications of Xivana may be applied to grapevines per growing season, with the last application no later than pre-bunch closure.

Xivana Prime 20 SC Fungicide is intended for use in a spraying program with a range of fungicides as part of a fungicide resistance management program.

Efficacy and target crop/animal safety

Efficacy

The applicant presented results from 9 Australian replicated small-plot field trials conducted in grapevines from 2017–20. Additional data was provided on safety in grapevines from a further 6 trials. In the trials, sprays were applied at key stages, including over flowering and prior to infection. Disease pressure ranged in the trials from low to very high.

Xivana Prime 20 SC Fungicide (or a development fluoxapiprolin formulation) was tested at rates of 12.5 to 100 mL/100 L, with some trials including an adjuvant at the registered label rate, in programs of up to 4 sprays. The trials were conducted in New South Wales, South Australia, Victoria and Western Australia in locations representative of Australian wine growing regions. Efficacy was assessed on natural infections of *Plasmopara viticola*, which causes downy mildew in grapevines. All trials used a randomised complete block design with 3 to 5 replicates. Disease incidence was assessed by the presence of disease on randomly selected canes, leaves, and grape bunches, and severity was rated as a percentage of leaf or bunch area affected. The product was applied as a preventative treatment in spray volumes ranging from 298 to 1,500 L/ha at intervals of 8 to 24 days ranging from early to late stages of crop development.

Xivana Prime 20 SC Fungicide provided significant control of *Plasmopara viticola* on canes, leaves, and bunches when applied at 37.5 to 50 mL/100 L in 8 out of 9 crop trials. Xivana Prime 20 SC Fungicide was as effective as, or more effective than, a range of industry standard fungicides.

Crop safety

Detailed assessments of phytotoxicity were made in the 9 efficacy trials, and a further 6 crop safety trials in grapevines. Assessments included damage to foliage and fruit. A total of fifteen trials demonstrated Xivana Prime 20 SC Fungicide was safe in a total of 9 varieties of wine and table grapes, at rates up to 100 mL/100 L (2× label rate) and at up to 3× concentration volume.

Organoleptic properties

The applicant presented results from 6 trials, including 4 from Europe, investigating the effects on finished wine made from grapes treated with Xivana Prime 20 SC Fungicide. The results confirmed that treatment of grapevines with the product did not have an adverse effect on wine processing parameters. No significant difference in the taste of finished wine was detected when a panel of judges tasted wine made from grapes treated with Xivana Prime 20 SC Fungicide and compared to wine of the same variety produced from untreated grapes.

Resistance management

Fluoxapiprolin is a new piperidinyl thiazole isoxazoline active constituent belonging to the oxysterol binding protein inhibitor mode of action (OSBP). The fungicide resistance action committee (FRAC) has assigned fluoxapiprolin to FRAC group 49. The primary mode of action of OSBPs is the inhibition of an oxysterol binding protein homologue. Oxysterol binding proteins are implicated in the movement of lipids between membranes, among other processes. Inhibiting OSBP may disrupt other processes in the fungal cell, such as signalling, maintaining cell membranes, and the formation of more complex lipids that are essential for the cell to survive. Fluoxapiprolin is a contact fungicide.

The following resistance management statement is proposed for the product label:

It is recommended that Xivana be applied with a registered downy mildew protectant fungicide from a different mode of action group applied at registered rates for resistance management purposes. This use is subject to a CropLife Australia Resistance Management Strategy. Refer to croplife.org.au for more information.

Recommendations

Trial data support that Xivana Prime 20 SC Fungicide will provide acceptable control against downy mildew in grapevines when used as part of a preventative treatment program with other registered fungicides from different mode of action groups. Acceptable crop safety is expected when the product is used as directed. The directions for use are appropriate and consistent with fungicide use in commercial agriculture in Australia.

There are no objections on efficacy or target crop safety grounds to the registration of the product Xivana Prime 20 SC Fungicide, containing 20 g/L fluoxapiprolin.

Labelling requirements

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Xivana® Prime 20 SC

FUNGICIDE

ACTIVE CONSTITUENT: 20 g/L FLUOXAPIPROLIN

GROUP	49	FUNGICIDE

For the control of downy mildew in grapes as specified in the DIRECTIONS FOR USE table

1-110 L

RESTRAINTS

DO NOT apply by aircraft.

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

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

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

DO NOT apply unless the wind speed is between 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.

DO NOT apply by a boom sprayer.

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

- 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 oneach side of the application site.

