Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active MANDIPROPAMID in the product

REVUS® FUNGICIDE

APVMA Product Number 63052

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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 and Environmental Health (OCSEH), Department of Sustainability, Environment, Water, Populations and Communities (DSEWPaC), 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 ingredients.

The information and technical data required by the APVMA to assess the safety of new chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in the APVMA's publications *Ag MORAG: Manual of Requirements and Guidelines* and *Vet MORAG: Manual of Requirements and Guidelines*.

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 Australian Pesticides and Veterinary Medicines Authority (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 persons 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 applications for registration of **REVUS® 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 grounds include **occupational health and safety, chemistry and manufacture, residues, safety and first aid, environmental fate and toxicity, trade** and **efficacy**. Submissions should state the grounds on which they are based. Comments received outside these grounds cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on 22 June 2011 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. A summary of relevant comments and the APVMA's response will be published on the APVMA website.

When making a submission please include:

- Contact name
- Company or Group name (if relevant)
- Postal Address
- Email Address (if available)
- The date you made the submission.

All personal and ***confidential commercial information (CCI)***[1] material 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:

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

Further information

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

Copies of full technical evaluation reports covering 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: http://www.apvma.gov.au

1 INTRODUCTION

Applicant

Syngenta Crop Protection Pty Limited

Details of Product

It is proposed to register Revus® Fungicide containing 250 g/L mandipropamid as a suspension concentrate intended for use in the control of downy mildew (*Plasmopara viticola*) in grapevines. Revus® Fungicide is intended to be used at the rate of 40 – 60 mL product/100 L of water.

Grapevine downy mildew occurs frequently in the grape producing regions of Australia, it mainly occurs in regions that experience high summer rainfalls but may occur in any region if conditions are conducive to the development of the disease. If the disease occurs during flowering or early fruit set the disease can cause total loss of berries. If left unchecked at any time during the growing season the disease may result in significant leaf damage and defoliation, which may ultimately affect the quality of fruit.

Mandipropamid is a new active constituent to the Australian market. It is a fungicide that belongs to the mandelic acid amine sub-group of the carboxylic acid amide fungicides chemical group. The Fungicide Resistance Action Committee (a specialist technical group of CropLife International) has classified mandipropamid as having the target site of cellulose synthase in cell wall biosynthesis. CropLife Australia Fungicide Resistance Management Review Group has designated an activity group for carboxylic acid amide fungicides (Group 40). The proposed use pattern is subject to a CropLife anti–resistance strategy. Restraints included on the proposed product label are consistent with the current CropLife Australia resistance management strategy for Group 40 fungicides.

Mandipropamid as a 250g/L suspension concentrate formulation is currently registered for use on grapes in the United States of America, South Korea and Slovenia. It is also registered for use on potatoes in New Zealand, a number of European countries (including Austria, Germany, Ireland, Great Britain, Belgium, Finland, Switzerland, Norway and the Netherlands), some South American countries (Argentina, Chile, Bolivia, Colombia, Ecuador), China and Tunisia. In the USA it is also registered for use on a range of leafy vegetables, brassicas, bell peppers, cucurbits and onions; and is registered for use on tomatoes, lettuces and some other crops in a number of countries including Norway, Croatia, Indonesia and Slovenia.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Revus® Fungicide and approval of the new active constituent mandipropamid.

2 CHEMISTRY AND MANUFACTURE

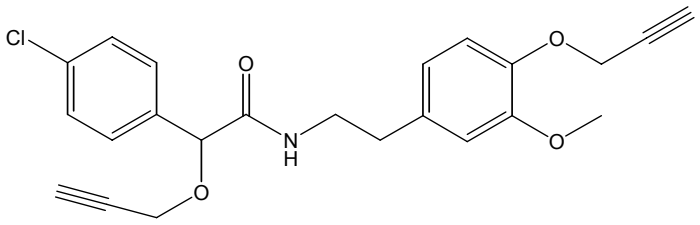
2.1 Active Constituent

Mandipropamid is a new active constituent for use in grapevines for the control of downy mildew.

Manufacturing Site

The active constituent Mandipropamid is manufactured by Syngenta Crop Protection AG at Syngenta Crop Protection Monthey SA, Route de l'Ile au Bois, CH-1870 Monthey.

Chemical Characteristics Of The Active Constituent

COMMON NAME (ISO):	Mandipropamid
IUPAC NAME:	2-(4-chlorophenyl)-N-[3-methoxy-4-(prop-2-yn-1-yloxy)phenethyl]-2-(prop-2-yn-1-yloxy)acetamide
CAS NAME:	2-(4-chlorophenyl)-N-[2-[3-methoxy-4-(prop-2-ynyloxy)phenyl]ethyl]-2-(prop-2-ynyloxy)acetamide
CAS REGISTRY NUMBER:	374726-62-2
MANUFACTURER'S CODE:	NOA 446510
MOLECULAR FORMULA:	$C_{23}H_{22}ClNO_4$
MOLECULAR WEIGHT:	411.9
STRUCTURE:	
CHEMICAL FAMILY:	Amide fungicides

Proposed APVMA Active Constituent Standard for MANDIPROPAMID

CONSTITUENT	SPECIFICATION	LEVEL
Mandipropamid	Light beige powder with no obvious odour	Minimum 930g/kg

Physicochemical Properties of the Active Constituent

COLOUR:	Light beige
ODOUR:	Odourless
PHYSICAL STATE:	Powder
MELTING POINT:	96.4ºC to 97.3ºC (purity 99.0%)
BOILING POINT:	Thermal decomposition starts at about 200ºC (purity 99.0%)
DENSITY:	1.24 x 103 kg/m^3 (purity 99.0%
UV ABSORPTION:	ε (L mol^{-1} cm^{-1}]): 20144 at 223 nm; 2724 at 276 nm (neutral solution in methanol); No absorption maximum between 350 nm and 750 nm
PARTITION COEFFICIENT (LOG K_{OW}):	3.2 at 25°C (purity 99.0%)
VAPOUR PRESSURE:	9.4 x 10^{-7} mm Hg at 20, 25 and 50ºC (purity 99.0%)
SOLUBILITY AT 25ºC: **IN WATER:** **(PURITY OF ACTIVE 99.0%; PH 8.1)**	4.2 mg/L
IN ORGANIC SOLVENTS: **(PURITY OF ACTIVE 95.2%)**	acetone 300 g/L ethyl acetate 120 g/L hexane 42 mg/L methanol 66 g/L octanol 4.8 g/L toluene 29 g/L
HENRY'S LAW CONSTANT:	< 9.2 x 10^{-5} Pa m3/mol at 25ºC (calculated)
DISSOCIATION CONSTANT IN WATER:	No pKa was found in the range of 1.0 to 12.0 (purity 99.0%)
FLAMMABILITY:	Not highly flammable (purity 95.2%)
AUTO-FLAMMABILITY:	No ignition below the melting point (purity 95.2%)
THERMAL STABILITY:	Stable at room temperature in nitrogen or air (purity 95.2%)
EXPLOSIVE PROPERTIES:	Not explosive (purity 95.2%)
OXIDISING PROPERTIES:	Not an oxidizing substance

2.2 Product

Revus® Fungicide

DISTINGUISHING NAME	Revus® Fungicide
FORMULATION TYPE	Suspension concentrate (SC)
ACTIVE CONSTITUENT CONCENTRATION	Mandipropamid (250 g/L)

Physical and Chemical Properties of Revus® Fungicide

PHYSICAL STATE:	Liquid
COLOUR:	Light beige
ODOUR:	No particular odour
SPECIFIC GRAVITY:	1.072 g/mL @ 20°C
PH (1% SOLUTION):	6.9 @ 25°C
ACIDITY/ALKALINITY	0.01% (calculated as NaOH)
VISCOSITY:	424 mPa s at sheer rate 10 s^{-1} @ 20°C
EXPLOSIVE PROPERTY:	Not explosive
OXIDISING PROPERTIES:	Not an oxidising substance
FLASH POINT:	Not detected below 101°C (at 1002.6 mbar)
AUTO IGNITION:	480 ± 5°C
SURFACE TENSION (20°C):	36.4 mN/m – neat product 49.8 mN/m – 30 g/L aqueous solution 58.5 mN/m – 3 g/L aqueous solution 66.2 mN/m – 1 g/L aqueous solution
WET SIEVE RESIDUE:	75 mm sieve: 0.06%
POURABILITY:	Pour residue: 2.0% Rinsed residue: 0.2%
PERSISTENT FOAMING:	0 mL after 1 minute at 3% concentration in CIPAC water D
SUSPENSIBILITY:	99% at both 3% and 0.3% concentrations in CIPAC water D
SPONTANEITY OF DISPERSION:	98% and 99% at concentrations 3% and 0.3%, respectively, in CIPAC water D
CORROSIVE HAZARD:	Slight corrosion to tin plate; corrosion to sheet metal, sheet steel; No corrosion to stainless steel, HDPE and PET
DANGEROUS GOODS CLASSIFICATION:	Not classified as Dangerous Goods
STORAGE STABILITY:	Stability data provided by the applicant indicates that the product is expected to remain within specification for at least 2 years when stored under normal conditions in HDPE and PET containers.
LOW TEMPERATURE STABILITY:	Chemically and physically stable after 7 days at 0°C

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

Mandipropamid is a new fungicide to the Australian market. The product, Revus® Fungicide, contains 250 g/L of mandipropamid. Revus® Fungicide will be used for the control of downy mildew in grapes.

