Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active mandestrobin

in the product Intuity Fungicide

APVMA Product Number 69787

JULY 2016

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This publication is available from the APVMA website: www.apvma.gov.au.

CONTENTS

LIST OF TABLES

PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Ageing, Office of Chemical Safety (OCS), Department of the Environment, and State Departments of Primary Industries.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of Public Release Summaries for products containing new active constituents.

The information and technical data required by the APVMA to assess the safety of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined in the APVMA's website at: www.apvma.gov.au.

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 its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment.

About this document

This is a public release summary.

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

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

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

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for approval of mandestrobin and registration of Intuity 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 Tuesday 9 August 2016 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 active constituent should be approved and/or 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 group name (if relevant)
- email or postal address (if available)
- the date you made the submission.

All personal information, and confidential information judged by the APVMA to be *confidential commercial information (CCI)*[1] contained in submissions will be treated confidentially.

Written submissions on the APVMA's proposal to grant the application for registration that relate to the grounds for registration should be addressed in writing to:

Case Management and Administration Unit
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

Phone: +61 2 6210 4701
Fax: +61 2 6210 4721
Email: enquiries@apvma.gov.au

Further information

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

Further information on public release summaries can be found on the APVMA website: www.apvma.gov.au

[1] A full definition of 'confidential commercial information' is contained in the Agvet Code.

1 INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Intuity Fungicide, and approval of the new active constituent, mandestrobin.

1.1 Applicant

Sumitomo Chemical Australia Pty Limited.

1.2 Details of the product

The APVMA is considering the proposal to register Intuity Fungicide, containing 250 g/L mandestrobin, as a suspension concentrate formulation. It is intended for control of blossom blight and brown rot in stone fruit. Intuity will be applied at a rate of 120 mL/100 L. A maximum of two applications are allowed on stone fruit per season.

The active constituent mandestrobin is a racemic mixture of two stereoisomers. It has been demonstrated that only the R-isomer has significant fungicidal activity.

1.3 Resistance management

Mandestrobin, a new active to the Australian market, is a strobilurin fungicide, belonging to the sub-class methoxy-acetamide. Mandestrobin is a Quinone outside Inhibitor (QoI) of fungal pathogens. The Fungicide Resistance Action Committee (FRAC), a specialist technical group of CropLife International, has designated mandestrobin as a Group 11 fungicide.

The maximum number of applications that may be applied per season is two, with a minimum interval of 14 days between applications.

1.4 Overseas registrations

Health Canada's Pest Management Regulatory Agency (PMRA) has granted full registration for mandestrobin and four associated end-use products for the management of various fungal diseases in canola and other oilseed crops, corn, grape, legume vegetables, strawberry and other low growing berries, as well as turfgrass.

The European Commission has authorised the use of mandestrobin in the European Union for the management of sclerotinia rot in winter oilseed (canola).

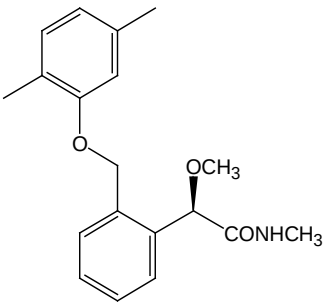
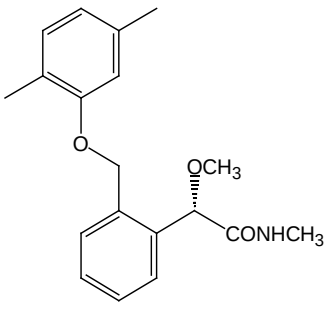
2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

Chemical characteristics of active constituent

COMMON NAME (ISO):	Mandestrobin
IUPAC NAME:	(*RS*)-2-methoxy-*N*-methyl-2-[α-(2,5-xylyloxy)-*o*-tolyl] acetamide 2-[2-(2,5-Dimethylphenoxymethyl)phenyl]-2-methoxy-N-methylacetamide
CAS NAME:	2-[(2,5-dimethylphenoxy)methyl]-α-methoxy-*N*-methylbenzeneacetamide
MANUFACTURER'S CODE/S	S-2200
CAS REGISTRY NUMBER:	173662-97-0
MINIMUM PURITY:	940 g/kg
MOLECULAR FORMULA:	$C_{19}H_{23}NO_3$
MOLECULAR WEIGHT:	313.39

Chemical characteristics of active constituent, continued

STRUCTURE:	 S-2167 S-2200 *R* isomer  S-2354 S-2200 *S*-isomer
CHEMICAL FAMILY:	Strobilurin—methoxy-acetamide

Physico-chemical properties of active constituent

PHYSICAL FORM:	Crystalline powdery solid		
COLOUR:	White		
ODOUR:	Odourless		
MELTING POINT:	102^{0}C (mean of three determinations)		
BOILING POINT:	296^{0}C (mean of three determinations)		
RELATIVE DENSITY:	1.205 (range 1.2009 to 1.2026) at 20^{0}C		
SOLUBILITY :	15.8 mg/L at 20^{0}C		
SOLVENT SOLUBILITY AT 20^{0}C	Acetone	310 g/L	
	Dichloromethane	480 g/L	
	Ethyl acetate	186 g/L	
	Hexane	2.49 g/L	
	Methanol	217 g/L	
	n-Octanol	30.8 g/L	
	Toluene	128 g/L	
VAPOUR PRESSURE AT 20^{0}C:	3.36 x 10^{-8} Pa		
HYDROLYSIS RATE:	Both the *R*-isomer and *S*-isomer were stable to hydrolysis at pH 4, 7 and 9. No degradation products were detected and no interconversion between the *R* and *S* isomers was observed. DT_{50} at pH 4, 7 and 9 at 25^{0}C: >1 year, as <10% of each isomer degrades for 5 days at 50^{0}C.		
UV:	Solution	λ_{max} (nm)	ε (L/cm·mol)
	Acidic	273	1920
	Neutral	273	1740
	Basic	273	1880
DISSOCIATION CONSTANT (PK_A):	No spectral shift was observed TGAC peak maxima at 273 nm. Solutions ranged from pH 2 to pH 10. It can be concluded the active has no dissociative activity in this pH range.		

Physico-chemical properties of active constituent, continued

<table>
<tr><td>STABILITY:</td><td>Does not decompose or sublime. Expected to remain in compliance with its specifications under normal conditions and is unlikely to be adversely affected by the presence of metals or metal ions from the packaging material.</td></tr>
<tr><td>OCTANOL/WATER PARTITION COEFFICIENT (KOW):</td><td>Log POW at 25^{0}C = 3.51 (POW = 3240)
(effect of pH on partition coefficient was not determined as S-2200 S-isomer and S-2200 R-isomer do not dissociate under acidic or basic conditions)</td></tr>
<tr><td>VOLATILITY (HENRY'S LAW CONSTANT):</td><td>6.66 x 10-7 Pa.m3/mol at 20^{0}C</td></tr>
<tr><td>DIRECT PHOTO-TRANSFORMATION:</td><td>Photodegradation of R-isomer in sterile pH 7 buffer at 25^{0}C
<table>
<tr><td>Label</td><td>DT50 (days)</td><td>DT75 (days)</td><td>DT90 (days)</td></tr>
<tr><td>Benzyl</td><td>5.3 or 4.6</td><td>10.5 or 9.2</td><td>17.5 or 15.3</td></tr>
<tr><td>Phenoxy</td><td>3.6</td><td>7.2</td><td>12.0</td></tr>
</table>
S-2200-OR and S-2200-ORC were identified as the major degradation products at maximum levels of 23% and 14% of applied radioactivity, respectively.
Two other degradation products, S-2200-PR and De-Xy-2200, were present in the approximate range of 5 to 10%. A large number of minor unknowns were present at <10% of applied radioactivity.
The DT50's for two of the degradation products were calculated to be:
<table>
<tr><td>Analyte</td><td>DT50 (days)</td></tr>
<tr><td>S-2200-OR</td><td>5.1 or 4.0</td></tr>
<tr><td>S-2200-PR</td><td>2.5 or 2.2</td></tr>
</table></td></tr>
<tr><td>QUANTUM YIELD:</td><td>R-isomer quantum yield in pH 7 buffer: 0.283
S-isomer quantum yield in pH 7 buffer: 0.269</td></tr>
<tr><td>PHOTO-CHEMICAL OXIDATIVE DEGRADATION:</td><td>The decomposition rate constant in air following reaction with hydroxyl radicals was calculated to be 96.3802 x 10-12 cm3 molecule-1 s-1. Assuming that the 12 hour daytime hydroxyl radical concentration is 1.5 x 106 molecules.cm-3, the half-life was calculated to be 0.111 days (12 hour day) or 1.332 hours.
No ozone reaction could be estimated.</td></tr>
</table>

