Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active fenpyrazamine in the product Prolectus Fungicide

APVMA Product Number 68251

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

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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, Office of Chemical Safety (OCS), Department of the Environment (DotE), and State Departments of Primary Industries.

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

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

This public release summary is intended as a brief overview of the assessment that has been conducted by the APVMA and of the specialist advice received from its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment.

About this document

This is a public release summary.

It indicates that the 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 stakeholders on the information contained within this document.

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of **PROLECTUS FUNGICIDE** should be granted. Submissions should relate only to matters that the APVMA is required, by legislation,

to take into account in deciding whether to grant the application. These matters include aspects of **public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade,** and **efficacy and target crop or animal safety**. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **Tuesday 9 February 2016** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

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

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

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

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

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

[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.

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

1 INTRODUCTION

1.1 Applicant

Sumitomo Chemical Australia Pty Ltd.

1.2 Purpose of application

Sumitomo Chemical Australia Pty Ltd has applied to the APVMA for registration of the new product Prolectus Fungicide containing the new active constituent, fenpyrazamine (400 g/L) as a suspension concentrate (SC) formulation.

This publication provides a summary of the information reviewed and an outline of regulatory considerations for the proposed registration of Prolectus Fungicide.

1.3 Product claims and use pattern

Prolectus Fungicide (containing 400 g/L fenpyrazamine) is intended for the control of grey mould (*Botrytis cinerea*) in: wine grapes at a time between 10% flowering and just prior to bunch closure; and, in table grapes between 10% flowering and prior to harvest.

The use of Prolectus Fungicide will be restricted to ground application and will involve a spray concentration of 100 mL product (40 g ac)/100 L, with recommended spray volumes of 500–1000 L/ha for wine grapes and 1000–1500 L/ha for table grapes. A maximum of two applications per season, with a minimum 14 day re-treatment is proposed.

1.4 Mode of action

Fenpyrazamine is a pyrazole fungicide that presents its fungicidal activity through inhibition of germ tube elongation and mycelium elongation. For resistance management purposes, fenpyrazamine has been designated as a Group 17 fungicide by the Fungicide Resistance Action Committee (FRAC).

1.5 Overseas registrations

Products containing fenpyrazamine are currently registered overseas including in the European Union (EU), the USA, Chile, Japan and Korea. These registrations cover a range of crops including almonds, grapes, lettuce, tomato, zucchini, cucumber, blueberry, cranberry, strawberry, pistachio, ginseng and ornaments.

2 CHEMISTRY AND MANUFACTURE

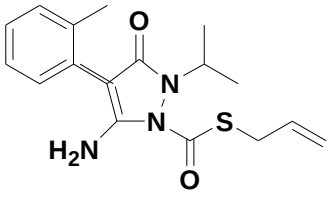
2.1 Active constituent

Fenpyrazamine is a new active constituent which belongs to the chemical class hydroxyanilide.

Manufacturing site

The active constituent fenpyrazamine will be manufactured by Sumitomo Chemical Company Limited, Japan at a site approved by the APVMA. It has a manufacturing purity range between approximately 94.7% and 99.3%; slightly different physio-chemical properties are observed between the lowest and highest purity as shown below.

Chemical characteristics of fenpyrazamine

COMMON NAME (ISO):	Fenpyrazamine
IUPAC NAME:	*S*-allyl 5-amino-2,3-dihydro-2-isopropyl-3-oxo-4-(*o*-tolyl)pyrazole-1-carbothioate
CAS NAME:	S-2-propen-1-yl 5-amino-2,3-dihydro-2-(1-methylethyl)-4-(2-methylphenyl)-3-oxo-1H-pyrazole-1-carbothioate
CAS REGISTRY NUMBER:	473798-59-3
MANUFACTURER CODE:	S-2188
MINIMUM PURITY:	940 g/kg
MOLECULAR FORMULA:	$C_{17}H_{21}N_3O_2S$
MOLECULAR WEIGHT:	331.43
STRUCTURE FAMILY:	
CHEMICAL FAMILY:	Pyrazole fungicides

Physico-chemical properties of fenpyrazamine

PHYSICAL FORM AT 25°C (99.3% PURITY):	White solid with slight odour	
PHYSICAL FORM AT 25°C (94.7% PURITY):	Very pale yellow solid with odour characteristic of garlic	
MELTING POINT:	116.4°C (389.6 K)	
BOILING POINT:	239.8°C	
RELATIVE DENSITY AT 20OC:	1.262 at 99.3% purity 1.250 at 94.7% purity	
VAPOUR PRESSURE	$<10^{-5}$ Pa at 25°C (by gas saturation method, too low to be determined by experimentally) 2.89×10^{-8} Pa at 25°C by MPBPQin calculation	
PARTITION CO-EFFICIENT (99.3% PURITY)	3307.32 (log Pow = 3.52) at 25±1°C The effect of pH on partition coefficient was not determined as the technical grade active does not dissociate under acidic or basic conditions	
HENRY'S LAW CONSTANT	1.62×10^{-4} Pa.m^3/mole at 20 °C	
SOLUBILITY IN WATER AT 20°C:	20.4 mg/L (99.3% purity)	
SOLUBILITY IN VARIOUS SOLVENTS AT 20°C (99.3% PURITY)	n-hexane: n-octanol: toluene: acetone: methanol: dichloromethane: ethyl acetate:	902 mg/L 84403 mg/L 112978 mg/L > 250 g/L > 250 g/L > 250 g/L > 250 g/L

SOLUBILITY IN VARIOUS SOLVENTS AT 20°C (94.7% PURITY)	n-hexane: 811 mg/L n-octanol: 99223 mg/L toluene: 129308 mg/L acetone: > 250 g/L methanol: > 250 g/L dichloromethane: > 250 g/L ethyl acetate: > 250 g/L
UV (99.3% PURITY)	*Solution* — *λmax (nm)* — *Molar absorptivity, (ε) (mol/L)$^{-1}$cm^{-1}* Acidic — 243 — 16600 274 — 13800 Un-adjusted — 243 — 16700 274 — 13900 Basic — N/A — N/A No maxima were observed under basic conditions as fenpyrazamine had decomposed.
HYDROLYSIS (99.4% PURITY):	Stable to hydrolysis at pH 4. DT_{50} at pH 7 at both 20 and 25ºC: > 1 year (extrapolated from 50-70 ºC) DT_{50} at pH 9 at 20ºC (extrapolated from 25-50 ºC):24 days DT_{50} at pH 9 at 25ºC (measured): 11 days The major hydrolysis product at pH 7 and 9 was identified as S-2188-DC (maximum 88.9%), which was almost hydrolytically stable but partially oxidised to S-2188-OH (maximum 17.6%).
DIRECT PHOTOTRANSFORMATION (99.4% PURITY):	In sterile water at pH 7 and 25 ºC (Pyrazolyl-5-^{14}C and phenyl-^{14}C radio labelled) : *Label* — *DT_{50} (days)* — *DT_{90} (days)* Pyrazolyl — 1.7 — 5.5 Phenyl — 1.6 — 5.4
QUANTUM YIELD (99.4% PURITY):	In pH 7 buffer: 0.021
CALCULATED THEORETICAL LIFETIME (94.7% PURITY):	Photodegradation in sterile water at pH 7 and 25°C in summer sunlight at UK/US conditions (ca Watt/m^2 at 300 - 400 nm): *Label* — *DT_{50} (days)* — *DT_{90} (days)* Pyrazolyl — 1.7 — 5.5 Phenyl — 1.6 — 5.4
DISSOCIATION CONSTANT (pK_a) AT 99.3% PURITY:	No dissociation activity was observed in the approximate pH range 1 – 13