Following oral administration in rats, absorption of mandipropamid was relatively extensive at low doses suggesting saturation at the high dose level. It was poorly distributed in tissues and found mainly in the liver and kidney. The distribution of radioactivity following repeated dosing showed a similar profile to that found after a single dose indicating that mandipropamid does not accumulate in tissues. Major metabolic transformations of mandipropamid involved the loss of one or both propargyl groups followed by glucuronidation and O-demethylation. The parent compound and its major metabolites were detected primarily in rat faeces and urine. Orally administered mandipropamid was almost completely eliminated from ratsa within 48 hr and only trace amounts left after 7 days. Dermal absorption studies indicated that absorption of mandipropamid through the skin is limited. Mandipropamid had low acute oral, dermal and inhalational toxicity in rats. It was a slight skin and eye irritant in rabbits but not a skin sensitiser in guinea pigs. The formulated product, containing 250 g/L mandipropamid had low acute oral, dermal and inhalational toxicity in rats. It was a slight a skin and eye irritant in rabbits but not a skin sensitiser in guinea pigs.

Repeat dose studies on mandipropamid indicated that the liver was the main target organ in all the species studied. There was an increase in the liver weight as well as increased activity of liver enzymes. In addition to the liver, increased kidney weights were observed in rats. Mandipropamid was neither a reproductive toxicant in rats nor a developmental toxicant in rats or rabbits. It was neither genotoxic, carcinogenic nor neurotoxic.

A quantitative risk assessment for chronic and short-term dermal and inhalational exposure to mandipropamid was not conducted as no systemic effects were observed at the highest dose of 1000 mg/kg bw/d in a 28-day dermal toxicity study in rats; mandipropamid has a very low vapour pressure and is unlikely to present an inhalation hazard and there are no genotoxic, carcinogenic, reproductive, developmental or neurotoxic concerns with mandipropamid. Personal and protective equipment recommendations will only need to be specified for acute risks (e.g. slight skin and eye irritation).

Based on an assessment of the toxicology, it was considered that there should be no adverse effects on human health from the use of Revus® Fungicide when used in accordance with the label directions.

3.2 Summary of the Evaluation of Toxicological Studies

The toxicological database for mandipropamid, which consists primarily of toxicity tests conducted in laboratory animals, is quite extensive. 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 be generated 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. Such dose levels as the No Observable Effect Level (NOEL) are used to develop acceptable limits for dietary or other intakes (ADI and ARfD) at which no adverse health effects in humans would be expected.

The Office of Chemical Safety and Environmental Health (OCSEH) within the Department of Health and Ageing, Australia conducted the toxicology assessment of mandipropamid.

Toxicokinetics and Metabolism

Following a single oral dose of methoxyphenyl-U-14C- mandipropamid, absorption from the GI tract was 67-74% at 3 mg/kg bw and 30-45% at 300 mg/kg bw in rats. The extent of absorption was similar between male and female rats, but more extensive at the low dose suggesting saturation at the high dose level. The time to achieve maximum plasma concentration (Tmax) was determined to be 8.5 hr for males and 4.5 hr for females following a single oral administration of 3 mg/kg bw methoxyphenyl-U-14C- mandipropamid, while at 300 mg/kg bw it was 24 hr for males and 10 hr for females. Recovery of radioactivity following a single oral dose of 3 or 300 mg/kg bw radio-labelled mandipropamid was 88-98% by day 7, with most of the dose eliminated by 48 hours. The predominant route of elimination was faecal, with elimination also seen in urine to a lesser extent. The percentage of urinary excretion by males for both doses was less than females, and vice versa for faecal elimination. There was also evidence of enterohepatic circulation, with 55-73% of a 3 mg/kg bw dose detected in the bile of bile duct cannulated rats over 48 hr, though only 22-28% was detected in the bile at 300 mg/kg bw. The liver had highest concentration of radioactivity at all measurement times. Identified compounds accounted for 77-83% of administered dose after 96 hr in urine and feaces. Major metabolic transformations of the parent compound involved the loss of one or both propargyl groups followed by glucuronidation and O-demethylation.

In several dermal absorption studies, dermal absorption factors of 0.5% for the undiluted formulation and 0.1% and 0.2% for the two proposed spray strength dilutions (40mL product/100L of water and 60 mL product/100 L water) were obtained.

Acute toxicity studies

Mandipropamid had low acute oral (LD_{50} >5000 mg/kg bw, no deaths), dermal (LD_{50} >5050 mg/kg bw, no deaths) and inhalation toxicity (4-hr LC_{50} >5101 mg/m^3, no deaths) in rats. It was a slight skin and eye irritant in rabbits but was not a skin sensitiser in guinea pigs.

The product Revus® Fungicide containing 250 g/L mandipropamid as the active ingredient had low acute oral (LD_{50} >5000 mg/kg bw, no death), dermal (LD_{50} >5000 mg/kg bw, no deaths) and inhalation toxicity (LC_{50} >4890 mg/m^3, no deaths) in rats. It was a slight skin and eye irritant in rabbits but was not a skin sensitiser in guinea pigs.

Short term and subchronic toxicity studies

Repeat dose studies in mice, rats and dogs showed that the liver was the main target organ. In rats and dogs, altered liver enzyme activities were observed. Liver weights were commonly increased in all three species and histopathological changes, specifically hepatocellular hypertrophy in rats and increased pigment in dogs, were noted suggesting that this is an adaptive effect and is likely due to increased requirements for xenobiotic metabolism in the liver. Increased kidney weights observed in rats without corroborative gross morphological, histopathological or clinical chemistry findings may be due to increased requirements for renal excretory activity.

Long term toxicity and carcinogenicity studies

No evidence of an increased incidence of neoplasia was observed in chronic studies in mice and rats. In a range of in vitro and in vivo assays, mandipropamid was not mutagenic and/or clastogenic.

The renal toxic effects of mandipropamid were noted by histological findings in a chronic rat study, where increases in the incidence and severity of chronic progressive nephropathy (CPN) were seen, particularly in male rats. These renal effects were not evident in mice or dogs. Because CPN is a rodent-specific effect and there is no direct correlation between rat CPN and human renal disease, increased risks of potential renal tubule tumour formation due to an exacerbation of CPN by mandipropamid is unlikely to be relevant for human health risk assessment.

Reproduction and Developmental Studies

In a two-generation rat reproduction study, the only parental effect was increased liver and kidney weight. No effects on reproduction were observed. Decreased pup body weight and increased liver weight observed in both sexes were considered to be a secondary non-specific consequence of maternal toxicity.

There was no evidence of teratogenicity or indications of increased neonatal sensitivity effects on fertility in the developmental and reproduction toxicity studies. In the rat and rabbit developmental toxicity studies, no maternal or developmental effects were observed at the OECD Test Guideline 414 limit dose of 1000 mg/kg bw/d.

Genotoxicity Studies

In a range of in vitro and in vivo assays, mandipropamid was not mutagenic and/or clastogenic.

Neurotoxicity Studies

No neurotoxic effects were noted in rats after exposure to mandipropamid.

3.3 Public Health Standards

Poisons Scheduling

The National Drugs and Poisons Schedule Committee (NDPSC), now the Advisory Committee on Chemicals Scheduling (ACCS), considered the toxicity of the product and its active ingredients and assessed the necessary controls to be implemented under states' poisons regulations to prevent the occurrence of poisoning.

At its 58th meeting, on 16-17 February 2010, the NDPSC agreed, based on its acute toxicity profile, to include mandipropamid in Schedule 5 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP), now the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

NOEL/ADI /ARfD

The Acceptable Daily Intake (ADI) is that quantity of an agricultural compound which can safely be consumed on a daily basis for a lifetime and is based on the lowest NOEL obtained in the most sensitive species. This NOEL is then divided by a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals. The ADI for mandipropamid was established at 0.05 mg/kg bw/day based on a NOEL of 5 mg/kg bw/day in a 12-month study in dogs and applying a safety factor of 100.

The acute reference dose (ARfD) is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated event. The ARfD is derived from the lowest NOEL as a single or short-term dose which causes no effect in the most sensitive species of experimental animal tested, together with a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

Establishment of an ARfD is not necessary because mandipropamid has no significant toxicity after a single or few doses.

4 RESIDUES ASSESSMENT

4.1 Introduction

Revus® Fungicide is a suspension concentrate formulation intended for control of downy mildew in wine and table grapes. As part of the residues assessment for mandipropamid, plant and animal metabolism studies, supervised residue trials, crop rotation studies, processing studies, and trade aspects were considered and summaries are provided below.

4.2 Metabolism

Metabolism data for ^{14}C-labelled mandipropamid in grapes was provided. Small plots of grapevines were treated with multiple foliar applications (at either 30 or 90 g ai/100 L) of mandipropamid labelled with ^{14}C at either the methoxyphenyl or chlorophenyl rings. Samples of leaves and fruit were collected 0, 14 and 28 days after the last application for the 30 g ai/100 L plots and 28 days after the last application for the 90 g ai/100 L plots.

By far the most significant residue in grapes by 28 days after the final application was the parent compound, which comprised around 60% of the total radioactive residue (TRR). Other metabolites (>0.01 mg/kg parent equivalents) were identified, involving loss of the propargyl and methyl groups. The metabolism study was conducted using applications at twice the spray concentration proposed for the label (15 g ai/100 L), and with twice the maximum number of applications proposed for the label (3 per season). Scaling the residues observed for application rate and number of applications means that no component other than the parent compound is likely to be observed in grapes at >10% of the residue and/or above 0.01 mg/kg. Further, given that the proposed use pattern in Australia will involve harvest around 90-120 days rather than 28 days after the final application, total residue levels are expected to have decreased even further. In addition, the Office of Chemical Safety has advised that only mandipropamid should be considered toxicologically significant for the purpose of establishing a residue definition for dietary risk.

Therefore, a residue definition of parent compound only is supported for plant commodities for enforcement and dietary risk purposes.

Metabolism data was provided for ^{14}C-labelled mandipropamid in lactating goats. Two goats were dosed daily for 7 days with mandipropamid labelled with ^{14}C at the chlorophenyl ring by orally administering gelatine capsules containing 45 mg of the labelled compound. Two other animals were similarly dosed for 7 days with mandipropamid labelled at the methoxyphenyl ring. Urine and faeces were collected from the cages every 24 hours in the afternoon. Milk was collected twice daily in the morning and afternoon. Milk and excreta were collected from the day prior to commencing dosing until the day of sacrifice. The day after the seventh dose, the animals were sacrificed. Samples of leg muscle, omental fat, peri-renal fat, kidney, liver, bile, gastrointestinal tract and tenderloin were collected. The two types of muscle were combined, as were the two types of fat.