Physico-chemical properties of active constituent, continued

FLAMMABILITY:	Not flammable
AUTO-FLAMMABILITY:	No auto-ignition temperature was observed up to 400^{0}C
OXIDISING PROPERTIES:	Not oxidising. Maximum burn rate was 0.44 mm/s for a 50% mixture with cellulose. Burn rate of 60% mixture of barium nitrate reference material with cellulose was 0.55 mm/s.
EXPLOSIVE PROPERTIES:	Not explosive
THERMAL STABILITY:	A sharp endothermic event was observed for S-2200 TGAC at 100.5^{0}C using DSC analysis. The endothermic event corresponds to the melting point of the test substance and is not due to thermal instability Therefore, the test substance was determined to be thermally stable within the temperature range of 20 to 500^{0}C.
STABILITY:	The test substance was found to be stable when stored at ambient temperature in commercial packaging for one year. The appearance of polyethylene bag (packaging material) did not change during the storage period. Did not decompose under storage at ambient temperature or at 54^{0}C for 14 days.
AQUEOUS PHOTOLYSIS (QUANTUM YIELD)	The photolytic half-life values of S-2200 at north latitudes 100 to 800 in the four seasons have been determined from the calculation results (S-2167 and S-2354 i.e. R-isomer and S-isomer respectively) using the GCSOLAR programme. The conclusion was that the half-life values of S-2200 at north latitudes 300, 400 and 500 in summer were calculated to be 1.20–3.03 days.

APVMA active constituent standard

On the basis of the data provided, and the toxicological assessment, it is proposed that the following APVMA Active Constituent Standard be established for mandestrobin active constituent:

CONSTITUENT	SPECIFICATION	LEVEL
Mandestrobin	Mandestrobin	940 g/kg minimum

Based on a review of the data provided by the applicant, the APVMA proposes to be satisfied that the chemistry and manufacturing details of mandestrobin are acceptable.

2.2 Product

The product Intuity Fungicide will be available in HDPE packaging in the following sizes: 1 L, 5 L, 10 L and 20 L.

Intuity fungicide

DISTINGUISHING NAME:	Intuity fungicide
FORMULATION TYPE:	Suspension concentrate (SC)
ACTIVE CONSTITUENT CONCENTRATION:	250 g/L mandestrobin

Physical and chemical properties of the product

ACTIVE CONTENT	250.9 ± 2.1 g/L of mandestrobin
PHYSICAL FORM:	Opaque white liquid with traces of oil on the top but without sediment on the bottom (no claying). Homogeneous after gentle shaking.
ODOUR:	Glue-like chemical odour
PH VALUE:	6.70 (undiluted)
RELATIVE DENSITY (D_4^{20}):	1.0534
SURFACE TENSION:	41.4 mN/m at 25^0C
VISCOSITY:	Exhibiting a non-Newtonian (shear thinning) fluid behaviour: 341 mPa.s to 35 mPa.s at 20^0C at the shear rate of 10.58 s-1 and 665 s-1, respectively.
PERSISTENT FOAM	4 mL after 1 min
SUSPENSIBILITY	98.9% after 30 min at 30°C
SPONTANEITY OF DISPERSION	98.2% after 5 min at 30°C
WET SIEVE TEST	0.03% retained on a 75µm sieve
PARTICLE SIZE DISTRIBUTION	0.167 µm at Dv,10 2.314 µm at Dv,50 7.782 µm at Dv,90

Physical and chemical properties of the product, continued

POURABILITY	2.7% for pour residue 0.2% for rinsed residue
FLASH POINT:	Not flammable
OXIDISING PROPERTIES:	No oxidising properties
EXPLOSIVE PROPERTIES:	No explosive properties
AUTO-IGNITION TEMPERATURE:	Not applicable
PACK SIZES:	1 L, 5 L, 10 L and 20 L
PACKAGING MATERIAL:	HDPE containers with plastic lids
PRODUCT STABILITY:	Product is expected to remain stable over the proposed 2–year shelf life

Conclusions

The APVMA has evaluated the chemistry aspects of mandestrobin active constituent and product Intuity Fungicide including the manufacturing process, quality control procedures, batch analysis results and analytical methods and found them to be acceptable.

Based on assessment of data provided by the applicant, the APVMA is satisfied that the chemistry and manufacture aspects of mandestrobin are acceptable.

Based on a review of the chemistry and manufacturing details provided by the applicant, registration of Intuity Fungicide is supported.

3 TOXICOLOGICAL ASSESSMENT

Sumitomo Chemical Australia Pty Limited has applied for registration of a suspension concentrate end-use product, Intuity Fungicide. The product contains the new active constituent mandestrobin at 250 g/L. The product is for the control of blossom blight and brown rot in stone fruit.

3.1 Evaluation of toxicology

The toxicological database for mandestrobin, which consists primarily of toxicity studies conducted in rats, mice, rabbits and dogs, is considered sufficient to determine the toxicology profile of mandestrobin and characterise the risk to humans. In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate such effects might occur in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur.

Chemical class

Mandestrobin is a novel strobilurin fungicide.

Toxicokinetics and metabolism

Mandestrobin was rapidly absorbed (>90% dose) and then distributed to organs, with the highest concentrations in the liver, kidney, uterus and ovaries. There was no evidence of accumulation in tissues. Mandestrobin was extensively metabolised to numerous metabolites with unchanged parent at <0.2% of the administered low dose. The primary routes of metabolism were oxidation and subsequent conjugation with glucuronic acid, demethylation with subsequent oxidation or oxidation with subsequent demethylation. Mandestrobin was rapidly excreted; with more than 70% eliminated within 48 hours of administration. Excretion was mainly in the faeces (65% following single dose) via the bile with some urinary excretion (16– 21% following single dose).

Percutaneous absorption

There were no data available for dermal absorption.

Acute toxicity

Mandestrobin has low acute oral (LD_{50} of > 2000 mg/kg bw/d), low acute dermal (LD_{50} of > 2000 mg/kg bw/d) and low acute inhalation (LC_{50} of > 4964 mg/m^3) toxicity. In rabbits, it was a moderate eye irritant but was not

irritating to skin. Mandestrobin is not a sensitising compound in guinea pig skin under the Guinea Pig Maximisation Test (GPMT) method.

Intuity Fungicide has low acute toxicity by the oral (LD_{50} > 2000 mg/kg bw), dermal (LD_{50} > 2000 mg/kg bw), and inhalational routes (4-hr LC_{50} > 4370 mg/m^3). It is not a skin or eye irritant in rabbits, and was not a skin sensitiser in guinea pig (Buehler method).

Systemic toxicity

The systemic toxicity of mandestrobin in dietary studies consisted primarily of decreased bodyweight and bodyweight gain, liver toxicity such as increased liver weight and centrilobular hepatocellular hypertrophy with associated clinical chemistry seen at higher doses. This systemic toxicity profile was observed in subchronic and chronic studies in rats (54/61.1 mg/kg bw/d, Male/Female (M/F)), mice (807.3/1111.2 mg/kg bw/d, M/F) and dogs (90.9/102.7 mg/kg bw/d, M/F), with the available data indicating that the rat was the most sensitive species. No short term oral studies were submitted for mandestrobin. No treatment-related adverse effects were seen in a short-term dermal toxicity study in the rat at the limit dose.