PHOTOCHEMICAL OXIDATIVE DEGRADATION (99.3% PURITY):	Photochemical reaction with OH radicals. Assuming a 12 hr day and a hydroxyl radical concentration of 1.5 x 10^6 OH/cm³ (EPA), the decomposition half-life was calculated to be 1.221 hrs.
FLAMMABILITY (94.7% PURITY):	Not classified as flammable
OXIDISING PROPERTIES (94.7% PURITY):	Not likely to possess oxidizing properties
AUTO-FLAMMABILITY (94.7%):	Not auto-flammable
SURFACE TENSION (94.7%) AT 20^{O}C:	66.9 mN/m
CORROSION CHARACTERISTICS:	Not corrosive to the polyethylene packaging
PH:	Does not dissociate

The APVMA has evaluated the chemistry aspects of fenpyrazamine active constituent (manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable. Other compounds of toxicological significance are not expected to occur in fenpyrazamine Technical Grade Active Constituent (TGAC) as a result of the raw materials and the synthetic route used.

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

APVMA ACTIVE CONSTITUENT STANDARD

CONSTITUENT	SPECIFICATION	LEVEL
Fenpyrazamine	Fenpyrazamine	Not less than 940 g/kg

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

2.2 Formulated product

The chemistry aspects of the product, Prolectus Fungicide (physico-chemical properties, formulation process, quality control procedures, batch analysis results, stability, analytical methods and packaging) have been evaluated by the APVMA.

The product Prolectus Fungicide will be packaged and marketed in 1 L, 5 L, 10 L and 20 L high-density polyethylene (HDPE) containers.

Prolectus Fungicide

DISTINGUISHING NAME:	Prolectus Fungicide
FORMULATION TYPE:	Soluble Concentrate (SC)
ACTIVE CONSTITUENT CONCENTRATION:	Fenpyrazamine (400 g/L)

Physical and chemical properties of Prolectus Fungicide

PHYSICAL FORM:	Brown suspension
PH VALUE (NEAT):	7.2
SUSPENSIBILITY (%):	105 (within the range of experimental uncertainty)
SPONTANEITY OF DISPERSION (%):	105 (within the range of experimental uncertainty)
VISCOSITY AT 20^{O}C	551 cps
SPECIFIC GRAVITY:	1.062
PERSISTENT FOAM:	2 mL after 1 minute
PARTICLE SIZE:	D(v, 0.5): 1.1 µm D(v, 0.9): 4.7 µm
WET SIEVE:	< 0.1% retained on 75 µm sieve
POURABILITY:	Un-rinsed: 3.9%; rinsed: 0.4%
STORAGE STABILITY:	The product is expected to remain within specification for at least 2 years when stored under normal conditions in HDPE containers
LOW TEMPERATURE STABILITY:	Chemically and physically stable in HDPE after 6.5 days and 10 days at 0°C

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

3 TOXICOLOGICAL ASSESSMENT

Sumitomo Chemical Australia Pty Ltd has applied to the Australian Pesticides and Veterinary Medicines Authority (APVMA) for the registration of the product Prolectus Fungicide containing a new active constituent fenpyrazamine (400 g/L). Prolectus Fungicide is a suspension concentrate (SC) formulation proposed for the control of grey mould (*Botrytis cinerea*) in table and wine grapes.

The use of Prolectus Fungicide will be restricted to ground application and will involve a spray concentration of 100 mL product (40 g ac)/100 L, with recommended spray volumes of 500–1000 L/ha for wine grapes and 1000–1500 L/ha for table grapes. The maximum number of applications is two with a minimum interval of 14 days between applications.

The toxicological database for fenpyrazamine, which consists primarily of toxicity studies conducted in rats, mice, rabbits and dogs, is considered sufficient to determine the toxicology profile of fenpyrazamine and characterise the risk to humans. In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified.

Findings of adverse effects in any one species do not necessarily indicate such effects might 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.

3.1 Chemical class

Fenpyrazamine is a pyrazole fungicide that presents its fungicidal activity through inhibition of germ tube elongation and mycelium elongation. Other chemicals with a similar fungicidal mode of action include fenhexamid.

3.2 Toxicokinetics and metabolism

In toxicokinetics studies in rats, fenpyrazamine was rapidly (T_{max} = 1 to 6 hr) and extensively (>90% dose) absorbed and widely distributed into organs and tissues, with the highest concentrations found in liver and thyroids (identified as target organs in toxicity studies). Metabolism of administered fenpyrazamine was essentially complete, with trace amounts of unchanged parent chemical identified in excreta. Fenpyrazamine elimination was rapid ($t_{1/2}$ = 2 to 3 hr and 14 to 17 hr for the low and high dose respectively) and complete, proceeding mainly through urine (>80%) and to lesser extent (<18%) faeces, with minimal amounts detected in expired air. At 168 hours post dosing, the highest residual level was found in the liver and stomach, each representing 0.04–0.05% of the dose. There was no evidence of radiolabel retention in particular organs or

tissues following single high dose administration, whereas repeat dosing caused some degree of toxicokinetic accumulation. However, fenpyrazamine is not considered to be bio-accumulative.

Percutaneous absorption

There were no data available for dermal absorption.

Acute toxicity

Fenpyrazamine was a low acute oral and dermal toxicant in rats (LD_{50} > 2000 mg/kg bw). While an acute inhalational toxicity study in rats identified fenpyrazamine as a low acute inhalational toxicant (LC_{50} >4840 mg/m^3), the study contained notable deviations from standard test guidelines, and was considered of reduced regulatory value. In rabbits, it was non-irritating to the eyes and skin, and was not a sensitising compound in guinea pig skin under the GPMT method.

The Prolectus Fungicide formulation was of low acute toxicity by the oral (LD_{50} >2000 mg/kg bw with no deaths), dermal (LD_{50} >2000 mg/kg bw with no deaths), and inhalational routes (4-hr LC_{50} >5612 mg/m^3 with no deaths). It was not a skin or eye irritant in rabbits, and was not a skin sensitiser in guinea pig (Buehler method).

Systemic effects

Repeat dose studies with fenpyrazamine have been conducted in rats, mice and dogs. The common toxicology endpoints in all species include test substance related and dose dependent reductions in food consumption, lower body weight (and decreased body weight gain), and an increase in the organ weight, incidence and severity of histopathological changes (hepatocellular hypertrophy as well as reduced fatty turnover) in the liver. The liver as a main target organ is consistent with the findings in toxicokinetics, ie, rapid and extensive absorption, metabolism and excretion of the test substance, and the liver retaining the highest radiolabel levels throughout the toxicokinetic studies (up to day 7 post dosing). The most sensitive species in repeat-dose toxicity studies was the rat, with the lowest No Observable Effect Level (NOEL) in this species being 12.72/15.64 mg/kg bw/d in males and females respectively (300 ppm), established in the two-year chronic toxicity and carcinogenicity study.

In addition to the liver, the thyroid was another target organ identified in rats, but not in mice or dogs. Similar to the liver changes, a dose-dependent and temporal related increase in thyroid weight and the incidence of histopathological changes (follicular hypertrophy and/or hyperplasia) were detected in long term repeat dose studies in rats, particularly in the two-year combined chronic and carcinogenicity study and the two-generation reproduction study.