Levels of total radioactive residue in goat muscle were <0.01 mg/kg, and as a result, residues in muscle were not further investigated. For milk and fat, the only component identified was the parent compound.

Parent compound was not detected at all in kidney for either label, while in liver it was only a minor component (0.8-1.4% of the TRR, or 0.0038-0.0065 mg/kg) of the radioactive residue. In kidney, the predominant metabolite was NOA 458422 (mandipropamid methoxyphenyl-despropargyl), comprising 15.0-17.7% of the TRR. Other metabolites in kidney were CGA 380775 (*bis*-despropargyl mandipropamid; 5.8-9.3% of the TRR), CGA 380778 (mandipropamid mandelamide-despropargyl; 5.6% of the TRR) and SYN 518495 (mandipropamid mandelamide-despropargyl desmethyl; 3.3-6.5% of the TRR).

In liver, NOA 458422 was one also of the metabolites (5.3-5.8% of the TRR). Other components were SYN 521195 (mandipropamid desmethyl; 2.2-7.3% of the TRR) and CGA 380775 (3.4-3.6% of the TRR).

Detectable residues of mandipropamid and its metabolites are not likely to be found in animal commodities, therefore a residue definition of parent compound only is supported for animal commodities (see section 4.7: Animal Commodity MRLs for further details).

The following residue definition is therefore proposed for both plant and animal commodities, for the purposes of both enforcement and dietary risk assessment:

Mandipropamid

4.3 Analytical methods

Determination of mandipropamid residues in plant commodities

A method was developed and validated for analysis of mandipropamid in tomato fruit, puree and juice, cucumber, grapes, wine, raisins, grape pomace, potatoes, spinach, melon peel and flesh, onions, leeks, capsicum, wheat straw, rape seed and orange. Samples were extracted with acetonitrile/water. Clean up was achieved using solid phase extraction, followed by LC/MS/MS analysis.

The method was validated with limits of quantitation (LOQs) of 0.01 mg/kg for representative plant commodities. Recoveries were conducted with fortification at concentrations of 0.01 or 0.1 mg/kg and ranged from 73-106%.

Determination of residues of mandipropamid in animal tissues

A method was presented for determination of mandipropamid in meat, offal, milk and eggs. Samples were extracted using acetonitrile and water, followed by a clean-up step by solid phase extraction. Analyses were conducted using LC/MS/MS. Recoveries were determined by fortification of samples at 0.01 or 0.1 mg/kg, and were, for mandipropamid: 84-104% in milk, 85-90% in egg, 84-96% in beef muscle, 80-97% in beef fat, 81-90% in beef liver, 73-103% in beef kidney, and 81-87% in chicken muscle, 77-86% in chicken fat, and 81-92% in chicken liver. The LOQ is 0.01 mg/kg.

The methods are suitable for the proposed purposes and are acceptable.

4.4 Residue definition

Based on the results of the submitted metabolism studies and toxicological advice from the Office of Chemical Safety and Environmental Health, the following residue definition is recommended for mandipropamid for the purposes of dietary exposure assessment and for compliance and monitoring:

COMPOUND	RESIDUE DEFINITION
Mandipropamid	Mandipropamid

4.5 Storage stability

Stability over 12 months storage at -20 °C was tested for mandipropamid residues in a range of samples, including tomatoes, tomato paste, grapes, grape juice, potatoes, potato flakes, lettuce, cucumber, wheat grain, straw and forage, and soybean grain, meal, hulls and oil. With a few exceptions (lettuce after 6 months storage, wheat grain after 3 and 12 months storage, and wheat straw after 6 months storage), all storage recoveries corrected for the concurrent procedural recovery were within the generally accepted limits of 70-120%. Mandipropamid residues in all samples, including grapes and grape juice, are stable on storage at -20 °C for 12 months.

4.6 Residue trials

The proposed use pattern in grapes is up to three dilute foliar applications of mandipropamid using a spray concentration of 10-15 g ai/100 L. Applications are to be made at 10-21 day intervals with no applications after the end of flowering (BBCH growth stage 69). A withholding period is not required when the product is used as directed.

Eight Australian trials for mandipropamid in grapes were provided, including 2 or 3 foliar applications prior to the end of flowering at 1x and 2x the proposed spray concentration, with the last application at a range of growth stages from BBCH 57 to 69. For the trials at 1x the spray concentration with the last application at BBCH 69 (end of flowering), in line with the proposed use pattern, residues in mature grapes were 0.04, 0.05, 0.06 (2), 0.08, 0.11, and 0.17 mg/kg. An MRL of 0.3 mg/kg is therefore recommended for mandipropamid in grapes.

Processing studies

Processing studies were supplied for grapes. The following processing factors were determined:

COMMODITY	PROCESSING FACTOR (FROM THE RAW COMMODITY)
Grape juice (Australian trials)	0.24, 0.25, 0.27, 0.33 (3), 0.5 (3), 0.55, 0.6 (2), 0.63, 0.64, 0.67 (4), 0.75, 1 (mean = 0.53)
Grape juice (US trials)	0.19 (2), 0.41, 0.69 (mean = 0.37)

COMMODITY	PROCESSING FACTOR (FROM THE RAW COMMODITY)
Dried grapes (US trials)	2.2, 3.9, 4.4, 8.8 (mean = 4.8)
Grape pomace (dry; Australian trials)	6.1, 6.4 (2), 7.2, 8.4, 8.8, 11 (2), 12, 13 (3), 14, 18, 19 (2), 20, 22 (2), 23 (mean = 14)
Wine (Australian trials)	<0.06, <0.09, <0.13, <0.17 (4), 0.18, <0.2 (2), <0.25, 0.27, <0.33 (6), 0.38, <1 (mean = 0.27)
Wine (US trials)	0.97, 1, 1.5, 2.9 (mean = 1.6)

Processing of grapes into raisins was only undertaken for the US residues trials. The raisin processing factors were 2.2, 3.9, 4.4 and 8.8. Multiplying the highest processing factor (8.8) by the grape highest residue (0.17 mg/kg) gives an HR-P of 1.50 mg/kg. Therefore, an MRL of 2 mg/kg is proposed for DF 0296: dried grapes.

Grapes were processed into juice for both the Australian and US residues trials. Processing factors for juice ranged from 0.19 to 0.69 for the US trials and 0.24-1 for the Australian trials. Residues are therefore not expected to concentrate in grape juice, and the MRL for grapes accommodates the presence of residues in grape juice.

In the Australian trials, wine processing factors ranged from <0.06 to <1, indicating that mandipropamid residues do not concentrate in wine. For the US trials however, the processing factors were 0.97, 1, 1.5 and 2.9. This may be a consequence of the shorter withholding period resulting in residues being less conjugated and bound than those in the Australian grapes harvested at longer intervals after application. More tightly bound residues would be more likely to finish up in the pomace than in wine. Therefore, the Australian processing factors are a more realistic representation of the likely fate of residue in Australian grapes than the figures from the US trials. It should be further noted that 20 determinations of processing factors were made in the Australian trials, against four from the US trials. As the highest processing factor for Australian wine was <1, it is unlikely that mandipropamid residues in grapes treated in accordance with the proposed GAP will concentrate in wine. Multiplying the highest processing factor for which residues were found in wine (0.38) by the highest grape residue (0.17 mg/kg) yields a wine HR-P of 0.065 mg/kg, well below the proposed MRL of 0.3 mg/kg. Therefore, the grape MRL accommodates the presence of residues in wine.

Animal feeds

Evaluation of the processing studies for grapes showed that mandipropamid residues could concentrate in grape pomace (see the above discussion on processing). The following entry in Table 4 of the MRL Standard is recommended: grape pomace (dry): 5 mg/kg.

Crop rotation

No rotational crop studies were provided with the application. Grapes are not a rotational crop, therefore rotational crop residue and metabolism studies are not required for registration of the use of mandipropamid on grapes.

4.7 Animal commodity MRLs

The dietary intake of mandipropamid by cattle and poultry consuming treated grape pomace is estimated in the tables below.

Cattle - 500 kg bw, 20 kg DM/day

FEED GROUP	COMMODITY	% IN DIET	FEED INTAKE	RESIDUE, mg/kg	% DM	LIVESTOCK DIETARY EXPOSURE		
						mg/ANIMAL	ppm	mg/kg bw
By-products	Grape pomace	20	4	3.91	100	15.64	0.78	0.031

A cattle feeding study was not supplied with the application. A metabolism study in lactating goats was conducted. In this study, the doses ranged from 0.875-0.956 mg/kg bw/day, well above the calculated dose for cattle, although it is noted that the goats were only fed for 7 days as opposed to the standard 28 days for a feeding study. However, the milk residues peaked on day 3 of the study, indicating that further residue accumulation in tissues or milk was unlikely.

The likely maximum feeding level for cattle consuming grape pomace, the only livestock feed likely to result from use of the proposed products, is 0.031 mg/kg bw/day. This is well below the doses in the metabolism study (0.875-0.956 mg/kg bw/day). Scaling the residues of individual components to the expected maximum feeding level in cattle shows that no individual component of the residue is likely to be detectable in commodities from animals fed grape pomace. The highest individual metabolite residue in the goat metabolism study was 0.0351 mg/kg, for SYN 521195, in the liver of the animal given chlorophenyl labelled mandipropamid. In fat, only parent compound was identified, at a maximum level of 0.0187 mg/kg (equivalent to 77.4% of the TRR). Multiplying these figures by 0.031/0.875 (the likely maximum feeding level in cattle divided by the lowest feeding level in the goat study) gives expected maximum individual residue component concentrations of <0.01 mg/kg in liver and in fat, below the LOQ for mandipropamid or its metabolites in animal tissues.