Genotoxicity and carcinogenicity

Mandestrobin was not genotoxic in several *in vitro* and *in vivo* studies. No evidence of carcinogenicity was observed in mice treated with diets containing concentrations up to 7000 mg/kg or rats up to 15000 mg/kg.

Reproductive and developmental toxicity

Mandestrobin was not a reproductive toxicant in rabbits or developmental toxicant in rats or rabbits. In the reproductive toxicity study in the rats, systemic toxicity signs including increased relative liver weights, moderate diffuse hepatocyte hypertrophy and increased thyroid weights in F_0 males (3000 mg/kg). Significantly decreased relative and absolute spleen weight in males F_1 pups at weaning were observed at $\geq$ 3000 mg/kg. The LOEL for maternotoxicity was determined to be 1000 mg/kg due to decreased food intake in both rats and rabbits.

Immunotoxicity and neurotoxicity

There was no evidence of immunotoxicity in rats following 28 days of dietary exposure. Some evidence of acute neurotoxicity was noted at the highest dose tested, although repeat dose neurotoxicity studies did not report any neurotoxic effects. It is considered unlikely that mandestrobin has neurotoxic potential.

Toxicity of metabolites

None of the metabolites of S-2200; 2-COOH-S-2200, 5-COOH-S-2200, 2-CH_2OH-S-2200, 4-OH-S-2200 and De-Xy-S-2200 were mutagenic. All the metabolites except 5-COOH-S-2200 were of low acute oral toxicity (LD_{50} > 2000 mg/kg bw/d). 5-COOH-S-2200 was of moderate acute oral toxicity (300 < LD_{50} < 2000 mg/kg bw/d).

3.2 Public health standards

Poisons scheduling

On 17 March 2016, the delegate of the Secretary of the Department of Health made a delegate only decision, listing mandestrobin in Schedule 5 of the Poison Standard with an exemption cut-off for preparations containing 25 per cent or less of mandestrobin. The implementation date for this decision is 1 June 2016. The product at 250 g/L is therefore unscheduled and no signal headings are required.

ADI

The ADI for humans is the level of intake of a chemical that can be ingested daily over an entire lifetime without appreciable risk to health. It is calculated by dividing the overall NOEL for the most sensitive toxicological endpoint from a suitable study (typically an animal study) by an appropriate safety factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans, intraspecies variation, and the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

The toxicological database for mandestrobin included long-term oral and carcinogenicity studies in the mouse and rat, as well as a 52–week study in beagle dogs, and was considered complete. The critical health effect for mandestrobin was hepatocyte hypertrophy, correlating with increases in relative liver weights and macroscopic findings of large liver in male rats in the 104 week chronic oral toxicity/carcinogenicity study.

The most appropriate NOEL for establishing an ADI is 19.2 mg/kg bw/d from a 52–week study in dogs based on dark liver, centrilobular hepatocyte hypertrophy and pigmented hepatocytes in both sexes at doses of 92.0 mg/kg/d. A 100–fold safety factor is proposed, consisting of safety factors of 10 for potential intraspecies and interspecies variation.

The ADI is therefore established at 0.19 mg/kg bw/d using the NOEL of 19.2 mg/kg bw/d from a 52 week dietary chronic study in dogs and applying a 100–fold safety factor.

ARfD

The acute reference dose (ARfD) is the estimate of the amount of a substance in food or drinking water, expressed on a milligram per kilogram body weight basis, that can be ingested over a short period of time, usually in one meal or during one day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

An ARfD was not established since mandestrobin was not considered likely to present an acute hazard to humans. Acute oral toxicity and short-term dermal toxicity studies indicated mandestrobin was of low toxicity, with no clinical signs of toxicity reported. No reproductive and developmental toxicity was observed at limit-dose concentrations in either maternal dams or foetal pups, and mandestrobin was not acutely neurotoxic.

4 RESIDUES ASSESSMENT

4.1 Introduction

Sumitomo Chemical Australia Pty Limited has applied for registration of a suspension concentrate end-use product, Intuity Fungicide. The product contains the new active constituent mandestrobin at 250 g/L. The product is for the control of blossom blight and brown rot in stone fruit.

4.2 Metabolism

Mandestrobin (S-2200) was radiolabelled either in the in the phenoxy or benzyl rings.

Plants

Rapeseed: ^{14}C-mandestrobin was applied at 400 g ac/ha either once 54 days before harvest (DBH) or twice at 54 and 40 DBH. Following one application at 400 g ac/ha and a 54 day PHI, total radioactive residues in rape seed were 0.011–0.051 mg/kg eq. For the treatment involving 2 applications at 400 g ac/ha, total radioactive residues were 0.47–0.64 mg/kg eq in rape seed at a 40 day PHI and 3.44–4.00 mg/kg eq following a 14 day PHI. Parent mandestrobin was the major residue accounting for 20 to 22% of the TRR (0.77–0.79 mg/kg eq) in the forage and 25 to 31% of the TRR (0.14–0.16 mg/kg eq) in the seed for both treatment groups.

Wheat: ^{14}C-mandestrobin was applied once at 300 g ac/ha at 104 DBH. Total radioactive residues were 10.44–11.14 mg/kg eq in forage (14 day PHI), 6.21–9.04 mg/kg eq in hay (14 day PHI), 1.85–2.49 mg/kg eq in straw (104 day PHI) and 0.01–0.09 mg/kg eq in grain (104 day PHI). Parent mandestrobin accounted for 51 to 60% of the TRR (5.68–6.25 mg/kg eq) in forage, 23 to 26% of the TRR (1.63–2.05 mg/kg eq) in the hay, 1 to 2% of the TRR in the straw (0.026–0.05 mg/kg eq) in straw and was not detected in grain.

[^{14}C]De-Xy-S-2200 accounted for 12% TRR (0.29 mg/kg eq) in the straw and 61% of the TRR (0.05 mg/kg eq) in the grain for the benzyl labelled ^{14}C-mandestrobin treatment.

Lettuce: ^{14}C-mandestrobin was applied twice at 800 g ac/ha at 15 and 5 DBH. Lettuce plants were harvested five days after the initial application (intermediate harvest) and five days after the final application (mature harvest). Total radioactive residues were 27.9–35.1 mg/kg eq for the intermediate harvest and 41.59–43.14 mg/kg eq for the mature harvest. Parent mandestrobin was the major residue accounting for 93 to 94% of the TRR (25.9–33.0 mg/kg eq) in the intermediate harvest and 89 to 91% of the TRR (37.0–39.3 mg/kg eq) in the final harvest lettuce plants for both treatment groups.

Rotational crops: ^{14}C-mandestrobin was applied once to bare soil at 1600 g ac/ha. Following a 30, 120 and 365 plant back interval (PBI), lettuce, carrots and wheat were planted. Parent mandestrobin was a significant residue (>10% TRR) in immature lettuce (365 day PBI), mature lettuce (30 day PBI) and carrot roots (30 and 120 day PBI), with the highest level being 0.040 mg/kg eq (carrot roots, 30 day PBI, 78% TRR) 2-CH_2OH-S-2200 (including its glycoside conjugates) was a significant residue (>10% TRR) in wheat forage (30 day PBI) and carrot roots (30 and 120 day PBI), with the highest level being 0.60 mg/kg eq (wheat forage, 30 day PBI, 24%TRR). 5-CH_2OH-S-2200 (including its glycoside conjugates) was a significant

residue in immature lettuce (30 and 365 day PBI), mature lettuce (30 day PBI), wheat forage (30, 120 and 365 day PBI), wheat hay (120 and 365 day PBI) and carrot tops (365 day PBI), with the highest level being 0.69 mg/kg eq (wheat forage, 30 day PBI, 27% TRR). 4-OH-S-2200 (including its glycoside conjugates) was a significant residue in immature and mature lettuce (30, 120 and 365 day PBI) and wheat hay (30 and 120 day PBI), with the highest level being 0.53 mg/kg eq (wheat hay, 30 day PBI, 12% TRR). Further consideration of residues in rotational crops will be required before uses are approved in rotational systems.