Genotoxicity and carcinogenicity

Fenpyrazamine was not genotoxic in several *in vitro* and *in vivo* studies. In the two-year combined chronic and carcinogenic study in rats, neoplastic changes, including a slightly higher incidence of liver hepatocellular carcinoma, Leydig cell tumour and skin/subcutis keratoacanthoma in males, and uterus adenocarcinoma in females, were observed at 2400 ppm. A slightly higher incidence (6%) of follicular carcinoma in the thyroids was also detected in males at 2400 ppm. The OCS notes that the marginal increases identified occurred at the high dose (2400 ppm) only, without incidence/frequency at lower doses,

and that hepatocellular adenoma frequency was identical to concurrent controls. Additionally, pre-neoplastic lesions (eg hyperplasia) were not noted in histopathology, and no changes in the period to onset were identified (noting that hepatocellular carcinoma was only identified at terminal sacrifice, and animals presenting with hepatocellular carcinoma survived to final termination). The changes in the thyroid of rats may possibly be attributed to a species specific mechanism of thyroid hormone turnover in rats. However, in the submitted information, no thyroid hormones or TSH were measured in repeat-dose studies. Hence, there is no specific evidence available to support the hypothesis. While the thyroid changes only occurred in rats, and not in other laboratory species tested, the human relevance of these thyroid observations is uncertain. However, it is likely to be low, given the presence of the effect at the highest dose of the study only and its presence at the upper historical control limit provided.

On available data (noting mechanistic data and/or a MOA framework consideration of the observed effects were not provided), the OCS considers that on weight of evidence, fenpyrazamine is unlikely to be carcinogenic in the rat.

Reproductive and developmental toxicity

In the two-generation reproduction study in rats, fenpyrazamine caused an increase in the incidence of post implantation loss and postnatal loss, and lower pup weight in F_1 and F_2 pups at ≥ 1000 ppm (72.5 mg/kg bw/d), doses where parental toxicity in P and F_1 adult animals was observed (increased organ weight and histopathological changes occurred in the liver and thyroid). The NOEL for offspring toxicity was 20.3/28.5 mg/kg bw/d in males and females respectively (400 ppm).

Developmental studies in rats revealed various visceral and skeletal variations, including abnormal lobation and supernumerary lobe in the liver, left sided umbilical artery, skull zygomatic arch fusion, and costal cartilages asymmetrically aligned at sternum at doses >125 mg/kg bw/d, but the findings were considered related to maternal toxicity at this dose. Maternal toxicity at 125 mg/kg bw/d was present as only a slightly (but occasionally statistically significantly) lower accumulated body weight gain. The developmental NOEL in rats was 12.5 mg/kg bw/d.

In rabbits, implantation loss and abortion/premature delivery was a finding consistently observed in the dose range finding study and the formal study at ≥50 mg/kg bw/d with a dose-dependent pattern. However, fenpyrazamine did not cause external, visceral and skeletal malformations or variations of toxicological significance in the presented studies.

Overall, fenpyrazamine was not considered a reproductive toxicant in rats, or a developmental toxicant in rats and rabbits.

Neurotoxicity

Acute and subchronic neurotoxicity studies indicated that fenpyrazamine was not neurotoxic in rats.

Toxicity of metabolites

An acute oral toxicity study and a bacterial reverse mutation test were conducted on one metabolite (S-2188-DC) in rats. The acute oral LD_{50} was greater than 500 mg/kg bw (no deaths; only dose tested), and the bacterial reverse mutation test was negative for mutagenic effects.

3.3 Public health standards

Poisons scheduling

On 27 March 2015, the Delegate to the Secretary of the Department of Health published a final scheduling decision to create a new Schedule 5 entry for fenpyrazamine in the Poisons Standard for the Uniform Scheduling of Medicines and Poisons (www.tga.gov.au/publication/poisons-standard-susmp), with a cut-off to exempt in preparations at 40 per cent or less of fenpyrazamine and an implementation date of 1 June 2015.

Therefore, Prolectus Fungicide is exempt from classification under Schedule 5 as the concentration of fenpyrazamine is 400 g/L (.e 40% or less).

ADI

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

The critical effect of fenpyrazamine identified in chronic toxicology data was an increased incidence of hepatocellular hypertrophy with associated liver weight increases in both rat and dog. Additional findings in the rat included a range of clinical pathology changes in both sexes at moderate to higher doses. Dogs and rats appeared to be the more sensitive species for fenpyrazamine than mice. The most sensitive NOEL to establish an ADI is 300 ppm (12.72/15.64 mg/kg bw/d; M/F respectively), from the two-year chronic/carcinogenicity study in rats.

While a range of neoplastic findings in liver, thyroid, uterus, skin and Leydig cells were identified in the two-year rat study at the top dose of 2400 ppm, all findings except liver hepatocellular carcinoma were within historical controls. A broader weight of evidence consideration suggests that the marginal increase in the hepatocellular carcinoma finding is unlikely to be associated with fenpyrazamine treatment, and hence fenpyrazamine is unlikely to be carcinogenic.

Therefore, a default 100-fold safety factor, consisting of factors of 10 for intra-species and interspecies variation, was considered to be appropriate, and the ADI for fenpyrazamine is 0.13 mg/kg bw/d, based on application of a 100-fold safety factor to the NOEL of 300 ppm (12.72/15.64 mg/kg bw/d for M/F) for both sexes in a chronic dietary study in rats.

ARfD

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

An ARfD was established since fenpyrazamine was considered likely to present an acute hazard to humans. Adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available.

In a two-generation reproductive toxicity study in rats, the NOEL for offspring toxicity was 400 ppm (20.3/28.5 mg/kg bw/d in males and females respectively), based on post-natal loss and lower pup weight during the lactation period at 1000 ppm (52.4 mg/kg bw/d minimum). These effects occurred at the same dose level as parental toxicity (NOEL of 400 ppm, based on increased liver and thyroid weights and gross and histopathology in the liver (hepatocellular hypertrophy, reduced fatty turnover) and thyroids (follicular hypertrophy) in P and F_1 parental animals at 1000 ppm (52.4 mg/kg bw/day) and above.

As no significant treatment-related findings in the acute, short-term, two-generation reproduction or developmental toxicity studies or in the acute or sub-chronic neurotoxicity studies indicate increased concern for acute dietary risk, a default 100-fold safety factor, consisting of factors of 10 for intra-species and inter-species variation, was considered to be appropriate.

Consequently, the ARfD for fenpyrazamine was established at 0.2 mg/kg bw, based on a 100-fold safety factor and the NOEL of 400 ppm (20.3/28.5 mg mg/kg bw/d for M/F) for both sexes in a two-generation reproductive toxicity study in rats.

4 RESIDUES ASSESSMENT

4.1 Introduction

Sumitomo Chemical Australia Pty Ltd has applied to the Australian Pesticides and Veterinary Medicines Authority (APVMA) for the registration of the product Prolectus Fungicide containing a new active constituent fenpyrazamine (400 g/L). Prolectus Fungicide is a suspension concentrate (SC) formulation proposed for the control of grey mould (*Botrytis cinerea*) in table and wine grapes.