DIRECTIONS FOR USE TABLE

CROP	DISEASE	RATE	CRITICAL COMMENTS
Grapevines	Downy mildew (*Plasmopara viticola)*	**Dilute spraying** 37.5-50 mL/100 L water plus adjuvant **Concentrate spraying** Refer to the Application section in GENERAL INSTRUCTIONS	Apply as part of a preventative spray program. Start applications from 10 cm shoots onwards. Repeat the application 10-21 days later. DO NOT apply the last application of Xivana later than pre-bunch closure. Use the shorter interval and higher use rateduring periods of rapid growth and/or when conditions are conducive to disease development. **Apply a maximum of 2 applications of XivanaPrime per season.** Apply thoroughly to ensure complete coverage of allleaves and fruit. Apply by dilute or concentrate spraying equipment. Use a sufficient amount of water and/or adequate equipment to ensure penetration of the canopy and coverage of the leaves, flowers and bunches. Apply the same total amount of product to the target crop whether applying this product by dilute or concentrate spraying methods. For concentrate spraying, do notuse at rates greater than three times the dilute spraying rate (i.e. at a concentration factor greater than 3×) – refer “Application” section in GENERAL INSTRUCTIONS. For an appropriate adjuvant refer to GENERALINSTRUCTIONS. **Resistance management** It is recommended that Xivana be applied with a registered downy mildew protectant fungicide from adifferent mode of action group applied at registered rates for resistance management purposes. This use is subject to a CropLife Australia 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 PERIODS

Harvest
Grapes: NOT REQUIRED WHEN USED AS DIRECTED

Grazing
Grapes: DO NOT GRAZE LIVESTOCK IN TREATED VINEYARDS

EXPORT OF TREATED PRODUCE

Growers should note that suitable MRLs or import tolerances may not exist in all markets for produce treated with Xivana Prime 20 SC Fungicide. If you are growing produce for export, please check with Bayer Crop Science for the latest information on MRLs and import tolerances and for advice on any potential trade issues and their management.

Grapes for wine intended for export: For the latest information consult with Bayer Crop Science, your winery or the Australian Wine Research Institute (AWRI) before using Xivana Prime in grapes which may be used to make wine for export.

GENERAL INSTRUCTIONS

Mixing

Shake well before use. Half fill the spray tank with water. Pour in the required quantity of Xivana Prime 20 SC Fungicide with agitators running, then top up with water. Use spray mixture immediately after preparation, do not allow it to stand.

Application

Application should be by vertical sprayer or back pack sprayer equipment only. Thorough coverage of the target area is essential. Apply in sufficient water and use suitable application equipment to ensure thorough and even coverage of leaves and fruit. Adjust water volumes according to the crop growth stage.

Dilute spraying

- Use a sprayer designed to apply high spray volumes, 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 spray volume to cover the crop to the point of run-off. Avoid excessive run-off.
- The required spray volume to achieve point of run-off may be determined by applying different test volumes,using different settings on the sprayer, or from industry guidelines or other 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 to achieve point of run-off 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 500 L/ha
3. The concentration factor in this example is 3× (i.e. 1500 L÷500 L=3)
4. If the dilute label rate is 37.5 mL/100 L, then the concentrate rate becomes 3×37.5 that is 112.5 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 mayneed to be changed as the crop grows.

- Do not use at a concentration factor greater than 3× (e.g. at a rate higher than 150 mL/100 L where a dilutespraying rate of 50 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 Practices.

Adjuvant

Apply Xivana Prime with a spray adjuvant such as Maxx, Pulse Penetrant or Hasten. Apply the adjuvant at the recommended label rate. For alternative adjuvants, please contact Bayer Crop Science for more information.

Sprayer clean up

If clean up of spray equipment is required, rinse equipment twice with clean water after use.

Compatibility

For information on the compatibility of Xivana Prime with other products, contact your local Bayer Crop Science representative.

FUNGICIDE RESISTANCE WARNING

GROUP	49	FUNGICIDE

Xivana Prime 20 SC Fungicide is a member of the piperidinyl thiazole isooxazoline group of fungicides. For fungicide resistance management the product is a Group 49 fungicide. Some naturally occurring individual fungi resistant to the product and other Group 49 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungal population if these fungicides are used repeatedly. These resistant fungi will not be controlled by this product or other Group 49 fungicides, thus resulting in a reduction in efficacy and possible yield loss. Since the occurrence of resistant fungi is difficult to detect prior to use, Bayer Crop Science Pty Ltd accepts no liability for any losses that may result from failure of this product to control resistant fungi.