The proposed metabolic pathway for mandestrobin in plants is presented below:

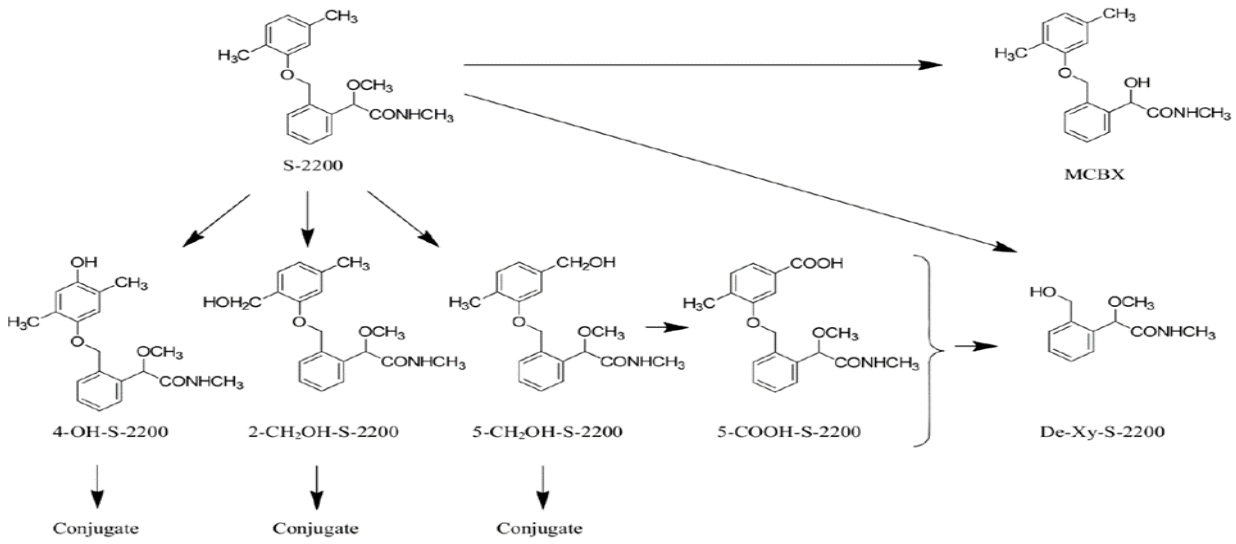


Figure 1: The proposed metabolic pathway for mandestrobin in plants (note that De-Xy-S-2200 was a major metabolite in wheat grain and straw only)

Animals

Lactating goats: ^{14}C-mandestrobin was orally administered daily for 7 consecutive days at 11.9 or 13.5 ppm in the feed respectively for the phenoxy and benzyl labels. The major residues from animals dosed with phenoxy labelled ^{14}C-mandestrobin, were parent mandestrobin (33% TRR or 0.01 mg/kg eq in milk (fat), 50% TRR or 0.006 mg/kg eq in fat and 23% TRR or 0.002 mg/kg eq in muscle) and 5-COOH-S-2200 (20% TRR or 0.06 mg/kg eq in liver and 25% TRR or 0.04 mg/kg eq in kidney). 4-OH-S-2200 glucuronide was also a major residue in in goat kidney (15% TRR or 0.03 mg/kg eq). The major residues from animals dosed with benzyl labelled ^{14}C-mandestrobin, were parent mandestrobin (35% TRR or 0.01 mg/kg eq in milk (fat), 23% TRR or 0.007 mg/kg eq in fat and 18.2% TRR or 0.003 mg/kg eq in muscle) and 5-COOH-S-2200 (11% TRR or 0.07 mg/kg eq in liver and 20% TRR or 0.08 mg/kg eq in kidney). 4-OH-S-2200 glucuronide was also a major residue in in goat kidney (13% TRR or 0.06 mg/kg eq).

The proposed metabolic pathway for mandestrobin in lactating goats is presented below.

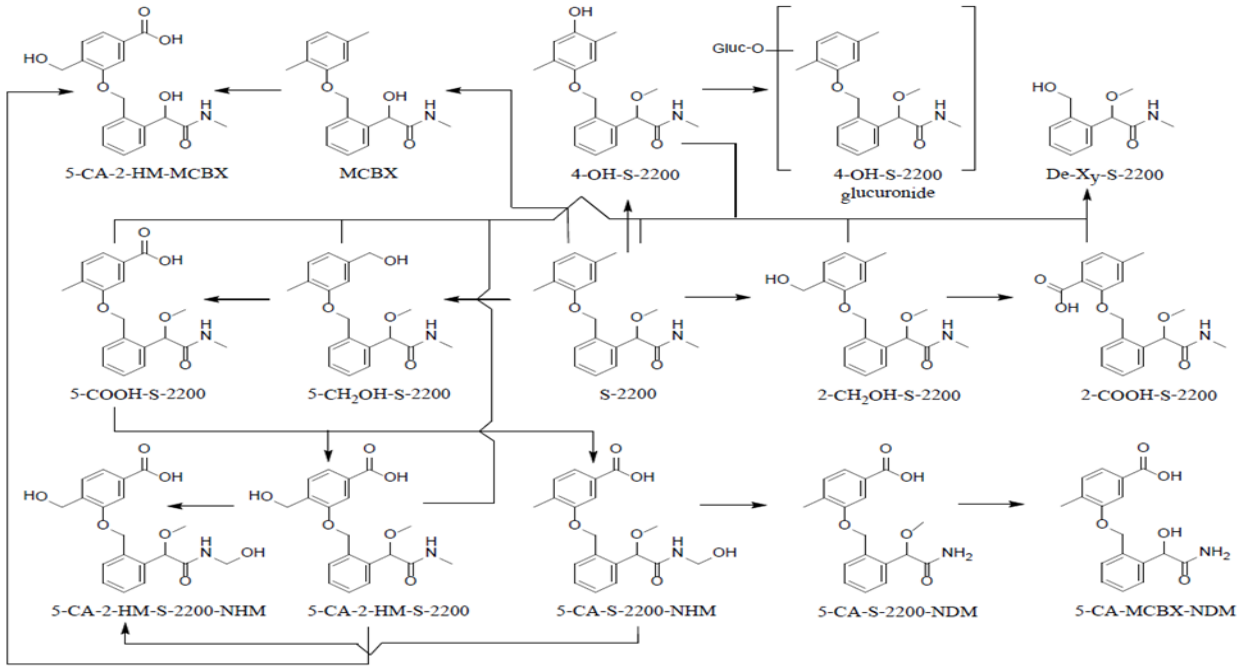


Figure 2: The proposed metabolic pathway for mandestrobin in lactating goats

Laying hens: ^{14}C-mandestrobin was orally administered daily for 14 consecutive days at 13.2 or 13.4 ppm in the feed respectively for the phenoxy and benzyl labels. The major residues from laying hens dosed with the phenoxy labelled ^{14}C-mandestrobin, were parent mandestrobin (51 % TRR or 0.06 mg/kg eq in eggs and 50% TRR or 0.02 mg/kg eq in fat) and 4-OH-S-2200 (15% TRR or 0.05 mg/kg eq in liver). The major residues from animals dosed with benzyl labelled ^{14}C-mandestrobin, were parent mandestrobin (33% TRR or 0.03 mg/kg eq in eggs and 34% TRR or 0.01 mg/kg in fat) and De-Xy-S-2200 (12% TRR or 0.04 mg/kg eq in liver).

The proposed metabolic pathway for mandestrobin in laying hens is presented below.