The use of Prolectus Fungicide will be restricted to ground application and will involve a spray concentration of 100 mL product (40 g ac)/100 L, with recommended spray volumes of 500–1000 L/ha for wine grapes and 1000–1500 L/ha for table grapes (a maximum application rate for any use of 1.5 L product/ha (600 g ac/ha)). The maximum number of applications is two with a minimum interval of 14 days between applications.

The proposed harvest withholding period is not required when used as directed for wine grapes and 7 days for table grapes. As part of the residue assessment for fenpyrazamine, plant and animal metabolism studies, supervised residue trials and trade aspects were considered. Trials in lettuce and canola were also considered, but these uses are not included in the proposed label use pattern for Prolectus Fungicide and are therefore not reported here.

4.2 Metabolism

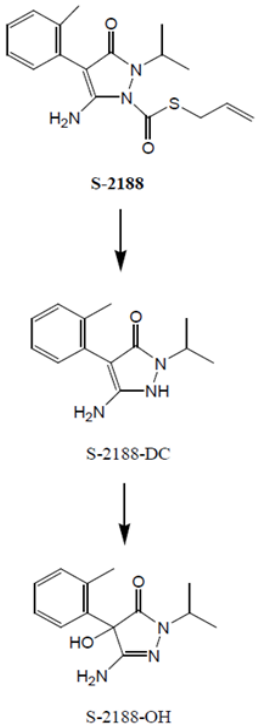
Plants

For grapes, two foliar applications of fenpyrazamine radiolabelled in either the phenyl or pyrazolyl ring were made at an approximate rate of 0.75 kg ac/ha during berry ripening. Mature grape berries and foliage were harvested at 14 and 21 days after the final application. The TRR (as parent equivalents) ranged from 16–44 mg/kg in grape berries and 104–321 mg/kg in grape foliage. Parent fenpyrazamine (S-2188) was the major residue found, comprising 88–95% TRR (13.8–41.5 mg/kg) in grape berries and 81–92% TRR (96-260 mg/kg) in foliage and most of this was found in the surface rinses. The metabolite S-2188-DC comprised 1–5% TRR (0.22–1.17 mg/kg) in grapes and 3–8% TRR (2.79–25.7 mg/kg) in foliage.

For lettuce, two foliar applications of fenpyrazamine radiolabelled in either the phenyl or pyrazolyl ring were made at an approximate rate of 0.85 kg ac/ha. Mature lettuces were harvested 14 days after the final application and the TRR was 12 mg/kg (parent equivalents) for both radiolabels. Parent fenpyrazamine was the major residue found, comprising 81–82% TRR (9.14–9.96 mg /kg) in lettuce leaves and most of this was found in the surface rinses. The metabolite S-2188-DC comprised 9–11% TRR (1.05–1.24 mg/kg) in lettuce leaves.

For canola (oilseed rape), two foliar applications of fenpyrazamine radiolabelled in either the phenyl or pyrazolyl ring were made at an approximate rate of 0.60 kg ac/ha at BBCH[B] 50 and BBCH 69. Immature forage was sampled 46 days after the first application while mature haulm and seed was sampled at 45 days after the second application. The TRR (as parent equivalents) ranged from 1.3–2.0 mg/kg (in immature forage, 2.5–2.9 mg/kg in haulm and 0.02–0.05 mg/kg in seed. Parent fenpyrazamine was the major residue found, comprising 61–67% TRR (0.88–1.22 mg/kg) in immature forage, 50–60% TRR (1.42–1.48 mg/kg) in haulm and 16–22% TRR (0.005–0.007 mg/kg) in seed. In forage and haulm, the majority of the fenpyrazamine was found in the surface rinses. The metabolite S-2188-DC comprised 8–9% TRR (0.10–0.19 mg/kg) in forage, 9–11% TRR (0.27 mg/kg) in haulm and 1.9–3.7% TRR (0.001 mg/kg) in seeds. It is noted that in canola, only 26.5–37.3 % TRR was extracted with acetone/water, water or sodium hydroxide and the unextractable radioactivity in seeds (31.2–38.3% TRR) was found to have been incorporated into protein (6.8–10.1% TRR), starch (3.6–5.6% TRR) and lignin (17.4–25.9% TRR).

As shown in Figure 1, the metabolic pathway of fenpyrazamine in plants (grapes, lettuce and canola) proceeds via cleavage of the carbamate linkage on the pyrazolyl ring to give S-2188-DC. Subsequent hydroxylation at the 4-position of the pyrazolyl ring and tautomerisation forms S-2188-OH (a minor



[B] Note that the BBCH growth stage of canola is explained here www.jki.bund.de/en/startseite/veroeffentlichungen/bbch-codes.html

Figure 1: Metabolic pathway for fenpyrazamine (S-2188) in plants (grapes, lettuce and canola)

metabolite).

Animals

For lactating goats, fenpyrazamine radiolabelled in the pyrazolyl ring was administered orally once per day for 5 days to one lactating goat at an actual dose level of 0.36 mg/kg bw/day, equal to 7.2 ppm in the feed. The TRR (as parent equivalents) was 0.02 mg/kg in milk, 0.01 mg/kg in muscle, 0.26 mg/kg) in liver, 0.16 mg/kg in kidney and 0.02 mg/kg in fat. Elimination through the urine and faeces occurred at 58.04% and 23.61% of the administered dose, respectively. The majority of radioactivity was extractable in milk (95.6% TRR), muscle (91.4% TRR), kidney (97% TRR) and fat (100% TRR). In liver, 62.7% TRR was extracted and the unextractable residue was characterised protease hydrolysis (28.3% TRR). Parent fenpyrazamine contributed to a significant portion of the TRR (13.7–17.5% TRR) in liver and fat but was not detected in milk, muscle and kidney. The major metabolite S-2188-DC was detected in all goat matrices at 8.6–41 % TRR.

For laying hens, fenpyrazamine radiolabelled in the pyrazolyl ring was administered orally once per day for 7 days to 10 laying hens at an actual dose level of 0.70 mg/kg bw/day, equal to 10 ppm in the feed. The TRR (as parent equivalents) was 0.005 mg/kg in egg yolk, 0.02 mg/kg in egg white, 0.02 mg/kg in milk, 0.01 mg/kg in muscle, 0.02 mg/kg in fat and 0.18 mg/kg in liver. Elimination through the excreta occurred at 88.72% of the administered dose. The majority of radioactivity was extractable in muscle (83.9% TRR) and fat (95.2% TRR). In hen egg yolks, 69.8% TRR was extracted and the unextractable residue was characterised by protease hydrolysis (20.4% TRR). In hen liver, 66.4% TRR was extracted and the unextractable residue was characterised by pronase hydrolysis (25.7% TRR). Parent fenpyrazamine contributed to a significant portion of the TRR (42.6% TRR) hen fat, a minor portion of the TRR (2.1–3.5% TRR) in hen egg yolk, hen egg whites and hen liver and was not detected in hen muscle. The major metabolite S-2188-DC was detected in all hen matrices at 3.1–25 % TRR, with the exception of hen fat where it was not detected.

The metabolic pathway of fenpyrazamine in both lactating goats (Figure 2) and laying hens (Figure 3) proceeds via cleavage of the carbamate linkage on the pyrazolyl ring to give S-2188-DC. The primary metabolites are further metabolised by conjugation. Fenpyrazamine is extensively metabolised to polar metabolites, and broken down and reincorporated into lactose in natural products.