Xivana Prime may be subject to specific resistance management strategies. For further information contact your local supplier, Bayer Crop Science representative, local agricultural department agronomist or refer to the CropLife Australia website.

PRECAUTIONS

Re-entry period

DO NOT enter treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

DO NOT contaminate streams, rivers or watercourses with the chemical or used containers.

STORAGE AND DISPOSAL

Keep out of reach of children. Store in the closed, original container in a cool, well-ventilated area. Do not store for prolonged periods in direct sunlight.

(non-returnable containers only)

Triple rinse containers 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 designation collection point. If not recycling, break, crush or puncture and deliver empty packaging to an approved waste management facility. If an approved waste management facility is not available, bury the empty packaging 500 mm below the surface in a disposal pit specially 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.

(returnable containers only)

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

May irritate the eyes. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. When opening the container and preparing the product for use, wear cotton overalls buttoned to the neck and wrists (or equivalent clothing) and elbow-length chemical resistant gloves. Wash hands after use. After each day's use, wash gloves and contaminated clothing.

FIRST AID

First aid is not generally required. If in doubt, contact a Poisons Information Centre (phone Australia 13 11 26) or a doctor.

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 orresponsibility for loss or damage arising from failure to follow such directions and instructions.

Xivana® is a Registered Trademark of the Bayer

Group.

APVMA Approval No.: 89997/126975

FOR 24 HOUR SPECIALIST ADVICE IN EMERGENCY ONLY

PHONE 1800 033 111

Acronyms and abbreviations

Shortened term	Full term
a.c.	Active constituent
ADI	Acceptable daily intake (for humans)
a.i.	Active ingredient
AR	Applied radioactivity
ARfD	Acute reference dose
AUC	Area under the curve
BALB/c 3T3	A cell line developed from disaggregated BALB/C mouse embryos
bw	Bodyweight
Cmax	Maximum concentration of a chemical in a compartment/organ of the body
DAT	Days after treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
EbC50	Concentration at which the biomass of 50% of the test population is impacted
EC50	Concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
ErC50	Concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
ESI	Export Slaughter Interval
EUP	End Use Product
F0	Original parent generation
FOMC	First order multi-compartment
FRAC	Fungicide Resistance Action Committee
g	Gram
GAP	Good Agricultural Practice

Shortened term	Full term
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	Hour
ha	Hectare
Hct	Heamatocrit
Hb	Haemoglobin
HILIC	High interaction liquid chromatography
HPLC	High pressure liquid chromatography or high-performance liquid chromatography
HR-P	Highest estimated residue
id	Intradermal
im	Intramuscular
ip	Intraperitoneal
IPM	Integrated pest management
iv	Intravenous
in vitro	Outside the living body and in an artificial environment
in vivo	Inside the living body of a plant or animal
kg	Kilogram
Kd/Kf	Soil adsorption coefficient
K_{OC}	Organic carbon partitioning coefficient
L	Litre
LC50	Concentration that kills 50% of the test population of organisms
LC-MS	Liquid chromatography-mass spectrometry
LD50	Dosage of chemical that kills 50% of the test population of organisms
LLNA	Local lymph node assay
LOD	Limit of Detection – level at which residues can be detected
Log K_{OW}	Log to base 10 of octanol water partitioning co-efficient, synonym P_{OW}

Shortened term	Full term
LOQ	Limit of quantitation – level at which residues can be quantified
mg	Milligram
mL	Millilitre
MRL	Maximum Residue Limit
MSDS	Material safety data sheet
NEDI	National estimated daily intake
NESTI	National estimated short-term intake
ng	Nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No observable effect concentration level
NOAEL	No observed adverse effect level
NOEDD	No observed effect dietary dose
OC	Organic carbon
OM	Organic matter
ORP1	Oxysterol-binding protein-related protein 1
OSBP	Oxysterol binding protein
PH	Phenyl
PY	Pyridine
po	Oral
ppb	Parts per billion
PPE	Personal protective equipment
ppm	Parts per million
Q-value	Quotient-value
RBC	Red blood cell count
REI	Re-entry interval
s	Second
sc	Subcutaneous

Shortened term	Full term
SC	Suspension concentrate
SFO	Simple first order
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
t½	Half-life
TGAC	Technical grade active constituent
TRR	Total radioactive residue
µg	Microgram
vmd	Volume median diameter
WG	Water dispersible granule
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
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
Hydrophobic	Repels water
Leaching	Removal of a compound by use of a solvent
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

References

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