Detectable residues of mandipropamid or any metabolite are therefore unlikely to be found in the muscle, fat, milk or offal of any mammalian livestock fed treated grape pomace. Further, it should be noted that a conservative approach was taken with the dietary burden calculation, with the highest residue for grape pomace, rather than the STMR, being used in the calculations. Therefore, MRLs at the LOQ (0.01 mg/kg) are supported for milk, mammalian meat (in the fat) and mammalian edible offal.

Grape pomace is not commonly used as a feed for poultry. Therefore, there is unlikely to be a dietary burden of mandipropamid in poultry feed as a result of registration of products containing mandipropamid for use in vineyards. As a consequence, it is proposed to establish MRLs for mandipropamid in poultry meat [in the fat], poultry edible offal, and eggs at 0.01 mg/kg, which is the validated limit of quantitation for mandipropamid in animal tissues including chicken muscle, fat, liver and eggs.

Based upon the metabolism studies, livestock dietary burden calculation, and the stockfeed residues data, the following animal commodity MRLs are recommended: edible offal [mammalian] (*0.01 mg/kg); eggs (*0.01 mg/kg); meat [mammalian] (in the fat) (*0.01 mg/kg); milks (*0.01 mg/kg); poultry, edible offal of (*0.01 mg/kg); and poultry meat (in the fat) (*0.01 mg/kg).

4.8 Spray drift

Spray drift modelling shows the risk of drift from vineyard applications onto adjacent pasture resulting in detectable residues of mandipropamid in meat or dairy products is very low. No-spray zones are not required to be included on product labels for the purposes of trade.

4.9 Bioaccumulation potential

Mandipropamid has an octanol/water partition coefficient ($log_{10}P_{OW}$) of 3.2 at 25 °C. In the goat metabolism study, total radioactive residues (TRR) in fat were 0.016 mg/kg for the ^{14}C-chlorophenyl labelled mandipropamid and 0.024 mg/kg for the ^{14}C-methoxyphenyl label. TRRs for muscle were 0.005 mg/kg for both labels. In fat, 75.1-77.4% of the TRR was determined to be parent compound. Residues in muscle were not identified due to the low levels present.

Given the $log_{10}P_{OW}$ of mandipropamid (>3), and its clear tendency to partition into fat rather than muscle as shown in the goat metabolism study, residues of mandipropamid are designated as fat soluble. MRLs for mandipropamid in mammalian and poultry meat have therefore been proposed to apply to fat.

4.10 Estimated dietary intake

The chronic dietary intake risk for mandipropamid has been assessed. The ADI for mandipropamid is 0.05 mg/kg bw/day, based upon a NOEL of 5 mg/kg bw/day and a 100-fold safety factor. The NEDI calculation is made in accordance with WHO Guidelines[2] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for mandipropamid, calculated using the animal commodity MRLs and the STMR and STMR-P for grapes and dried grapes respectively is equivalent to 0.3% of the ADI. DIAMOND Modelling[3] of chronic dietary exposure is also performed on new chemicals. The DIAMOND model estimated the chronic dietary exposure of mandipropamid as 3.6% of the ADI for the general population, using MRLs, and 0.46% using Supervised Trial Median Residue (STMR) values where available.

There is no acute reference dose (ARfD) for mandipropamid, as it was determined to be unnecessary given the absence of an identified short term hazard. Hence NESTIs cannot be calculated. It is concluded that short term intake of mandipropamid at the levels expected in practice is unlikely to be a hazard to people.

It is concluded that the dietary exposure to mandipropamid is low and the risk from residues in food is acceptable when *Revus® Fungicide* is used according to label directions.

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2 Guidelines for predicting dietary intake of pesticide residues, WHO, 1997.

3. DIAMOND: The Diamond Modelling Of Nutritional Data is a computer dietary modelling program based upon statistical software that is used by FSANZ.

4.11 Recommendations

The following amendments to the MRL Standard are recommended in relation to the proposed use of Revus® Fungicide:

Table 1

COMPOUND	FOOD		MRL (mg/kg)
ADD:			
Mandipropamid	DF 0269	Dried grapes	2
	MO 0105	Edible offal (mammalian)	*0.01
	PE 0112	Eggs	*0.01
	FB 0269	Grapes	0.3
	MM 0095	Meat (mammalian) [in the fat]	*0.01
	ML 0106	Milks	*0.01
	PO 0111	Poultry, edible offal of	*0.01
	PM 0110	Poultry meat [in the fat]	*0.01

*MRL set at the limit of quantitation.

Table 3

COMPOUND	RESIDUE DEFINITION
ADD:	
Mandipropamid	Mandipropamid

Table 4

COMPOUND	ANIMAL FEED COMMODITY		MRL (mg/kg)
ADD:			
Mandipropamid			
	AB 0269	Grape pomace, dry	5

The following withholding periods are required in conjunction with the above MRLs:

HARVEST WITHHOLDING PERIOD

Grapes: Withholding period not required when used as directed.

GRAZING WITHHOLDING PERIOD

Vineyards: Do not graze or cut for stock food.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported and main destinations

Some of the commodities of interest in connection with the proposed products, namely grapes (including dried grapes and wine), mammalian and poultry meat and offal, eggs, and dairy produce are considered to be major Australian export commodities.

Australian Table Grape Exports in 2007/08 (Australian Bureau of Statistics)

DESTINATION	VALUE, $ MILLION
Hong Kong	29.340
Indonesia	16.775
Thailand	12.587
Singapore	7.993
Malaysia	7.208
Vietnam	5.319
New Zealand	4.536
United Arab Emirates	3.667
Taiwan	3.325
Bangladesh	2.036
Sri Lanka	1.379
Other	6.346
TOTAL	100.511

Australian Wine Exports in 2007/08 (Australian Commodity Statistics 2008)

DESTINATION	VALUE, $ MILLION
Canada	258.9
China	60.5
Germany	49.2
Hong Kong	33.5
Ireland	69.2
Japan	48.0
Netherlands	70.6
New Zealand	83.9
Singapore	45.3
Sweden	40.8
Switzerland	15.4
Thailand	13.2
United Kingdom	876.5
United States	741.0
Other	250.6
TOTAL	2656.8

Exports of dried vine fruit from Australia are of minor importance in comparison with wine and table grapes, with exports of 4.9 kilotonnes in 2007/08 being worth $13 million.

5.2 Overseas registration status

Codex MRLs have been determined for mandipropamid in grapes and dried grapes (see table below).

Mandipropamid products are registered for use on grapes in Korea, Slovenia, Croatia, Tunisia, Turkey, Austria and Switzerland. Some MRLs are established for grapes and grape products (see table below).

The following relevant overseas MRLs have been established or proposed:

Overseas MRLs/tolerances for mandipropamid in grapes and grape products

COUNTRY/STATUS	COMMODITY	TOLERANCE, mg/kg	REFERENCE
Codex	Grapes	2	Codex Pesticide Residues in Food online database (www.codexalimentarius.net)
	Dried grapes	5	
Austria	Grapes	1	Applicant's supplied Part 5B.
EU (temporary)	Grapes (wine and table)	2	
Korea	Grapes	5	
Slovenia	Grapes	2	
Switzerland	Grapes	2	
USA	Grapes	1.4	
	Grapes, raisins	3	

Overseas animal commodity MRLs for mandipropamid

COUNTRY	COMMODITY	TOLERANCE, mg/kg
EU (temporary)	Meat (swine, bovine, sheep, goat, horse, ass, mule, hinny, other farm animals)	*0.02
	Fat (swine, bovine, sheep, goat, horse, ass, mule, hinny, poultry, other farm animals)	*0.02
	Poultry meat	*0.02
	Milk	*0.02
	Liver (swine, bovine, sheep, goat, horse, ass, mule, hinny, poultry, other farm animals)	*0.02
	Kidney (swine, bovine, sheep, goat, horse, ass, mule, hinny, poultry, other farm animals)	*0.02
	Other edible offal (swine, bovine, sheep, goat, horse, ass, mule, hinny, poultry, other farm animals)	*0.02
	Eggs (chicken, duck, goose, quail, other birds)	*0.02

Potential risk to trade

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

The use of Revus® Fungicide may result in finite residues of mandipropamid in grapes, dried grapes and wine. There is a theoretical risk to trade in treated grapes, and dried grapes and wine produced from treated fruit. Proposed Australian mandipropamid MRLs for grapes and dried grapes are lower than those MRLs that have been identified in other markets, where they are established. For instance, the Codex mandipropamid MRLs for grapes and dried grapes are 2 mg/kg and 5 mg/kg respectively, compared with those proposed for Australia of 0.3 mg/kg and 2 mg/kg.

Of the major international markets for Australian grapes, relevant MRLs are not known to be established in Bangladesh, Hong Kong, Indonesia, Malaysia, New Zealand, Singapore, Sri Lanka, Taiwan, Thailand, the United Arab Emirates and Vietnam.

Of the major international markets for Australian wine, relevant MRLs are not known to be established in Canada, China, Hong Kong, Japan, New Zealand, Singapore, and Thailand.

No information is currently available on destinations of Australian exports of dried grapes.

Finite residues of mandipropamid are not expected in animal commodities as a result of the proposed use of Revus® Fungicide on grape vines.

5.3 Conclusions

The proposed use of Revus® Fungicide may result in finite residues of mandipropamid in grapes, dried grapes and wine. Comment is sought on the potential for the proposed use of Revus® Fungicide to unduly prejudice Australian Trade and the ability of industry management systems to mitigate that risk.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Health hazards

Mandipropamid had low acute oral, dermal and inhalational toxicity in rats. The compound was a slight skin and eye irritant in rabbits but not a skin sensitiser in guinea pigs. Mandiropamid is not listed on the Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2009). With the available toxicology information, OCSEH has determined that mandipropamid is not classified as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

The formulated product, containing 250g/L mandipropamid had low acute oral, dermal and inhalational toxicity in rats. It was a slight skin and eye irritant in rabbits but not a skin sensitiser in guinea pigs. Based on the product toxicology information and concentrations of mandipropamid and other ingredients in the product, Revus® Fungicide is not classified as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

6.2 Formulation, packaging, transport, storage and retailing

Revus® Fungicide will be manufactured overseas and imported into Australia as a liquid in high-density polyethylene containers. It will be available in the following pack sizes: 1L; 5 L; and 10 L. Transport workers and store persons will handle the packaged products and could only become contaminated if packaging is breached.