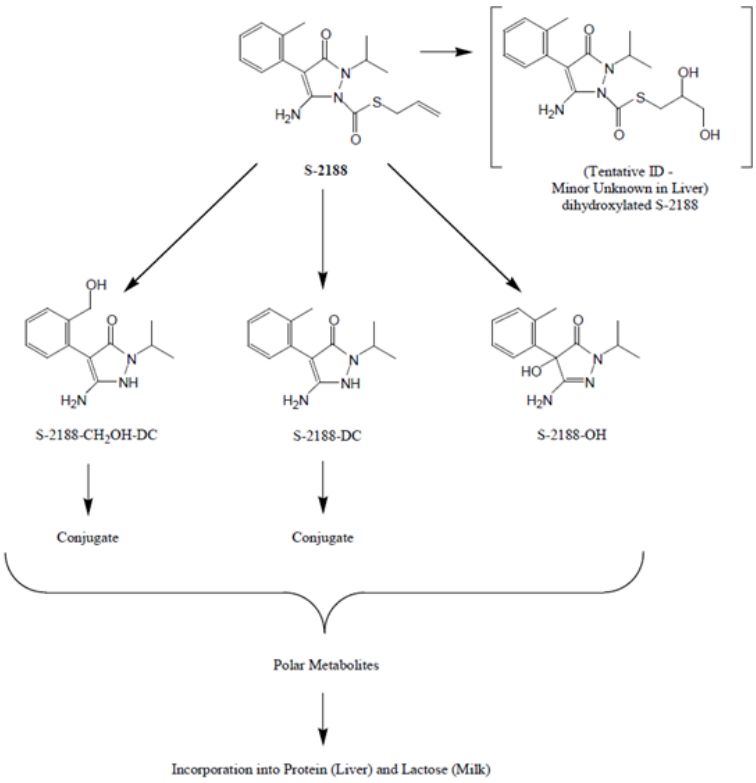


Figure 2: Metabolic pathway for fenpyrazamine (S-2188) in lactating goats

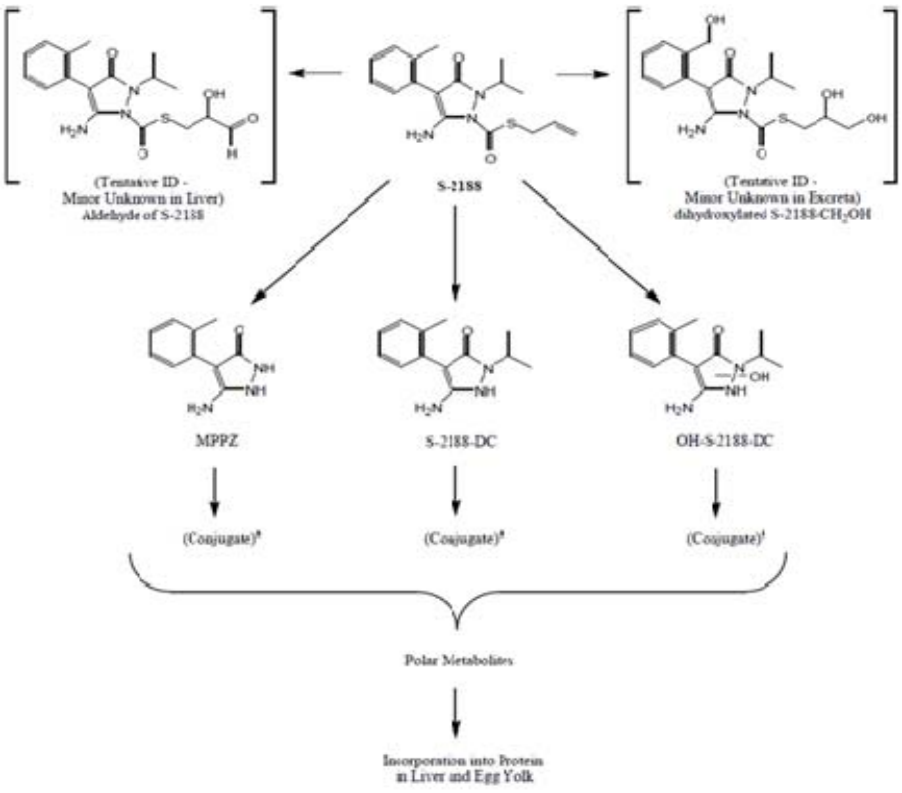


Figure 3: Metabolic pathway for fenpyrazamine (S-2188) in laying hens

4.3 Analytical methods

Plant Material

Residues of fenpyrazamine and the S-2188-DC metabolite were extracted from grape matrices with either acetone: water and $MgSO_4$:NaCl or ethyl acetate and a mixture of $MgSO_4$: sodium acetate and were analysed by LC-MS/MS. The LOQ each fenpyrazamine and S-2188-DC was 0.01 mg/kg as individual analytes. Recoveries of fenpyrazamine and S-2188-DC from fortified control samples of grapes were within acceptable limits.

Animal commodities

An analytical method derived from the QuEChERS multi-residue method that involved extraction with acetonitrile and analysis with LC-MS/MS was validated for the analysis of parent fenpyrazamine in animal commodities. The LOQ was 0.005 mg/kg for whole milk and 0.01 mg/kg for meat, liver, eggs and fat. Recoveries of fenpyrazamine from fortified control samples were within acceptable limits.

A routine analytical method was not provided for S-2188-DC. S-2188-DC is not included in the proposed enforcement residue definition, and its concentration can be estimated from metabolism studies for dietary exposure assessment for the purposes for the currently proposed uses.

4.4 Stability of pesticide residues in stored analytical samples

Residues of fenpyrazamine and S-2188-DC for found to be stable during frozen storage (≤ -18^{o}C) for at least 12 months in grapes (berries), canola (seeds), lettuce (heads) and cereal (grain).

4.5 Residue definition

Based on the results of the metabolism and residue studies, it is recommended that the residue definition for plant and animal commodities be parent fenpyrazamine only for enforcement and the sum of parent fenpyrazamine and metabolite S-2188-DC for the dietary exposure assessment. It is noted that S-2188-DC was a significant metabolite in all goat and hen matrices, however as the estimated feeding level is not expected to result in quantifiable residues of parent fenpyrazamine or metabolite S-2188-DC in animal commodities, the inclusion of S-2188-DC in the enforcement definition is not required at this time.

4.6 Residue trials

Details of 16 Australian and 17 European Good Laboratory Practice (GLP) residue trials conducted on wine grapes or table grapes have been provided. A number of the provided trials included processing into dried grapes and/or wine.

Wine grapes

The proposed use of Prolectus Fungicide (400 g/L fenpyrazamine) on wine grapes involves a maximum of two applications, made with a minimum 14 day re-treatment interval, at a concentration of 40 g ac/100L.

The draft label states 'Apply as part of a botrytis control spray program between 10% flowering (E-L 20) and berries pea size—just prior to bunch closure (E-L 31)'[C] and the proposed harvest withholding period (WHP) is not required when used as directed. The recommended spray volume for dilute spraying is 500–1000 L/ha.

Residue trials found parent fenpyrazamine residues to be <0.01 (n=13) and 0.02 mg/kg and it is recommended that a fenpyrazamine MRL be established at 0.05 mg/kg for wine (WHP not required when used as directed as supported by the label restraint 'DO NOT apply after E-L 31'). The proposed residue definition for risk assessment is the sum of parent fenpyrazamine and S-2188-DC (equivalents) and the STMR and HR for total residues of <LOQ (ie <0.02) and <0.03 mg/kg respectively will be used for the dietary risk assessment.