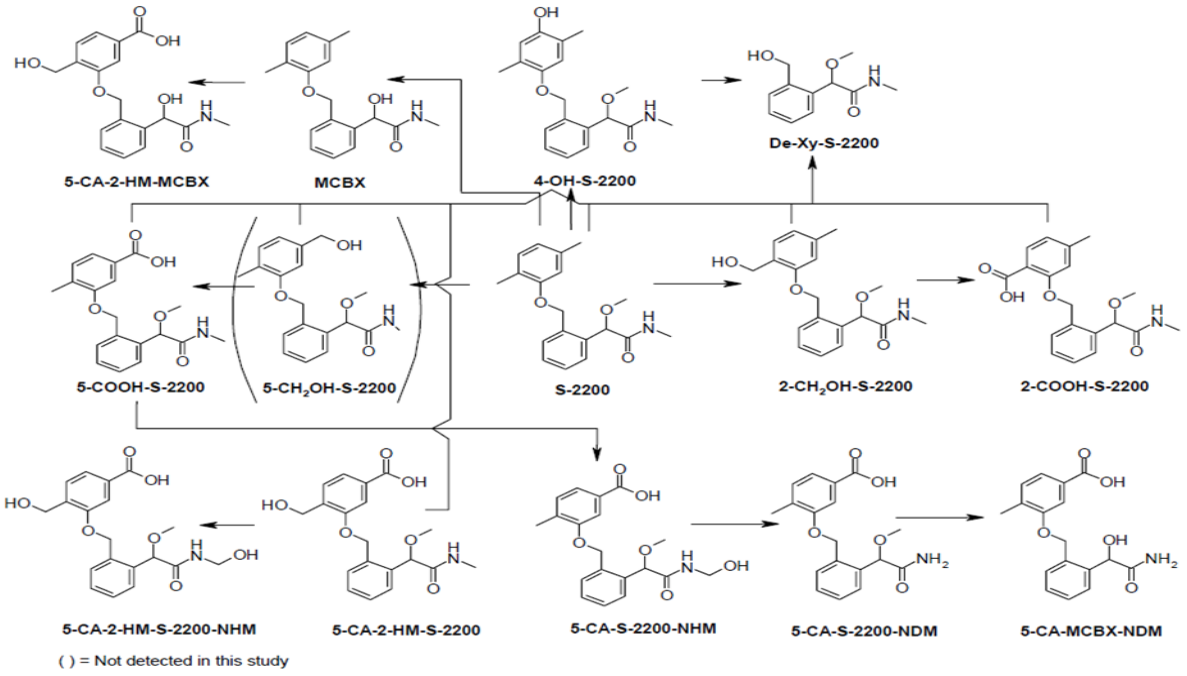


Figure 3: The proposed metabolic pathway for mandestrobin in laying hens

4.3 Analytical methods

Details of validated analytical methods involving extraction with acetone/water or acetonitrile/water and analysis with LC-MS/MS for the determination of mandestrobin in; peach, grape and barley (grain); and 2-CH_2OH-S-2200 and its conjugates in lettuce, oilseed rape (seed) and barley (grain and straw) have been provided. The limit of quantitation was 0.01 mg/kg for all analytes.

The Australian residue studies conducted on stone fruit involved extraction with acetone/water and analysis bv UHPLC-MS-MS. The recovery of mandestrobin (S-2200) and its metabolites De-Xy-S-2200, 2-CH_2OH-S-2200, 5-CH_2OH-S-2200 and 4-OH-S-2200 from stone fruit fortified at 0.01 mg/kg (LOQ) and 0.1 mg/kg were within the acceptable limits (70–120%, <20% RSD).

4.4 Residue definition

Based on the results of the metabolism and residue studies that found parent mandestrobin to be the major contributor to the total residues, with metabolites, when present, generally occurring at levels approximately equal to 100 times less than parent, it is recommended that the residue definition for mandestrobin be parent mandestrobin for both enforcement and dietary risk assessment.

4.5 Residue trials

The proposed use of mandestrobin on stone fruit involves an application rate of 30 g ac/100 L and a 7 day harvest withholding period. Following two applications of mandestrobin to peaches (n=7), cherries (n=4), nectarines (n=4) and plums (n=2) made 14 days apart at 35 g ac/ha (1.2X the proposed concentration), residues of parent mandestrobin were, 0.045, 0.16, 0.19, 0.24, 0.26, 0.27, 0.29, 0.31, 0.35, 0.49, 0.59, 0.68, 0.69, 0.82, 0.93, 0.95 and 2.6 mg/kg (STMR = 0.35 mg/kg) at a 6–7 day PHI. The OECD MRL calculator estimates an MRL of 3 mg/kg.

A mandestrobin MRL of 3 mg/kg for stone fruits is considered to be appropriate for the proposed use with a 7 day harvest withholding period.

4.6 Animal commodity MRLs

The use of mandestrobin has been supported for stone fruit only, with the grazing restraint 'DO NOT allow grazing of inter-rows in stone fruit orchards'. Stone fruit (or any of its processing waste) are not considered to be an animal feed commodity and therefore the use of mandestrobin should not result in significant animal exposure at this time. The establishment of animal commodity MRLs is therefore not required for the proposed use on stone fruit.

4.7 Estimated dietary intake

The chronic dietary exposure to mandestrobin 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 1995 National Nutrition Survey of Australia. 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 mandestrobin is equivalent to <1 % of the ADI.

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 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. An ARfD for mandestrobin was not considered to be necessary by the OCS and therefore a NESTI calculation is not required.

4.8 Fat solubility and bioaccumulation potential

The octanol-water partition coefficient ($log_{10}K_{OW}$) for mandestrobin is 3.51, indicating fat solubility. Significant animal exposure to mandestrobin residues is not expected to result from the proposed use.

4.9 Spray drift

The proposed use of mandestrobin on stone fruit involves a spray concentration of 30 g ac/100 L using orchard airblast equipment. A spray volume of 2500 L/ha was considered for stone fruit. Spray drift

modelling, using the average deposition from the APVMA spray drift standard application scenario for ‘Airblast—composite orchard’, shows that with respect to no-spray zones, a downwind buffer of 15 m is required. Due to the insignificant size of the calculated buffer it is considered that a no-spray zone is not required for the protection of international trade.

4.10 Recommendations

The following amendments to the APVMA MRL Standard are required for the current application:

Table 1

COMPOUND		FOOD	MRL (MG/KG)
ADD:			
Mandestrobin			
FS	0012	Stone fruits	3

Table 3

COMPOUND	RESIDUE
ADD:	
Mandestrobin	Mandestrobin

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Sumitomo Chemical Australia Pty Limited has applied for registration of a suspension concentrate end-use product, Intuity Fungicide. The product contains the new active constituent mandestrobin at 250 g/L. The product is for the control of blossom blight and brown rot in stone fruit.

5.1 Commodities exported

Stone fruit are considered to be major export commodity, and mandestrobin residues in stone fruit resulting from the use of Intuity Fungicide may have the potential to unduly prejudice trade.

5.2 Destination of exports

Australia exported $1.4 million worth of apricots, $31.5 million worth of cherries, $18.2 million worth of nectarines and peaches and $7.1 million worth of plums in the 2012–2013 financial year. The major markets are summarised below:

Table 1: Major destinations for Australian stone fruit exports

STONE FRUIT	MAJOR DESTINATIONS
Apricots	Asia including United Arab Emirates. Hong Kong, Singapore
Cherries	Asia including Hong Kong, Taiwan and Singapore; Europe including the United Kingdom and the Netherlands; the United Arab Emirates
Nectarines and peaches	Asia including Hong Kong, Singapore and Taiwan; the Middle East including the United Arab Emirates and Saudi Arabia; New Caledonia
Plums	Asia including Hong Kong, Singapore and Malaysia; the Middle East including the United Arab Emirates and Kuwait

5.3 Proposed use pattern

Intuity Fungicide (250 g/L Mandestrobin)

CROP	DISEASE	RATE	CRITICAL COMMENTS
Stone fruit including: peaches, nectarines, plums apricots and cherries	Blossom blight *(Monilinia laxa)* Brown rot *(Monolinia fructicola)*	120 ml/100 L *(30 g ac/100 L)*	For blossom blight control—spray at 20% and again at 90% flowering. For brown rot control—spray at 3 weeks and then 1 week pre-harvest with a minimum interval of 14 days. Good coverage is important to get good control. Concentrate spraying is not recommended. The addition of a non-ionic surfactant may improve efficacy.