6.3 Use pattern

Revus® Fungicide is a new fungicidal product, which will be used for the control of downy mildew in grapevines. It contains 250 g/L mandipropamid and the formulation is a suspension concentrate (SC).

6.4 Exposure during use

Farmers and their employees will be the main users of the products. The users may be exposed to the product when opening containers, mixing/loading, application and cleaning up spills and equipment. The main route of exposure to the product/spray will be dermal and inhalation, although ocular exposure is also possible.

6.5 Exposure during re-entry

There is no risk associated with re-handling associated with this product.

6.6 Recommendations for safe use

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

6.7 Conclusion

The registration of Revus® Fungicide, containing 250 g/L of mandiopropamid is supported.

Revus® Fungicide can be used safely if handled in accordance with the instructions on the product label. Additional information is available on the product MSDS.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

Syngenta Crop Protection Limited have applied for registration of the new agricultural product Revus® Fungicide, containing 250 g/L of the new active constituent mandipropamid as a suspension concentrate (SC) formulation, for use in the control of downy mildew (*Plasmopara viticola*) in grapes.

A comprehensive data package was provided for assessment of mandipropamid. The EU assessment report for the active constituent and use of an identical product on grapes in Europe was used to assist in the preparation of this report.

7.2 Environmental fate

Comments on physicochemical properties - Refer to Section 2 Chemistry

Mandipropamid is slightly soluble in water (solubility 0.1–10 mg/L), very slightly volatile (< 1×10^{-4} Pa) and very slightly volatile from water (non-dimensional Henry's Law Constant H < 1×10^{-5}). The molecule does not dissociate at environmentally relevant pH. Based on the n-octanol/water partition coefficient (K_{OW} of 1600, log K_{OW} = 3.2), mandipropamid has potential to bioaccumulate and is expected to have low soil mobility.

Hydrolysis

In a laboratory study conducted to standard guidelines, there was no hydrolysis of ^{14}C-labelled mandipropamid at 25°C (32 days) or 50ºC (7 days) at pH 4 (50ºC only), 5, 7 and 9.

Photolysis

In laboratory studies conducted to standard guidelines, the aqueous photodegradation of ^{14}C-labelled mandipropamid (labelled separately in either ring) was investigated in sterile pH 7 buffer and sterile natural water at 25°C under continuous illumination using filtered xenon arc lamp simulated sunlight sources. Mandipropamid was photolysed with a degradation half-life of 0.59, 0.85, 1.40 and 6.73 days, with the rate of degradation differing between different types of exposure vessel i.e.'very rapidly degradable' [DT_{50} under continuous illumination < 1 days] to 'fairly degradable' [DT_{50} = 4-10 days], based on Mensink *et al* ratings). These values correspond to half-lives of approximately 2 days Summer Sunlight Equivalent 30-50ºN in the top layer of an aqueous system. However, calculated half-life values from a further study are in the range 30-56 days in summer based on the quantum yield at 300 nm. A large number of degradates were observed at minor concentrations that were further converted to many polar fractions, with no degradates observed at > ~10% applied radioactivity (AR), and with photo-oxidation to carbon dioxide at about this level.

In soil photolysis studies conducted to standard guidelines, radiolabelled mandipropamid was applied to thin layers of soil and irradiated using filtered xenon arc lamp simulated sunlight sources. Mandipropamid was stable in samples kept in the dark, but degraded with half-lives of 14.9-18.4 days (dry soil) and 19.4-25.2 days (moist soil) continuous irradiation, equivalent to 20.1-30.7 days (dry soil) and 27.5-40.2 days (moist soil)

Summer Sunlight Equivalent at 40ºN. A range of metabolites was formed, all < 10% AR and all but the metabolite CGA 380775 < 5% AR, and most metabolites common to the soil metabolism studies.

Based on its vapour pressure and Henry's Law constant, mandipropamid is not expected to volatilise, but the half-life of mandipropamid in the atmosphere for reaction with hydroxyl radicals is estimated to be ~1.4 hours.

Soil metabolism

The degradation of mandipropamid was evaluated using ^{14}C-labelled mandipropamid (at three different parts of the molecule) under laboratory conditions in a total of six studies with five non-sterile soils (1 US soil and 4 European soils). Aerobic and/or aerobic/anaerobic soil metabolism studies were conducted according to standard European or US EPA guidelines (incubation duration 120 and 365 days, incubation temperature 20ºC and 25ºC, respectively, differing soil moisture contents), and effects of incubation at lower temperature, low soil moisture content and differing application rates were also investigated. The soils covered a range of soil textures (loamy sand to silty loam), soil pH (5.6–7.3) and organic carbon content (0.5-3.5%).

From a total of 25 studies, 15 can be considered to have been performed under comparable test conditions (aerobic, 19-25°C, 75% pF2 / pF2 / 40% WHC, soil concentrations 0.2-0.9 mg ac/kg). DT_{50} values for these studies ranged from 12.6-93 days (DT_{90} = 41.7-309 days) with SFO (single first order kinetics). Thus mandipropamid was 'readily degradable' (DT_{50} < 20 days) to 'slightly degradable' (DT_{50} = 60-180 days), based on Mensink *et al* ratings. However, in general the data were better fitted by FOMC (first order multicompartment kinetics), giving relatively long DT_{90} values (DT_{50} = 11.3-91.6 days, DT_{90} = 53.4-967 days). Relative to the comparable study under standard aerobic conditions, degradation was slower under anaerobic conditions (DT_{50} = 158-179 days), with lower temperature (DT_{50} = 159 days at 10ºC), drier soil (DT_{50} = 149 days at 30% field capacity) and increasing application rate (eg DT_{50} increasing from 38.9 days at 0.2 g ac/kg soil to 131 days at 1.5 g ac/kg soil). The degradation rate also differed between the two enantiomers of mandipropamid (slower with the S-enantiomer than the R-enantiomer).

There were no major metabolites detected in any of the studies, and CGA 380778 was the only minor metabolite to exceed 5% AR. Significant $^{14}CO_2$ evolution occurred, reaching 12.3-56.4% AR under standard aerobic test conditions. The hypothesised degradation pathway involved the formation of a range of metabolites including CGA 380778 where the two rings present in the parent molecule were retained, followed by cleavage of the molecule to form chlorophenyl-ring metabolites, CO_2 and non-extractable residues in soil. The pathway was similar for the two enantiomers and for aerobic and anaerobic conditions.

Aerobic soil metabolism studies were also provided for five metabolites formed in laboratory soil and/or aquatic metabolism studies, in each case in 3 different soils (double ring metabolites CGA 380778, SYN 536638 and SYN 521195, and chlorophenyl ring metabolites SYN 500003 and SYN 504851, DT_{50} values respectively, 3.1-33.4 days, 15.7-32.5 days, 0.26-0.34 days, 1.5-4.0 days and 1.2-5.7 days).

Aquatic metabolism

The fate of mandipropamid in aquatic systems was evaluated in two different water/sediment systems at 20ºC in the dark under both aerobic and anaerobic conditions, with incubation continuing for 100-365 days depending on the radiolabel, system and whether conditions were aerobic or anaerobic. Whole system DT_{50}

values for these studies ranged from 5.9-25.9 days under aerobic conditions and 4.5-23.7 days under anaerobic conditions, showing little difference between aerobic and anerobic conditions. Thus mandipropamid is classified as 'readily degradable' (DT_{50} < 20 days) to 'fairly degradable' (DT_{50} = 20-60 days) in water/sediment systems, based on Mensink *et al* ratings. Mandipropamid was stable in water, but partitioned to sediment, where it degraded; DT_{50} from water to sediment = 0.69-14.1 days under aerobic conditions and 0.96-20.2 days under anaerobic conditions. Corresponding DT_{50}s for degradation in sediment = 4.4-7.7 days and 3.0-5.5 days.

Major metabolites detected included the two-ring metabolites SYN 521195 and SYN 539678 (in both water and sediment, but predominantly sediment) and the two chlorophenyl ring metabolites SYN 500003 and SYN 504851 (in both water and sediment). The latter reached very high levels, peaking at the end of incubation and higher under anaerobic conditions (maximum in whole system = 38.5% AR under aerobic conditions, 73.5% under anaerobic conditions). Significant $^{14}CO_2$ production occurred under both aerobic and anaerobic conditions, predominantly from the methoxyphenyl ring reaching 32.7-40.3% AR. The hypothesised degradation pathway involved the formation of metabolites where the two rings present in the parent molecule were retained, followed by cleavage of the molecule to form the two chlorophenyl-ring metabolites, and formation of CO_2 and non-extractable residues in sediment.

An outdoor pond aquatic metabolism study was also conducted. Under these conditions, where evidence indicated aqueous photolysis also contributed to degradation, the whole system DT_{50} values were 5.5-5.9 days. A similar metabolite pattern formed in this study, but SYN 500003 and SYN 504851 did not accumulate to the high levels found under laboratory conditions.

Mobility

Volatility: Studies with radiolabelled mandipropamid under laboratory conditions indicate that mandipropamid was not significantly volatilised from moist soil or leaf surfaces.

Soil mobility: Laboratory batch equilibrium studies with mandipropamid in four European soils and three US soils indicated $K_{OC\ ads}$ values of 405-1294 mL/g, i.e. medium to low mobility in soil (K_{OC} respectively in the range 150-500 and 500-2000). Similar evaluations for metabolites indicated that those retaining both rings also had low to medium mobility in soil, while the chlorophenyl ring metabolites SYN 500003 and SYN 504851 had very high mobility in soil (K_{OC} in the range 0-50).