Table grapes

The proposed use of Prolectus Fungicide (400 g/L fenpyrazamine) on table grapes involves a maximum of two applications, made with a minimum 14 day re-treatment interval, at a concentration of 40 g ac/100L. The draft label states 'Apply as part of a botrytis control spray program between 10% flowering (E-L 20) and up to just prior to harvest (E-L 38)'[D] and the proposed harvest withholding period is 7 days. The recommended spray volume for dilute spraying is 1000–1500 L/ha.

A combined dataset, based on single applications made 7–14 days prior to harvest and two applications made at 21 and 7 days prior to harvest, was suitable for MRL estimation: 0.06, 0.14, 0.15, 0.22, 0.23, 0.25, 0.29, 0.37, 0.37, 0.45, 0.54, 0.62, 0.74, 0.77, 1.0, 1.03, 1.2 and 1.2 mg/kg (STMR = 0.41 mg/kg) for parent fenpyrazamine. Based on this, the OECD MRL calculator estimates an MRL of 2 mg/kg for table grapes. It is recommended that a fenpyrazamine MRL at be established at 2 mg/kg for table grapes. The proposed residue definition for risk assessment is the sum of parent fenpyrazamine and S-2188-DC (equivalents) and the STMR and HR for total residues of 0.49 and 1.76 mg/kg respectively will be used for the dietary risk assessment.

Processing studies

Grape pomace is a by-product from wine making that can be fed to livestock. The median and highest processing factor (PF) for wet pomace were 2.1 X and 5.8 X respectively and if they are converted to a dry weight basis with a standard dry matter content of 15%, then the median and highest PF for pomace on a dry weight basis are calculated to be 14 X and 39 X mg/kg respectively. If these PFs are applied to the HR for wine grapes of 0.02 mg/kg, then the HR-P are 0.28 and 0.78 mg/kg respectively. An MRL for AB 0269 Grape pomace, dry at 1 mg/kg is recommended.

[C] Note that the EL growth stage of grapes is explained here: www.awri.com.au/wp-content/uploads/grapegrowth.pdf

[D] Note that the EL growth stage of grapes is explained here: www.awri.com.au/wp-content/uploads/grapegrowth.pdf

The wine processing factors for parent fenpyrazamine in multiple trials were 0.3, 0.4, 0.4, 1.1, 1.5, and 2.4 X (median PF = 0.75 X).

Table grapes may be dried for the production of sultanas or raisins. The raisin PFs for parent fenpyrazamine were 0.5, 1.4 and 4.7 X. The table grape STMR and HR for parent fenpyrazamine are 0.41 and 1.2 mg/kg respectively. Based on the high raisin PF of 4.7 X, the STMR-P and HR-P for dried grapes are calculated to be 1.9 and 5.6 mg/kg respectively on a parent fenpyrazamine basis. An MRL for DF 0269 Dried grapes at 10 mg/kg is recommended.

4.7 Animal commodity MRLs

The lactating goat metabolism study found that a feeding level of 7.2 ppm in the feed for 5 days resulted in parent fenpyrazamine residue levels of 0.03 mg/kg in liver, 0.002 mg/kg in fat and <0.0013 mg/kg in milk, muscle and kidney. The potential exposure that may result from the consumption of grape pomace derived from treated wine grapes is 0.077 ppm in the feed, which is 94 X lower than the lactating goat metabolism study exposure level. The validated method LOQ is 0.005 mg/kg for milk and 0.01 mg/kg for meat, liver and fat. It is concluded that parent fenpyrazamine residue levels in mammalian animal commodities will not exceed the validated LOQ's as a result of the proposed use on wine grapes.

The establishment of fenpyrazamine MRLs for MO 0105 edible offal (Mammalian) and MM 0095 meat [mammalian] at *0.01 mg/kg and ML 0106 milks at *0.005 mg/kg is supported by the available data. Quantifiable residues in animal commodities on a total fenpyrazamine basis should not occur from the consumption of grape pomace derived from wine grapes, with the highest estimated total residue in mammalian animal commodities being 0.0022 mg/kg in kidney.

The laying hen metabolism study found that the feeding of fenpyrazamine at 10 ppm in the feed for 7 days resulted in parent fenpyrazamine residue levels of 0.008 mg/kg in fat, 0.004 mg/kg in liver, 0.001 mg/kg in egg yolks and whites and <0.0013 mg/kg in muscle. The potential exposure that may result from the consumption of grape pomace derived from treated wine grapes is 0.077 ppm in the feed, which is 130 X lower than the laying hen metabolism study exposure level. The validated method LOQ is 0.01 mg/kg for eggs, meat, liver and fat.

It is concluded that parent fenpyrazamine residue levels in poultry animal commodities will not exceed the validated LOQ's as a result of the proposed use on wine grapes. The establishment of fenpyrazamine MRLs at *0.01 mg/kg for PE 0112 Eggs, PM 0110 Poultry meat and PO 0111 'Poultry, edible offal of', is supported by the available data. It is calculated that quantifiable residues on a total fenpyrazamine basis should not occur from the consumption of grape pomace treated derived from wine grapes, with the highest estimated total residue in poultry commodities being 0.0017 mg/kg in liver.

4.8 Estimated dietary intake

The chronic dietary exposure to fenpyrazamine is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines[E] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for fenpyrazamine is equivalent to <2 % of the ADI.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food.

The NESTIs for fenpyrazamine are acceptable at <30% of the acute reference dose for children (2–6 years) and the general population (2+ years).

4.9 Bioaccumulation potential

The octanol-water partition coefficient ($\log_{10} K_{OW}$) for fenpyrazamine is 4.05, indicating fat solubility. The lactating goat and laying hen metabolism studies found that fenpyrazamine residues were higher in the fat than in the muscle but lower than that in offal (liver and kidney). MRLs for meat 'in the fat' are not recommended at this time as residues above LOQ are not expected in animal commodities.

4.10 Spray drift

The proposed use of Prolectus Fungicide involves a spray concentration of 40 g ac/100L, with recommended spray volumes of 500–1000 L/ha for wine grapes and 1000–1500 L/ha for table grapes. The maximum application rate of fenpyrazamine is therefore calculated to be 600 g ac/ha for table grapes. The proposed label contains the restraint 'DO NOT apply by air' and therefore the application by a ground vineyard air-blast application was considered.

The validated method LOQ for fenpyrazamine is 0.005 mg/kg for milk and 0.01 mg/kg for meat, liver and fat. In the goat metabolism study, dosing with fenpyrazamine at 7.2 ppm in the feed resulted in a highest parent fenpyrazamine residue level of 0.03 mg/kg in liver. For parent fenpyrazamine (the proposed residue definition for enforcement) residues in offal to be at the LOQ of 0.01 mg/kg for offal, the maximum feeding level is calculated to be 2.4 ppm in the feed. Assuming pasture consists of 1500 kg DM/ha this corresponds to a maximum permitted drift of 3.6 g ac/ha.

For ground application to grapevines at a maximum rate of 600 g ac/ha (assuming a spray volume of 1500 L/ha), the standard scenario (Airblast—vineyard) indicates drift will drop to 3.6 g ac/ha (0.006× field rate) by 16 metres downwind from the application area. The average deposition as a fraction of the applied field rate

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

over 300 meters is calculated to be 0.002× field rate, which is lower than the level corresponding to the maximum permitted drift of 3.6 g ac/ha (0.006× field rate).