RESTRAINTS:
Stone fruits: DO NOT apply more than two applications per season.
DO NOT apply by aircraft.

WITHHOLDING PERIODS:
Stone fruit: DO NOT harvest fruit for 7 days after application
Grazing: DO NOT allow grazing of inter-rows in stone fruit orchards

Treated crops for export to particular destinations outside Australia may require a longer interval before harvest to comply with residues standards of importing countries. Please contact your industry body, exporter or Sumitomo Chemical Australia before using Intuity Fungicide.

APPLICATION:
Stone Fruit:
Good coverage is important. Do not apply more than 2 sprays per season.
☐ 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 to the point of run-off. Avoid excessive run-off.
☐ The required water 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.

5.4 Comparison of Australian MRLs with Codex and International MRLs

Mandestrobin has not been considered by Codex, nor is it scheduled for evaluation by the JMPR.

As of 28 June 2016, Japan and Canada were the only countries to have MRLs established for mandestrobin:

- The Japanese residue definition for mandestrobin was set as the sum of the (R) and (S) isomers of parent mandestrobin and MRLs are 0.2 mg/kg for Peach, 2 mg/kg for Japanese Plum (including prunes) and 5 mg/kg for Nectarine, Apricot, Mume Plum and Cherry.

- The Canadian residue definition was set as mandestrobin and the following MRLs have been established: 7.0 mg/kg for Raisons, 5.0 mg/kg for Small fruit vine climbing (Crop Subgroup 13–07F, except fuzzy kiwifruit), 3.0 mg/kg for Low growing berry (Crop Subgroup 13–07G, except cranberry), 0.5 mg/kg for Rapeseed (Crop Subgroup 20A), and 0.02 mg/kg for Legume vegetables (succulent or dried) (Crop Group 6, except cowpea and field pea) and Corn (field, popcorn, sweet).

It is noted that the EU pesticides database states that mandestrobin was approved on 9 December 2015 but as of 5 July 2016 there was no European Authorisation in place and therefore EU MRLs have not been established.

5.5 Potential risk to trade

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

Stone fruit is a major export commodity. The proposed use of mandestrobin on stone fruit is expected to result in finite residues, with the STMR and HR at the proposed withholding period of 7 days being 0.35 and 2.64 mg/kg respectively.

The following label advice relating to trade has been proposed:

Treated crops for export to particular destinations outside Australia may require a longer interval before harvest to comply with residues standards of importing countries. Please contact your industry body, exporter or Sumitomo Chemical Australia before using INTUITY fungicide.

Data demonstrating the decline in residues to below the LOQ of 0.01 mg/kg in stone fruit is not available.

Mandestrobin MRLs have not been established by Codex or any other international authority, other than Japan and Canada. Comment is sought on potential risk to international trade and the ability for the industry to manage the risk.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Sumitomo Chemical Australia Pty Limited has applied for registration of a suspension concentrate end-use product, Intuity Fungicide. The product contains the new active constituent mandestrobin at 250 g/L. The product is for the control of blossom blight and brown rot in stone fruit.

6.1 Health hazards

Mandestrobin (CAS: 139528-85-1) is not listed on the Safe Work Australia Hazardous Substances Information System (HSIS) Database (SWA, 2015).

With the available toxicology information, the OCS recommends that the active constituent mandestrobin not be classified as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

Based on the product toxicology information, the OCS recommends that Intuity Fungicide is **not** classified as a hazardous substance in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

Formulation, packaging, transport, storage and retailing

Intuity will be available in the following pack sizes: 1 L in HDPE bottles, 5 L and 10 L in HDPE canisters and 20 L in HDPE drums.

Exposure during use

The product will be professionally used for commercial situations, and farmers and their employees will be the main users of the product. Workers may be exposed to the product when opening containers, mixing/loading/application, cleaning up spills, maintaining equipment and entering treated areas. The main routes of exposure to the product will be dermal, inhalational and ocular exposure.

In the absence of specific exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used by OCS to estimate exposure.

The toxicological endpoint of concern and identified NOEL for risk assessment is derived from a repeat dose study in animals, and in this instance a margin of exposure (MOE) of 100 or above is considered acceptable. The MOE takes into account both potential inter-species extrapolation and intra-species variability. Based on the risk assessment, the proposed use of the product for stone fruit is acceptable when a single layer of PPE and gloves are used by workers during mixing/loading and during application of the product.

Application of Intuity Fungicide by airblast application is unlikely to pose a risk to bystanders when used according to good agricultural practice.

Exposure during re-entry

The OCS notes that the re-entry risks associated with conducting activities where the product has been applied are expected to be by the dermal route, and that exposure to mandestrobin is expected to occur at specific periods of time after application to a crop. As the MOEs after very high exposure activities in stone fruit are acceptable (MOE > 1000) on day zero after application, the OCS considers that the risks associated with re-entry activities is low after the spray has dried, and a NIL re-entry statement is appropriate.

Recommendations for safe use

Users should follow the First Aid Instructions and Safety Directions on the product label.

Conclusion

The registration of Intuity Fungicide, containing 250 g/L mandestrobin for the control of blossom blight and brown rot in stone fruit is supported.

Intuity Fungicide can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product safety data sheet.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

Sumitomo Chemical Australia Pty Limited has applied for registration of a suspension concentrate end-use product, Intuity Fungicide. The product contains the new active constituent mandestrobin at 250 g/L. The product is for the control of blossom blight and brown rot in stone fruit.

7.2 Environmental fate

Hydrolysis

Mandestrobin is expected to be hydrolytically stable under normal environmental conditions.

Photolysis/photodegradation

Mandestrobin may be expected to photodegrade with a half-life of less than 1 week. Photolysis on soils is unlikely to be a major degradation route.

Biodegradation

Soil metabolism

In aerobic soils, the *R*-isomer degraded more slowly than the *S*-isomer with geometric mean half-lives (n = 6) of 105 days and 73.4 days respectively. The major soil metabolites identified (5- and 2-COOH-S-2200) were not persistent with half-lives in aerobic soil of 41 days or less. Despite individual laboratory soil half-lives up to 322 days, in field dissipation trials (n = 4 sites), mandestrobin dissipated rapidly with half-lives of 8.3 days or less. Residues were primarily restricted to the top 10 cm of soil and no major metabolites (>10%) were identified. In anaerobic soil mandestrobin showed only limited degradation over the 334 day incubation period.

In anaerobic soils, mandestrobin remains bound to the soil thus remaining almost unchanged.

Aquatic metabolism

In two aerobic water/sediment systems, with application to the water column, mandestrobin partitioned to the sediment with water column dissipation half-lives up to 23 days or less. Degradation in the sediment from these systems was slow and whole system half-lives ranged from 155 days to (extrapolated) 654 days.
In two anaerobic water/sediment systems, whole system half-lives were shorter for the *S*-isomer (extrapolated DT_{50} values of ~450–700 days, but no discernible degradation of the *R*-isomer was found in anaerobic sediments over the 365 day incubation period.

Mobility

Field dissipation trials were undertaken at four sites in Europe. Mandestrobin was applied at 200 g ac/ha and maximum residues were observed in the 0–10 cm soil horizon immediately following application (3 sites) or 2 days after application (1 site)> There was generally no movement below 10 cm. Mandestrobin dissipated rapidly with half-lives of 2.29–8.28 days according to DFOP kinetics. Degradates (5- and 2-COOH-mandestrobin) were only found intermittently and at low levels in the 0-10 cm layer only.

The adsorption behaviour of mandestrobin was examined in four European soils and one Japanese upland soil. Adsorption K_{Foc} values for mandestrobin were 287–797 L/kg and desorption $K_{Foc\text{-}des}$ values were 340–1003 L/kg indicating that mandestrobin has low to medium mobility. There was no evidence of any pH or %OC dependence.