Field dissipation

The rate of degradation of mandipropamid in field soils was determined in 10 trials in Europe at sites in Switzerland (rates 300 and 750 g ac/ha) and Germany, France and Spain (200 g ac/ha). Applications were made to bare soil or sparse grass cover, respectively maintained as bare soil or as grass cover. Calculated DT_{50} values ranged from 4.1-52.6 days (DT_{90} values 13.5-175 days) with SFO kinetics, but in several cases the data were better fitted by FOMC kinetics, giving much longer DT_{90} estimates (DT_{50} range 2.0-29.2 days, DT_{90} 47.9-481 days). Thus mandipropamid can be classified as 'readily degradable' to 'fairly degradable' under field conditions. The metabolite CGA 380778 was detected at low levels. Little downward movement of mandipropamid or CGA 380778 was detected.

A small confined outdoor plot study was also conducted, indicating DT_{50} and DT_{90} values of 27 days and 390 days, respectively (two compartment SFO kinetics). Transfer of mandipropamid into lower soil layers was negligible. A similar degradation pathway to that in the laboratory soil metabolism studies was indicated.

Bioaccumulation

Bioaccumulation studies with fathead minnow indicated ^{14}C-mandipropamid bioconcentration factors (BCFs) of 35-48 for whole fish and 164-184 for viscera/non-edible portions. Thus mandipropamid can be classified as 'slightly concentrating' (BCF < 100) in fish. Approximately 80% depuration from whole fish had occurred after 25 hours and almost complete elimination (99-100% in whole fish) after 8 days in both test concentrations.

Soil accumulation

Most of the DT_{90} values for mandipropamid in the field dissipation studies were less than 1 year, and in all cases the DT_{50} was < 30 days if the best fit to SFO or FOMC kinetics was used. Thus mandipropamid is not expected to accumulate significantly in soil. Based on the available information, DSEWPaC has estimated a worst case soil concentration of 1.32 mg ac/kg soil in the surface 5 cm after repeated years of application at the maximum proposed rate.

7.3 Environmental effects

In addition to mandipropamid, the toxicity of the proposed 250 g ac/L SC formulation was evaluated. Toxicity of a range of terrestrial and/or aquatic metabolites was also evaluated for a range of aquatic species and for earthworms. Studies were generally conducted to standard test guidelines (eg OECD and US EPA).

Birds

Mandipropamid is practically non-toxic to bobwhite quail and at most slightly toxic to mallard duck by acute oral exposure, and practically non-toxic to both species by short-term dietary exposure (acute oral LD_{50} > 2250 mg ac/kg bw for bobwhite quail, > 1000 mg ac/kg bw for mallard duck; 5 d dietary LC_{50} > 5620 ppm for both bobwhite quail and mallard duck). Reproduction studies indicated NOECs of 1000 ppm diet for both bobwhite quail and mallard duck.

Aquatic organisms

The concentration ranges which could be tested was affected by the solubility limits of mandipropamid and some of the tested metabolites in the test media. In most cases the results are expressed in terms of mean measured concentrations.

Fish: Based on a total of 7 studies conducted with rainbow trout, fathead minnow, common carp and sheepshead minnow, mandipropamid is moderately toxic to fish with acute exposure (96 h LC_{50} in the range 1-10 mg ac/L). The 96 h LC_{50} was 4.4 mg ac/L for rainbow trout, 8.63 mg ac/L for common carp, and 4.5 mg ac/L for sheepshead minnow. In the other studies the 96 h LC_{50} value exceeded the maximum concentration obtained (all in the range 2-6 mg ac/L). Limit tests at 100 mg formulation/L (resulting in a cloudy white dispersion) indicated that the proposed formulation was practically non-toxic to rainbow trout and common

carp (i.e. with a corresponding content of active constituent = ~25 mg ac/L). A 32 day early life-stage fathead minnow study indicated a NOEC of 0.5 mg ac/L and LOEC 1.0 mg ac/L. Thus mandipropamid is slightly toxic to fish with chronic exposure (NOEC = 0.1-1 mg ac/L).

96 h LC_{50}s for the metabolites CGA 380778, NOA 458422, SYN 500003 and SYN 504851 to rainbow trout were above the maximum concentration tested (all in the range 10-100 mg as/L, indicating at most slight toxicity to fish). In contrast, the 96 h LC_{50} for the metabolite SYN 536638 was 3.5 mg ac/L, i.e. moderately toxic and similar to mandipropamid.

Aquatic invertebrates: Mandipropamid is moderately to highly toxic to aquatic invertebrates with acute exposure (48 h EC_{50} = 7.1 mg ac/L for *Daphnia magna*, 96 h LC_{50} = 1.7 mg ac/L for mysid shrimp, and 96 h EC_{50} = 0.97 mg ac/L for eastern oyster). A limit test indicated that the proposed formulation is practically non-toxic to *Daphnia magna* (48 h EC_{50} > 100 mg formulation/L). In a 21 day reproduction study with *Daphnia magna* the NOEC was 0.28 mg ac/L and LOEC 0.87 mg ac/L. Thus mandipropamid is slightly toxic to aquatic invertebrates with chronic exposure (NOEC = 0.1-1 mg ac/L).

The 48 h EC50s for the metabolites NOA 458422, SYN 500003 and SYN 504851 to daphnids were above the maximum concentration tested (in the range 10-100 mg as/L or higher, indicating at most slight toxicity to daphnids). The 48 h EC_{50} for CGA 380778 was 55.9 mg ac/L (slightly toxic), while that for SYN 536638 was 4.2 mg ac/L, i.e. moderately toxic and similar to mandipropamid.

Algae and aquatic plants: Studies indicated that based on the toxicity results for biomass (area under the growth curve), mandipropamid can be classified as at most moderately toxic to algae and aquatic plants (not toxic up to its limit of solubility in the test medium). The species tested were a freshwater alga (*Pseudokirchneriella subcapitata* [formerly *Selenastrum capricornutum*]), a blue green alga (*Anabaena flos-aquae*), a fresh water diatom (*Navicula pelliculosa*), a marine diatom (*Skeletonema costatum*) and the freshwater duckweed *Lemna gibba*. A study with the proposed formulation indicated that it is slightly toxic to *Pseudokirchneriella subcapitata* (72 h EC_{50} = 15.3 mg formulation/L, equivalent to 3.7 mg ac/L).

E_bC50 (0-72 h) values for the metabolites CGA 380778, NOA 458422, SYN 500003, SYN 504851 and SYN 536638 to *Pseudokirchneriella subcapitata* were respectively, 14.1, 6.8, > 25, > 25 and > 5.5 mg ac/L. Corresponding ErC_{50} (0-72 h) values were 32.8, 28.8, > 25, > 25 and > 5.5 mg ac/L. Thus the metabolites ranged in toxicity from moderately to slightly toxic to algae.

Terrestrial invertebrates

Honey bees: Mandipropamid active constituent and the proposed 250 g ac/L SC formulation are very slightly toxic to bees by both acute oral and acute contact exposure (48 h acute oral and dermal LD_{50} > 200 µg ac/bee and > 858 µg formulation/bee).

Predators and parasites: Tier 1 rate/response laboratory studies using the 250 g ac/L SC formulation were provided for the cereal aphid parasitoid wasp *Aphidius rhopalosiphi* and the predatory mite *Typhlodromus pyri,* in both cases for mortality only (not repoduction). The 48-hour LR_{50} obtained for *A. rhopalosiphi* was 3308 mL formulation/ha (= 827 g ac/ha). The 7-day LR_{50} for effects of product formulation on mortality of *T. pyri* was above the highest treatment rate of 3600 mL formulation/ha (> 900 g ac/ha).

Field studies were conducted to examine effects on population development of *Typhlodromus pyri* in two vineyards in Germany, with four applications at 8-11 day intervals of the proposed 250 g ac/L SC formulation, totalling 870 g ac/ha, i.e. comparable to the maximum proposed use on grapevines in Australia. Multiple applications of the mandipropamid formulation had no significant effect on predatory mite population in either of the studies at any sampling date, whereas there were harmful effects on predatory mites from the reference product.

Soil macro-invertebrates: Mandipropamid active constituent and the proposed 250 g ac/L SC formulation are both very slightly toxic to the earthworm species *Eisenia foetida* (14 d LC_{50} > 1000 mg ac/kg dry soil [NOEC = 100 mg ac/kg soil] and > 1000 mg formulation/kg dry soil [NOEC = 1000 mg formulation/kg soil]). Tests with the metabolites CGA 380778, NOA 458422 and SYN 536638 also indicated 14 d LC_{50} values of > 1000 mg as/kg dry soil in each case. Earthworm reproduction studies indicated a 56 day NOEC of 32 mg ac/kg dry soil with the active constituent and 200 mg formulation/kg with the 250 g ac/L SC formulation (equivalent to 50 mg ac/kg dry soil). Tests with the 250 g ac/L SC formulation and the collembolan species *Folsomia candida* indicated a 28 d NOEC of 5 mg ac/kg dry soil. A litter bag study indicated that use in a similar fashion to that proposed on grapevines in Australia had no significant effects on organic matter decomposition and therefore on soil macroinvertebrates involved in that process.

Microorganisms

Soil respiration and nitrogen turnover: The effects of mandipropamid on soil non-target micro-organisms was examined in studies with mandipropamid applied at soil concentrations of 1.2 and 6.0 mg ac/kg soil dry weight (corresponding to application rates of 900 and 4500 g ac/ha retained in the surface 5 cm of soil). Deviations in carbon mineralisation and soil nitrogen transformation parameters from the control at the end of the test (28 days) were < 25%. Therefore mandipropamid is categorised as low risk to soil microflora (NOEC = 6.0 mg ac/kg soil dry weight).