A no-spray zone is not required for application to grapevines for the protection of international trade.

4.11 Recommendations

The following amendments are proposed to the MRL standard:

Table 1

COMPOUND		FOOD	MRL (MG/KG)
ADD:			
Fenpyrazamine			
DF	0269	Dried grapes (=Currants, Raisins and Sultanas)	10
MO	0105	Edible offal (Mammalian)	*0.01
PE	0112	Eggs	*0.01
MM	0095	Meat [mammalian]	*0.01
ML	0106	Milks	*0.005
PO	0111	Poultry, Edible offal of	*0.01
PM	0110	Poultry meat	*0.01
FB	1235	Table-grapes	2
FB	1236	Wine-grapes	0.05

Table 2

COMPOUND	RESIDUE
ADD:	
Fenpyrazamine	For enforcement: Fenpyrazamine For dietary exposure assessment: Sum of fenpyrazamine and 5-amino-1,2-dihydro-2-isopropyl-4-(*o*-tolyl)pyrazol-3-one (S-2188-DC), expressed as fenpyrazamine

Table 3

COMPOUND		ANIMAL FEED COMMODITY	MRL (MG/KG)
ADD:			
Fenpyrazamine			
AB	0269	Grape pomace, dry	1

The following withholding periods are required in relation to the above MRLs:

Wine grapes: Not required when used as directed

Table grapes: DO NOT harvest for 7 days after application
Grazing: DO NOT graze livestock in treated vineyards

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Sumitomo Chemical Australia Pty Ltd has applied to the Australian Pesticides and Veterinary Medicines Authority (APVMA) for the registration of the product Prolectus Fungicide containing a new active constituent fenpyrazamine (400 g/L). Prolectus Fungicide is a suspension concentrate (SC) formulation proposed for the control of grey mould (*Botrytis cinerea*) in table and wine grapes.

The use of Prolectus Fungicide will be restricted to ground application and will involve a spray concentration of 100 mL product (40 g ac)/100 L, with recommended spray volumes of 500–1000 L/ha for wine grapes and 1000–1500 L/ha for table grapes (a maximum application rate for any use of 1.5 L product/ha (600 g ac/ha)). The maximum number of applications is two with a minimum interval of 14 days between applications.

5.1 Commodities exported and main destinations

Grapes (including dried grapes) and wine are exported along with animals that have consumed feeds containing residues arising from the proposed use.

5.2 Destination and value of exports

Australian exports of wine were worth $1,867 million during 2012–13 financial year (Australian Commodity Statistics 2013[6]). The largest export markets by value are summarised below.

DESTINATION	VALUE ($ MILLION)
United States	482
United Kingdom	383
China	241
Canada	173
Hong Kong	84
New Zealand	77
Netherlands	70
Singapore	44
Japan	42

[6]www.agriculture.gov.au/abares/publications

Other	268
Total	**1,867**

In 2013, Australia exported more than 70,000 tonnes of fresh table grapes valued at $200 million. Hong Kong, Indonesia, Vietnam, New Zealand, Thailand, Singapore, Malaysia, the UAE, China and Russia were the major export destinations. Australia exported 1,200 tonnes of dried vine fruit worth $4.9 million during the 2012–13 (Australian Commodity Statistics 2013).

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

Total exports of dairy products in 2013/14 were worth $2.73 billion, with key export destinations including Japan, Singapore, China, Indonesia, Malaysia, Thailand, the Philippines, Korea, Russia, and the USA (Australian Commodity Statistics 2014[7]).

5.3 Proposed Australian use-pattern

Refer to Labelling requirements (page 48).

5.4 Overseas registration and approved label instructions

The applicant indicated that fenpyrazamine products are registered for use on wine grapes and table grapes in Europe with the following use patterns:

REGION	CROP	RATE (G AC/HA)	NUMBER OF APPLICATIONS	TOTAL G AC/HA/YEAR	WHP
Europe	Wine grapes	400–600	1	400–600	14 days
	Table grapes	400–600	1	400–600	7 days

[7] www.agriculture.gov.au/abares/publications

5.5 Comparison of Australian MRLs with Codex and overseas MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries.
Some countries may accept Codex CXLs when importing foods. Fenpyrazamine has not been considered by Codex but is on the priority list for evaluation by the JMPR in 2017.

COUNTRY/STATUS	RESIDUE DEFINITION	COMMODITY	TOLERANCE, MG/KG
Australia (proposed)	Fenpyrazamine (for enforcement)	Dried grapes	10
		Table grapes	2
		Wine grapes	0.05
EU	Fenpyrazamine	Products of animal origin–terrestrial animals	*0.01
		Table grapes	3
		Wine grapes	3
Japan	Fenpyrazamine	Grapes	10
US	Fenpyrazamine	Fruit, small vine climbing, except fuzzy kiwifruit, subgroup 13-07F *(includes grapes)*	3
		Grape, juice	4

The following relevant international MRLs have been established for fenpyrazamine:

5.6 Potential risk to trade

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

For wine grapes, an MRL at 0.05 mg/kg is proposed. The STMR and HR for parent fenpyrazamine in the Australian trials for wine grapes was <LOQ (i.e. below 0.01 mg/kg) and 0.02 mg/kg respectively and the median processing factor for wine is 0.75X. While Codex has not established MRLs for fenpyrazamine, the EU has established a wine grape MRL at 3 mg/kg, Japan has established a grape MRL at 10 mg/kg and the USA has established grape and grape juice MRLs at 3 mg/kg and 4 mg/kg respectively. The USA, UK, Netherlands and Japan are major destinations for Australian wine which have grape MRLs established at 3 mg/kg (or 10 mg/kg for Japan) and therefore the export risk to these destinations is considered to be low. Codex is currently expected to consider relevant MRLs in 2017/18. The trade risk for wine is considered to be low as residues above the LOQ of 0.01 mg/kg are unlikely to occur in wine.

For table grapes, an MRL at 2 mg/kg is proposed. The STMR and HR for parent fenpyrazamine in the Australian trials for table grapes were 0.41 and 1.2 mg/kg respectively. While codex has not established MRLs for fenpyrazamine, relevant MRLs for table grapes have been established by the EU and USA at 3 mg/kg and Japan at 10 mg/kg. The established international MRLs for grapes are higher than the proposed Australian MRL. The largest export markets of Australian table grapes are Hong Kong, Indonesia, Thailand, Vietnam and Singapore and therefore in the absence of Codex MRLs for fenpyrazamine, there is a potential risk to the trade of table grapes.

For dried grapes, an MRL at 10 mg/kg is proposed. The STMR-P and HR-P for dried grapes are calculated to be 1.9 and 5.6 mg/kg respectively on a parent fenpyrazamine basis.

The following label statement has been proposed to manage the trade risk associated with table grapes: ‘Treated table grapes for export to particular destinations outside Australia may require a longer interval before harvest to comply with residues standards of importing countries. Please contact your industry body, exporter or Sumitomo Chemical Australia before using PROLECTUS Fungicide’.