A lysimeter study was conducted over four years in a neutral soil (pH 6.3) with applications to oilseed rape in three successive years. The experimental study confirmed that the metabolites 2-COOH-S-2200 and 5-COOH-S-2200 were more mobile than mandestrobin. However, no compounds exceeded an annual average of 0.1 µg/L in the leachate and the data indicated that the peak of leaching of both parent and metabolites occurred within 3 years of application.

Bioaccumulation

Mandestrobin is not expected to bioconcentrate in organisms. The steady-state bioconcentration factors based on the measured mandestrobin concentrations were 25–26 for whole fish.

7.3 Environmental effects

Avian

Testing has shown mandestrobin to be practically non-toxic to birds through acute oral and short term dietary testing. The lowest No Observable Effects Concentration (NOEC) based on reproduction was 91.1 mg ac/kg bw/d with the bobwhite quail (no effect at limit dose).

Fish

Mandestrobin is highly toxic to fish (LC_{50} 0.94 mg/L; 28 d NOEC 0.15 mg/L), highly toxic to aquatic invertebrates based on testing to the mysid shrimp (LC_{50} 0.43 mg/L; 36 d NOEC 0.049 mg/L), and moderately toxic to algae (ErC_{50} 1.2 mg/L; NOEC 0.18 mg/L). The major metabolites were all less toxic to aquatic organisms than the parent compound.

Aquatic invertebrates

Mandestrobin is of moderate toxicity to *Daphnia magna*. The *R*-isomer is of comparable toxicity to the racemic mixture, however the endpoint for the *S*-isomer is greater than the highest dose tested demonstrating it to be at least 10 times less toxic than the *R*-isomer. Mandestrobin (racemic) was more toxic to the marine invertebrate, mysid shrimp, from both acute (96 h LC_{50} = 0.43 mg/L) and chronic exposure (36 d NOEC = 0.049 mg/L) than to *Daphnia magna* (48 h EC_{50} = 1.2 mg/L; 21 d NOEC = 0.56 mg/L).

Algae, diatoms and aquatic plants

Mandestrobin is moderately toxic to algae. The *R*-isomer is of comparable toxicity to the racemic mixture, however the endpoint for the *S*-isomer is more than 10 times higher than that of the *R*-isomer. The most sensitive species was the marine diatom with an E_rC_{50} of 1.2 mg/L. This was not dissimilar to some results for freshwater algal species.

Terrestrial invertebrates, microorganisms and plants

Mandestrobin was shown to not be of concern to bees, non-target arthropods, earthworms, soil micro-organisms, and non-target terrestrial plants (subject to appropriate downwind buffer zones).

7.4 Risk Assessment

Mandestrobin has been assessed for a maximum application rate of 300 g ac/ha, with a maximum of 2 sprays per season and 14 days between applications. The risk assessment, which was performed using standard methodology, showed an acceptable risk to all environmental organisms considered.

The spray drift risk assessment was undertaken as per the APVMA spray drift policy and demonstrated risk to aquatic organisms is acceptable, provided the inclusion of appropriate downwind aquatic spray drift buffer zones are applied. The runoff risk assessment to aquatic organisms was undertaken as per the Department of the Environment screening model and demonstrated that risk to aquatic organisms from runoff of the active constituent was acceptable.

The APVMA is satisfied that the proposed use of this product is unlikely to have an unintended effect that is harmful to animals, plants or things or to the environment.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed product use pattern

Sumitomo Chemical Australia Pty Limited has applied for registration of a suspension concentrate end-use product, Intuity Fungicide. The product contains the new active constituent mandestrobin at 250 g/L. The product is for the control of blossom blight and brown rot in stone fruit.

8.2 Summary of evaluation of efficacy and crop safety

The applicant has submitted thirteen studies comparing the efficacy and crop safety of mandestrobin formulations with industry standard fungicides for control of diseases in stone fruit. These trials were conducted over seven years (2006–2012) in a range of growing conditions throughout Australia. In these replicated trials various formulations of the product were tested including the proposed formulation for Intuity Fungicide at various rates as well as proposed label rates, assessments were made on efficacy to control disease on trees in orchard situations and compared to the industry best practice fungicides. Assessments were also made on crop safety.

Five of the studies on stone fruit were conducted with this product formulation. A number of rates were tested in the trials from 15, 25, 30, 35 and 40 g ac/L mandestrobin. The product was also trialled with up to four spray applications on various early and late stages of flower and fruit development. For blossom blight two spray applications were made at 20% and 90% bloom (120 mL/100 L or 30 g ac/100 L). For brown rot control spray applications were at three weeks and again at one week prior to harvest with a minimum interval of 14 days.

One of the studies compared the commercial mandestrobin formulation (250 g mandestrobin ac/L) with a more concentrated experimental formulation (300 g ac/L) and demonstrated bioequivalence with this formulation in cherries. In this trial four applications of each of these formulations were applied during the trial and no phytotoxicity was observed.

The commercial 250 g ac/L mandestrobin formulation provided adequate control of diseases such as blossom blight in peaches and cherries, and brown rot in peaches, cherries and nectarines, reducing the incidence to levels obtained with current industry fungicide treatments when used at the rates of 25 to 35 g ac/100 L (proposed label rate is 120 mL/100 L or 30 g ac/100 L) and two spray applications during flowering.

Crop safety

There was no evidence of phytotoxicity on flowers, foliage or fruit of the plants in these trials, even when the product was used at higher than label rates and up to four spray applications.

Resistance management

Mandestrobin is a quinone outside inhibitor of fungal pathogens. The Fungicide Resistance Action Committee (a specialist technical group of CropLife International) has designated mandestrobin as a Group 11 fungicide.

For resistance management purposes, Intuity is Group 11 fungicide.

8.3 Conclusions

The claims on the proposed label that Intuity Fungicide provides acceptable control of blossom blight and brown rot in stone fruit when used as directed is supported by the results from the Australian trials.

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.

The application by Sumitomo Chemical Australia for the registration of Intuity Fungicide is supported on efficacy and crop safety grounds when used in accordance with label instructions.

9 LABELLING REQUIREMENTS

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

INTUITY™

Fungicide

ACTIVE CONSTITUENT: 250 g/L MANDESTROBIN

GROUP	11	FUNGICIDE

For the Control of Blossom Blight in Stone Fruit as specified in the Directions for Use Table.

CONTENTS: 1 L, 5 L, 10 L, 20 L

Sumitomo Chemical Australia Pty Ltd
51 Rawson Street
Epping NSW 2121
Tel: 02 8752 9000
A.B.N. 21 081 096 255

DIRECTIONS FOR USE:

Restraints

DO NOT apply more than two applications per season.
DO NOT apply by aircraft.

CROP	DISEASE	RATE	CRITICAL COMMENTS
Stone fruit including: peaches, nectarines, plums, apricots and cherries	Blossom blight (*Monilinia laxa*) Brown rot (*Monolinia fructicola)*	120 mL/100 L	For blossom blight control—spray at 20% and again at 90% flowering, with a minimum interval of 14 days. For brown rot control, spray the first application at 3 weeks pre-harvest and the second at 1 week pre-harvest, with a minimum interval of 14 days. Good coverage is important to get good control. Concentrate spraying is not recommended. The addition of a non-ionic surfactant may improve efficacy.

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

WITHHOLDING PERIODS:

STONE FRUIT: DO NOT HARVEST FRUIT FOR 7 DAYS AFTER APPLICATION.

GRAZING: DO NOT ALLOW GRAZING OF INTER-ROWS IN STONE FRUIT ORCHARDS

Trade Advice

Treated crops for export to particular destinations outside Australia may require a longer interval before harvest to comply with residues standards of importing countries. Please contact your industry body, exporter or Sumitomo Chemical Australia before using INTUITY fungicide.

SPRAY DRIFT RESTRAINTS

Except when applying with orchard/vineyard airblast equipment, DO NOT apply with spray droplets smaller than a MEDIUM spray droplet size category according to nozzle manufacturer specifications that refer to the ASAE S572 Standard of the British Crop Production Council guideline.