Individual soil fungi/oomycetes: Soil fungi plate tests indicated that the NOEC to *Mucor circinelloides* var. *griseocyanlls*, *Marasmius oreades* and *Paecilomyces marquandii* was > 13.4 mg ac/kg dry soil, whereas the NOEC and EC50 for mycelium growth of *Phytophthora nicotianae* (a oomycete pathogenic species, as is the target organism, *Plasmopara viticola*) were 0.40 and 0.96 mg ac/kg dry soil, respectively.

Terrestrial plants

Non-guideline glasshouse studies were conducted with 6 standard test species using the proposed formulation. The NOEC for all species in a seedling emergence study (spray applied to soil post sowing) and the NOEC in a vegetative vigour study (spray applied to young seedlings) was 450 g ac/ha, the maximum rate tested. Tier II glasshouse studies conducted with 10 standard test species according to US EPA guidelines with the proposed formulation indicated a NOEC for all species in the seedling emergence study of 750 g ac/ha, and a NOEC for all species in the vegetative vigour study of 900 g ac/ha (in both cases the maximum rate tested).

7.4 Risk assessment

Syngenta Crop Protection Limited have applied for registration of the new agricultural product Revus® Fungicide (containing 250 g/L of the new active constituent mandipropamid) for control of downy mildew in grapes. A comprehensive data package was provided for assessment. The EU assessment report for the active constituent and use of an identical product on grapes in Europe was used to assist preparation of this report.

Revus® Fungicide will be applied by ground application only, therefore the risk assessment has considered application by orchard airblast sprayer. The maximum application rate for grapes using dilute spraying is 60 mL product/100 L water, which at a maximum anticipated spray volume of 1500 L/ha results in a rate of 225 g ac/ha. The label stipulates a maximum of 4 applications per year, with no more than 2 consecutive applications when applied alone and a minimum spray interval of 10 d (for resistance management reasons). As a worst case, a maximum cumulative application rate of 900 g ac/ha was considered, with 4 applications at successive 14 day intervals.

An acceptable risk to birds and mammals with acute or chronic exposure was indicated, based on worst case scenarios where 100% of the diet was obtained from contaminated feed.

For aquatic exposure, predicted concentrations in water in a 15 cm deep, 3 m wide pond downwind of the treated area were compared to endpoints for acute and chronic exposure. These were, respectively, the eastern oyster 96 h EC_{50} = 0.97 mg ac/L, and the daphnid 21 d NOEC = 0.28 mg ac/L. Concentrations resulting from repeat spraying were estimated assuming first order kinetics and a worst case DT_{50} for mandipropamid from water of 14.1 days and spray interval of 10 days. A risk to aquatic organisms was indicated with direct overspray to a 15 cm deep ppond on one or more occasions, thus direct overspray must be avoided. Evaluation of 10% spray drift to a 15 cm deep, 3 m wide pond downwind of the treated area indicated that a low risk to aquatic and benthic organisms would result, even with 4 repeated drift events at 10 day intervals. Evaluation using modelling with the APVMA Airblast – Vineyard scenario indicated that spray drift was well below 10% by 5 m downwind. Thus no Downwind No-Spray Zone to aquatic areas is needed to protect aquatic environments. Modelling also indicated that the risk to aquatic ecosystems from the run-off of mandipropamid is acceptable for both the aquatic and sediment compartments.

The risk to bees from direct exposure to the spray during application to vineyards was found acceptable based on acute toxicity endpoints (acute oral and contact LD_{50} > 200 µg ac/bee), and higher tier tests were not required. Tier I laboratory tests were available for the cereal aphid parasitoid wasp and a predatory mite, plus two vineyard field studies for predatory mites conducted under spray regimes corresponding with that proposed. Based on these studies, it is concluded that the risk to terrestrial invertebrate predators and parasites from the proposed use of mandipropamid on grapevines is acceptable.

Comparison of worst case predicted soil concentrations with acute and chronic exposure endpoints for earthworms and collembola indicated an acceptable risk, even after repeated long-term application. The risk to soil microorganisms from residues of mandipropamid was also found acceptable.

According to standard guideline tests, the product applied at the maximum proposed single application rate for use on grapevines or rates up to 3 × (emergence) or 4 × the single application rate had no significant

harmful effects on seedling emergence or early growth for a standard range of test species. Thus the risk to non-target terrestrial plants from direct spray or spray drift of Revus® Fungicide is acceptable.

The risk assessment determined that the chemical is unlikely to pose an environmental risk under the proposed use pattern and with the proposed environmental protection statements on the draft label, provided some amendments are made to update the label to current requirements.

8 EFFICACY AND SAFETY ASSESSMENT REVUS® FUNGICIDE

Grapevine Downy mildew is one of the most devastating of fungal diseases of grapevines and occurs world-wide. The fungus also can rapidly develop fungicide resistance, the most recent occurrence being in the Hunter Valley of New South Wales to the normally highly- effective fungicide Ridomil Gold Plus. As this is one of the few currently-registered fungicides which has been adopted as an industry standard for control of Downy Mildew of grapevines in Australia, it is imperative to obtain a product in a different chemical group which has high efficacy against the pathogen, before fungal resistance to Ridomil Gold Plus becomes widespread throughout Australia.

8.1 Proposed Product Use Pattern

It is proposed that Revus® Fungicide (250 g/L mandipropamid as a suspension concentrate) be used with a non-ionic wetting agent added, only if other products mixed with it indicate that a wetter should be used. The product is to be applied as a foliar spray at or before the time of appearance of the first symptoms of the target disease, with a pressurised boom spray unit fitted with the appropriate spray nozzles. Thus it is to be used primarily as a protectant.

8.2 Summary of Evaluation of Efficacy and Crop Safety

A total of 10 field trials on grapevines were established in New South Wales, Victoria and South Australia. Sites were selected in areas where the crops were commercially grown and where the target disease, Downy Mildew, was likely to occur. Spray application of the candidate fungicides were assessed for efficacy compared with industry standard fungicide/s currently recommended for control of that disease. The candidate used in the trials was assessed at the proposed label rates, and applied as directed on the draft label.

Trial design was suitable in all instances. Field trials were located at sites where there was a history of regular occurrence of the target disease. Weather conditions at most of the sites were suitable to ensure that the development of the disease progressed to levels suitable for efficacy evaluation of the candidate. Where primary infection did not establish at the beginning of the trial due to preceding dry weather, then artificial inoculation of two shoots per trial plot was suitably employed to establish useful levels of infection.

Nine trials were randomised complete block experiments, each with four replicates. These were undertaken on grape vines in Victoria (Yarra Valley and King Valley), NSW (Hunter Valley) and South Australia (Adelaide Hills) and included the grape varieties chardonnay, sauvignon blanc, pinot noir, semillion, and shiraz. A tenth trial compared the protectant activity and curative activity of the proposed product against inoculated vines in field situations and in a small glasshouse trial.

Application of trial fungicide treatments in the trials commenced before first symptoms of infection had appeared. This is consistent with the fact that the candidate's action is primarily that of a protectant, although it also has been shown in one trial to have some eradicative properties.

The formulation tested in field trials was as described in the application for registration of the product.

Application was done with either a motorised back-pack mister/blower or an air-shear sprayer fitted with a boom containing the appropriate spray nozzles. These operate on the same principles as modern commercial spray units.

The results of the grapevine trials submitted in the application for registration indicate that the candidate, when applied alone as directed, gave a reduction in disease incidence which varied from 24% to 100% which is at least equal to, or better than the industry standards. Similarly the use of the candidate gave control of disease severity which varied from 24% to 100%. Generally, the higher the level of disease incidence, the better was the disease control by the use of the candidate. As the candidate is in a different chemical group to the other fungicides registered to control Downy Mildew on grapevines, if it can be shown to give good disease control, its use, alternating with fungicides in other chemical groups would be especially valuable in reducing the possibility of fungicide-resistant strains of Downy Mildew from develop.

The information provided shows that the candidate has efficacy equal to or better than industry standards when used on grapevines for the control of the target pathogen.

Integrated Pest Management

The affect on terrestrial invertebrates including predatory mites indicates that the product has a low level of toxicity to those organisms and should have minimal impact on them where integrated pest management is being practiced, please refer to Section 7.3 above. A statement has been included on the label stating that the “product may be used where integrated pest management is being practised”.

Crop Safety

The information and data presented indicate that Revus® Fungicide is safe to use on grapevines when used as directed. No adverse symptoms were apparent on any of the grape varieties tested when applied at the re4commended label application rates.

Resistance Management

Mandipropamid belongs to the mandelic acid amine sub-group of the carboxylic acid amide fungicides. The Fungicide Resistance Action Committee (a specialist technical group of CropLife International) has classified mandipropamid as having the target site of cellulose synthase in cell wall biosynthesis. One other carboxylic acid amine (dimethomorph) is registered for use as a fungicide in Australia. Dimethomorph belongs a separate sub-group of the carboxylic acid amide fungicides. CropLife Australia Fungicide Resistance Management Review Group has designated an activity group for carboxylic acid amide fungicides (Group 40). It is proposed that the use pattern will be subject to a CropLife anti–resistance strategy. Restraints included on the proposed product label are consistent with the current CropLife Australia resistance management strategy for Group 40 fungicides.

8.3 Conclusion

The claim on the proposed label that the product Revus® Fungicide provides acceptable control of downy mildew on grapevines 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 Syngenta Crop Protection PTY Ltd for the registration of Revus® Fungicide is supported on efficacy and crop safety grounds when used in accordance with label instructions.

9 LABELLING REQUIREMENTS

CAUTION

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

DIRECTIONS FOR USE

Restraints:

DO NOT apply more than 3 sprays of REVUS per season.
DO NOT apply more than 2 sequential sprays of REVUS alone before applying at least the same number of sprays from a different resistance group.
DO NOT make REVUS alone the last spray of the season.
DO NOT apply with aircraft.
DO NOT graze vegetation in treated vineyards or cut for stock food.