DO NOT apply when wind speed is less than 3 or more than 20 kilometres per hour, as measured at the application site.

DO NOT apply during surface temperature inversion conditions at the application site.

Users of this product MUST make an accurate written record of the details of each spray application within 24 hours following application, and must KEEP this record for at least 2 years. The spray application details that must be recorded are:

1 date with start and finish times of application 2 location address and paddock(s) sprayed 3 full name of this product 4 amount of product used per hectare and number of hectares applied to 5 crop or situation and weed or pest 6 wind speed and direction during application 7 air temperature and relative humidity during application 8 nozzle brand, type, spray angle, nozzle capacity and spray system pressure measured during application 9 name and address of person applying this product. (Additional record details may be required by the state or territory where this product is used.)

MANDATORY NO-SPRAY ZONES

DO NOT apply if there are aquatic and wetland areas including aquacultural ponds, surface streams and rivers within 10 metres downwind from the application area.

GENERAL INSTRUCTIONS

MIXING

Measure the required amount of INTUITY Fungicide, add to the partly filled spray tank and then add the remainder of the water.

APPLICATION:

Stone Fruit:

Good coverage is important. **DO NOT** apply more than 2 sprays per season.

- 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 to the point of run-off. Avoid excessive run-off.
- The required water 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.

Wetting Agent

The addition of a non-ionic surfactant may improve efficacy.

FUNGICIDE RESISTANCE WARNING:

GROUP	11	FUNGICIDE

INTUITY Fungicide is a member of the Quinone outside Inhibitor (QoI) group of fungicides. For fungicide resistance management INTUITY Fungicide is a Group 11 fungicide. Some naturally occurring individual fungi resistant to the product and other Group 11 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 and other Group 11 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, Sumitomo Chemical Australia Pty Ltd accepts no liability for any losses that result from failure of this product to control resistant fungi.

Resistance management strategy:

DO NOT apply INTUITY Fungicide more than two times per season, with a minimum 14 day interval.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

Very toxic to aquatic life. **DO NOT** contaminate streams, rivers or waterways with the product or used containers.
DO NOT apply INTUITY Fungicide if wind is likely to cause drift onto natural and impounded lakes, waterways, streams or rivers. A 10 metre buffer must be observed between sprayed areas and downwind natural and impounded lakes, dams, waterways, streams or rivers.

STORAGE AND DISPOSAL:

Store in the closed original container in a well-ventilated area, as cool as possible, although avoid freezing. Do not store for prolonged periods in direct sunlight.
Triple or preferably pressure 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 designated collection point.

If not recycling, break, crush, or puncture and deliver empty packaging for appropriate disposal to an approved waste management facility. If an approved waste management facility is not available bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots, in compliance with relevant Local, State or Territory government regulations. DO NOT burn empty containers or product.

SAFETY DIRECTIONS:

When opening the container and preparing spray wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length chemical resistant gloves.
When using the prepared spray wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and a washable hat.
Wash hands after use. After each day's use wash contaminated clothing.

RE-ENTRY:

Do not allow entry into 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.

FIRST AID:

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131 126; New Zealand 0800 764 766.

MATERIAL SAFETY DATA SHEET:

Additional information is listed in the Material Safety Data Sheet (MSDS) obtained from Sumitomo Chemical Australia Pty Ltd.

IN A TRANSPORT EMERGENCY DIAL : 000 POLICE OR FIRE BRIGADE	**SPECIALIST ADVICE IN EMERGENCY ONLY PHONE : 1800 024 973 ALL HOURS - AUSTRALIA WIDE**

Important Notice
These goods are to be used only for the purpose and as specified on the label, and are not suitable for any other purpose. To the fullest extent permitted by law, we do not accept or bear any liability on any basis for any loss, damage, cost or expense, arising in any way, directly or indirectly, in connection with the goods.

APVMA Approval No.:

Batch No:

Date of Manufacture:

ABBREVIATIONS

ε	epsilon
λ_{max}	Maximum Wavelength
ac	Active constituent
ADI	Acceptable Daily Intake (for humans)
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
ATP	Adenosine triphosphate
bw	Bodyweight
^{0}C	Degrees Centigrade
^{14}C	Carbon 14
cm	Centimetre
d	Day
DAT	Days After Treatment
DBH	Days Before Harvest
DFOP	Double first order in parallel
DSC	Differential Scanning Calorimetry
DT_{50}	Time taken for 50% of the concentration to dissipate
$D_{v,50}$	Diameter where 50% of the volume consist of smaller particles/droplets
EC_{50}	Concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
ErC_{50}	Concentration at which the rate of growth of 50% of the test population is impacted
eq	Equivalent
F_O	Original parent generation
F_1	First Generation
g	Gram
GPMT	Guinea Pig Maximisation Test

h	Hour
ha	Hectare
HDPE	High Density Polyethylene
HR	Highest Residue
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	Intradermal
IPM	Integrated Pest Management
in vitro	Outside the living body and in an artificial environment
in vivo	Inside the living body of a plant or animal
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
kg	Kilogram
K_{FOC}	Adsorption coefficient, also K_{OC}
K_{OW}	Log to base 10 of octanol water partitioning co-efficient, synonym P_{OW}
L	Litre
LC-MS/MS	Liquid Crystal Mass Spectrometry/Mass Spectrometry
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
LOQ	Limit of Quantitation – level at which residues can be quantified
M/F	Male/Female
mg	Milligram
mL	Millilitre
min	Minutes
mN	Millinewton
mol	Mole (SI base unit)
MOE	Margin of Exposure
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet

n	Number
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	Nanogram
nm	Nanometre
NOEC/NOEL	No Observable Effect Concentration/Level
NOHSC	National Occupational Health and Safety Commission
OC	Organic Carbon
OCS	Office of Chemical Safety (in the Department of Health)
OECD	Organisation for Economic Co-operation and Development
Pa	Pascals
PBI	Plant Back Interval
pH	Potential of hydrogen
PHED	Pesticide Handler Exposure Database
PHI	Pre-Harvest Interval
P_{ow}	Log to base 10 of octanol water partitioning co-efficient, synonym K_{ow}
PRS	Public Release Summary
ppb	Parts per billion
PPE	Personal Protective Equipment
ppm	Parts per million
RSD	Relative Standard Deviation
s	Second
SC	Suspension Concentrate
STMR	Supervised Trials Medium Residues
TGAC	Technical grade active constituent
TRR	Total Radioactive Residue
µg	Microgram

µm	Micrometre
WHO	World Health Organization
UHPLC-MS-MS	Ultra-High Pressure Liquid Chromatography Mass Spectrometry-Mass Spectrometry
WHP	Withholding Period

GLOSSARY

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
Leaching	Removal of a compound by use of a solvent
Metabolism	The chemical processes that maintain living organisms
pH	A figure expressing the acidity or alkalinity of a solution on a logarithmic scale on which 7 is neutral, lower values are more acidic and higher values more alkaline. The pH is equal $-\log_{10} [H^+]$ where $[H^+]$ is the hydrogen ion concentration in moles per litre
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

Australian Pesticides and Veterinary Medicines Authority, *Registration and Permits, Data Guidelines* (2015), apvma.gov.au/registrations-and-permits/data-guidelines.

National Occupational Health and Safety Commission (NOHSC), *Approved Criteria for Classifying Hazardous Substances, 3rd Edition [NOHSC:1008(2004)]*, NOHSC, Canberra, 2004. Available at: www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/ns2004criteriaforclassifyinghazardous

Safe Work Australia (SWA), *Hazardous Substances Information System (HSIS) Database*, SWA, Canberra, 2015. Available at: hsis.safeworkaustralia.gov.au/

United States Environmental Protection Agency (US EPA), *The Pesticide Handlers Exposure Database (PHED), Version 1.1–PHED Surrogate Exposure Guide, Estimates of Worker Exposure*. US EPA, Washington, DC, United States, 1998