Spray Drift Restraints:

DO NOT apply in vineyards when the wind speed is less than 3 or more than 20 kilometres per hour as measured 15 metres outside of the vineyard on the upwind side.
DO NOT apply during surface temperature inversion conditions at the application site.
DO NOT direct the spray above vines during airblast applications.
TURN OFF outward pointing nozzles at row ends and outer rows during airblast applications.

Users of this product **MUST make an accurate written record** of the details of each spray application within 24 hours following application and **KEEP** this record for a minimum of 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/situation and weed/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.)

Crop	Disease	Rate	Critical Comments
Grapes	**Downy Mildew** *Plasmopara viticola*	**Dilute spraying** 40 mL per 100 L of water **Concentrate spraying** Refer to the Application section	**This use is subject to a CropLife anti-resistance strategy.** Apply by dilute or concentrate spraying equipment. **Apply the same amount of product to the target whether applying this product by dilute or concentrate spraying methods.** Apply at 10-14 day intervals as part of a Downy Mildew control program before the first sign of infection. Use the shorter interval during periods of rapid growth or when conditions are more conducive to disease development. DO NOT apply later than end of flowering.

Crop	Disease	Rate	Critical Comments
		Dilute spraying 60 mL per 100 L of water **Concentrate spraying** Refer to the Application section	**This use is subject to a CropLife anti-resistance strategy.** Apply by dilute or concentrate spraying equipment. **Apply the same amount of product to the target whether applying this product by dilute or concentrate spraying methods.** Apply at 10-21 day intervals as part of a Downy Mildew control program before the first sign of infection. Use the shorter interval during periods of rapid growth or when conditions are more conducive to disease development. Spray intervals of more than 14 days should only be used once significant new growth has ceased. Begin spraying Revus within the recommended spray interval of the previous Downy Mildew fungicide. DO NOT apply later than end of flowering.
		Dilute spraying 40 mL + full recommended rate (tank mix) of a registered protectant Downy Mildew fungicide per 100 L of water **Concentrate spraying** Refer to the Application section	**This use is subject to a CropLife anti-resistance strategy.** Apply by dilute or concentrate spraying equipment. **Apply the same amount of product to the target whether applying this product by dilute or concentrate spraying methods.** Apply at 10-21 day intervals as part of a Downy Mildew control programme before the first sign of infection. Use the shorter interval during periods of rapid growth or when conditions are more conducive to disease development. Spray intervals of more than 14 days should only be used once significant new growth has ceased. Begin spraying Revus within the recommended spray interval of the previous Downy Mildew fungicide. DO NOT apply later than end of flowering.

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

WITHHOLDING PERIOD

NOT REQUIRED WHEN USED AS DIRECTED.
DO NOT GRAZE VEGETATION IN TREATED VINEYARDS OR CUT FOR STOCK FOOD.

GENERAL INSTRUCTIONS

REVUS is a fungicide from the mandelamide group with translaminar and protectant properties. REVUS is best used as a protective treatment program to prevent spore germination.

Mixing

REVUS is a Suspension Concentrate (SC) formulation that mixes readily with water and is applied as a spray.

1. Partly fill the spray tank with water.
2. Start the agitation.
3. Add the correct amount of product to the spray tank with the agitation system running.

4. Continue agitation while topping up the tank with water and while spraying.
5. Use the spray mix as soon as possible after preparation.

A non-ionic surfactant may be mixed where it is required for other compatible products mixed with REVUS but is not necessary when applying REVUS alone.

Application

Ground Application only

Apply by high volume (dilute) sprayer or by concentrate sprayer. Ensure that the correct amount of REVUS is applied per hectare irrespective of the total spray volume applied. Total volume of spray mix applied should be sufficient to ensure thorough spray coverage is achieved.

Dilute spraying

Use a sprayer designed to apply high volumes of water up to the point of run-off and matched to the crop being sprayed. Set up and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient water to cover the crop to the point of 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 for each 100 L of water. Spray to the point of run-off. The required dilute spray volume will change and the sprayer set up and operation may also need to be changed, as the crop grows.

Concentrate spraying

Use a sprayer designed and set up for concentrate spraying (that is a sprayer that applies water 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 water 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 1,000 L/ha.
2. Your chosen concentrate spray volume: for example 250 L/ha.
3. The concentration factor in this example is 4 x (ie 1,000 ÷ 250 L = 4).
4. If the dilute label rate is 40 mL/100 L, then the concentrate rate becomes 4 x 40, that is 160 mL/100 L of concentrate spray.

The chosen spray volume, amount of product per 100 L of water, and the sprayer set up and operation may need to be changed as the crop grows. For further information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow industry Best Practices.

Compatibility

REVUS is physically compatible with a wide range of products including Thiovit Jet, Topas 100 EC, Switch, Proclaim, Kocide Blue Xtra, Oxydul DF; however the biological compatibility of some mixtures may not have been fully tested under all environmental and biological conditions.

A mixture of REVUS with any other product may in some circumstances be ineffective or may cause damage.

If tank mixes are to be used observe all directions, precautions and limitations on all products to be used.

As formulations of other manufacturer's products are beyond the control of Syngenta, and the quality of water may vary with location, all mixtures should be tested prior to mixing commercial quantities.

Fungicide Resistance Warning GROUP 41 FUNGICIDE

REVUS Fungicide belongs to the mandelic acid amide sub-group of the carboxylic acid amide fungicides. For fungicide resistance management, the product is a Group 40 fungicide.
Some naturally occurring individual fungi resistant to the product and other Group 40 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungi population if these fungicides are used repeatedly. These resistant fungi will not be controlled by this product or other Group 40 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, Syngenta Crop Protection Pty Ltd accepts no liability for any losses that may result from the failure of this product to control resistant fungi.

Export Wine

Where this product will be used on grapes that will be used to produce wine destined for export markets, seek advice from the Australian Wine Research Institute or Syngenta Crop Protection to ensure the wine will meet the requirements of the intended importing country.

PRECAUTIONS

Re-entry Period: DO NOT enter treated area without protective clothing until spray has dried.

INTEGRATED PEST MANAGEMENT

This product can be used where integrated pest management is being practiced.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

Toxic to aquatic life. DO NOT contaminate streams, rivers or watercourses with this product or used containers.

STORAGE AND DISPOSAL

Store in the closed original container in a cool, well ventilated area. DO NOT store for prolonged periods in direct sunlight.
Triple or preferably pressure rinse containers before disposal. Add rinsings to treatment 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
May irritate the eyes and skin. Avoid contact with eyes and skin.
When opening the container and preparing spray wear:

- **elbow-length chemical-resistant gloves**
- **goggles**

Wash hands after use. After each day's use, wash gloves and goggles.

FIRST AID
If poisoning occurs contact a doctor or Poisons Information Centre. Phone 131 126.

MATERIAL SAFETY DATA SHEET
If additional hazard information is required refer to the Material Safety Data Sheet. For a copy phone 1800 067 108 or visit our website at www.syngenta.com.au

MANUFACTURER'S WARRANTY AND EXCLUSION OF LIABILITY
Syngenta has no control over storage, handling and manner of use of this product. Where this material is not stored, handled or used correctly and in accordance with directions, no express or implied representations or warranties concerning this product (other than non-excludable statutory warranties) will apply. Syngenta accepts no liability for any loss or damage arising from incorrect storage, handling or use.

Batch Number	
Date of Manufacture	

ABBREVIATIONS

ac	active constituent
ACCS	Advisory Committee on Chemicals Scheduling
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ALT	Alanine aminotransferase
AR	Applied radioactivity
ARfD	Acute reference dose
BBCH	Scale used to identify phenological developmental stages of plants (Biologische Bundesanstalt, Bundessortenamt and CHemical industry)
BCF	Bioaccumulation factor
bw	bodyweight
d	day
DMBA	7,12-dimethylbenzthracene
°C	Degrees Centigrade
CAA	Carboxylic Acid Amide
CHO	Chinese Hamster Ovary
CIPAC	Collaborative International Pesticides Analytical Council
CPN	Chronic Progressive Nephropathy
DAT	Days After Treatment
DMBA	7,12-dimethylbenzthracene
DSEWPaC	Department of Sustainability, Environment, Water, Populations and Communities
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
EC_{50}	concentration at which 50% of the test population are immobilised
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EEC	Estimated Environmental Concentration

E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
ETU	Ethylene thiourea
EU	European Union
EUP	End Use Product
F_1	First generation
FMOC	First Order Multicompartment Kinetics
g	gram
GAP	Good Agricultural Practice
h	hour
ha	hectare
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HR-P	Calculated highest residue - processed commodity
HSIS	Hazardous Substance Information System
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
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LC/MS/MS	liquid chromatography-tandem mass spectrometer
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOEC	Lowest Observable Effect Concentration
LOQ	Limit of Quantitation – level at which residues can be quantified
LR_{50}	Application rate that kills 50% of the test population of organisms

mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
NOHSC	National Occupational Health and Safety Commission
NOEC/NOEL	No Observable Effect Concentration Level
NTP	National Toxicity Program
OC	Organic Carbon
OCSEH	Department of Health and Ageing, Office of Chemical Safety and Environmental Health
OECD	Organisation for Economic Cooperation and Development
OM	Organic Matter
PET	polyethylene terephthalate
P_{ow}	octanol/water partition coefficient
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
RBC	Red Blood Cell
s	second
SC	Suspension Concentrate
SCE	Sister Chromatid Exchange
SFO	Single First Order Kinetics
STMR	STMR Supervised Trials Median Residue
STMR-P	STMR corrected for processing
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons

SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SWA	Safe Work Australia
TMDI	Theoretical Maximum Daily Intake
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T_{max}	Time to achieve maximum concentration
TRR	Total Radioactive Residue
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
WG	Water Dispersible Granule
WHC	Water Holding Capacity
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 an absorbed material from 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	Water repelling
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octonol water partitioning co-efficient
Metabolism	The conversion of food into energy
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

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