For animal commodities, The European Union has established an MRL for all products of animal origin (terrestrial animals) at *0.01 mg/kg but Codex and other countries have not established fenpyrazamine MRLs for animal commodities. As residues are not expected in animal commodities as a result of the proposed use and MRLs are recommended at LOQ (*0.01 mg/kg for meat and offal and *0.005 mg/kg for milk), the potential risk to trade of animal commodities is considered to be low.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Sumitomo Chemical Australia Pty Ltd has applied to the Australian Pesticides and Veterinary Medicines Authority (APVMA) for the registration of the product Prolectus Fungicide containing a new active constituent fenpyrazamine (400 g/L). Prolectus Fungicide is a suspension concentrate (SC) formulation proposed for the control of grey mould (*Botrytis cinerea*) in table and wine grapes.

6.1 Health hazards

The active constituent fenpyrazamine (CAS 473798-59-3) is not listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2015). With the available toxicology information, OCS recommends that fenpyrazamine not be classified a hazardous substance in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

Based on the product toxicology information and concentrations of active constituent fenpyrazamine, Prolectus Fungicide is not classified as a hazardous substance in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

6.2 Formulation, packaging, transport, storage and retailing

The active constituent fenpyrazamine will be manufactured overseas. The product Prolectus Fungicide will be manufactured in Australia and formulated in 1, 5, 10 or 20 L pack sizes in HDPE bottles (1 L), canisters (5 and 10 L) or drums (20 L) with plastic screw tops.

On 27 March 2015, the Delegate to the Secretary of the Department of Health published a final scheduling decision to create a new Schedule 5 entry for fenpyrazamine in the Poisons Standard for the Uniform Scheduling of Medicines and Poisons (www.tga.gov.au/publication/poisons-standard-susmp), with a cut-off to exempt in preparations at 40 per cent or less of fenpyrazamine and an implementation date of 1 June 2015.

Therefore, Prolectus Fungicide is exempt from classification under Schedule 5 as the concentration of fenpyrazamine is 400 g/L (ie 40% or less).

6.3 Use pattern

The use of Prolectus Fungicide will be restricted to ground application and will involve a spray concentration of 100 mL product (40 g ac)/100 L, with recommended spray volumes of 500–1000 L/ha for wine grapes and 1000–1500 L/ha for table grapes (a maximum application rate for any use of 1.5 L product/ha (600 g ac/ha)). The maximum number of applications is two with a minimum interval of 14 days between applications.

The applicant specified that the product will be applied by airblast (maximum spray tank capacity of 4000 L). It is used in wine grapes at a time between 10% flowering (E-L 20) and just prior to bunch closure (E-L 31), and in table grapes between 10% flowering (E-L 20) and prior to harvest (E-L 38). From information available to OCS, this period roughly corresponds to spring and summer periods.

The draft product label indicates the following restraints relevant to human health risk assessment:

- Do not apply by air
- Do not apply more than two sprays per season as over-use may lead to development of resistance.

The draft product label specifies a harvesting withholding period of seven days for table grapes, and states that a WHP is not required when used as intended on wine grapes.

6.4 Exposure during use

Farmers and their employees, as well as contract sprayers will be the main users of Prolectus Fungicide. Workers may be exposed to the product when opening containers, mixing/loading/application, cleaning up spills, maintaining equipment and entering treated crops. The main routes of potential exposure to the product will be dermal, inhalational and ocular.

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

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

Application of Prolectus Fungicide by airblast may lead to unintended bystander exposure *via* chemical spray drift. This may be in the form of a single random exposure or repeat exposures of residents who reside adjacent to areas being treated with the product. Parameters for assessing bystander exposure have not been finalised by the APVMA, though good agricultural practices are expected to be followed.

6.5 Exposure during re-entry

The OCS notes that the re-entry risks associated with conducting activities where the product has been applied are expected to be by the dermal route, and that exposure to fenpyrazamine is expected to occur at specific periods of time after application to a crop. As the MOEs after very high exposure activities in table grapes are acceptable (MOE > 500) on day zero after application, the OCS considers that the risks associated with re-entry activities are low after the spray has dried, and the following standard re-entry statement is recommended:

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

6.6 Recommendations for safe use

Users should follow the first aid instructions, safety directions and re-entry statements on the product label.

6.7 Conclusion

The registration of Prolectus Fungicide, containing 400 g/L fenpyrazamine for the control of grey mould (*Botrytis cinerea*) in grapes is supported.

Prolectus Fungicide can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product Safety Data Sheet (SDS).

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

Sumitomo Chemical Australia Pty Ltd has applied to the Australian Pesticides and Veterinary Medicines Authority (APVMA) for the registration of the product Prolectus Fungicide containing a new active constituent fenpyrazamine (400 g/L). Prolectus Fungicide is a suspension concentrate (SC) formulation proposed for the control of grey mould (*Botrytis cinerea*) in table and wine grapes.

The use of Prolectus Fungicide will be restricted to ground application and will involve a spray concentration of 100 mL product (40 g ac)/100 L, with recommended spray volumes of 500–1000 L/ha for wine grapes and 1000–1500 L/ha for table grapes (a maximum application rate for any use of 1.5 L product/ha (600 g ac/ha)). The maximum number of applications is two with a minimum interval of 14 days between applications.

Environmental fate and effects studies were provided in support of the application. These were considered sufficient to undertake a standard environmental risk assessment.

7.2 Environmental fate

Hydrolysis

Although fenpyrazamine is stable to hydrolysis under neutral or acidic conditions, it degraded moderately rapidly at 20°C and pH 9, with an estimated DT_{50} of 24 days. It degraded to S-2188-DC, with only some other minor metabolites detected. The metabolite S-2188-DC did not appear to significantly degrade further only partially oxidising to S-2188-OH with it accounting for 54% of the applied radioactivity at the end of the study.

Photolysis

Aqueous photolysis

Fenpyrazamine degraded readily via photolysis under conditions equivalent to those experienced in summer in northern Europe. The DT_{50} under those conditions was calculated as 1.7 days. The major degradates were S-2188-DC and MCNI, the latter reaching its maximum amount at the end of the study. The DT_{50} of the degradate S-2188-DC was also estimated and found to be moderately degradable, with a DT_{50} of 13 days.

Soil photolysis

Fenpyrazamine was found to be stable to photolysis in laboratory conditions with DT_{50}'s varying from 74–80 days.

Biodegradation

Aerobic soil metabolism

Fenpyrazamine is not readily biodegradable, with minimal degradation observed over 28 days. However, in soil biotic degradation is a major pathway and fenpyrazamine generally degraded fairly readily, with DT_{50} values of 24–68 days. There is little difference in the degradation rate between the phenyl and pyrazole labelled fenpyrazamine. Single-phase first order (SFO) kinetics provided a reasonable explanation of the degradation kinetics. Two metabolites were formed and identified as S-2188-DC and S-2188-OH but these only reached a maximum of 2.4% of applied radioactivity. Additional degradation products were up to 11 minor unidentified metabolites ≤2.2% of applied radioactivity and carbon dioxide (maximum 8.5% of applied radioactivity). The remainder consisted of soil bound residues, up to 51% of applied radioactivity. The identity of these bound residues was not determined, but there is evidence suggesting that these are simple polar compounds, structurally dissimilar to fenpyrazamine.

Anaerobic soil metabolism

Under anaerobic conditions fenpyrazamine degraded more slowly, with a DT_{50} of 129 days but was still regarded as slightly degradable. Oxygen levels were consistent with anaerobic conditions, but these could not be confirmed by the measured Redox potential, due to insufficient information on the reference electrode. Therefore the DT_{50} value needs to be treated with caution as aerobic degradation pathways cannot be excluded. The two metabolites observed for aerobic conditions were also observed for anaerobic conditions but were found in significantly greater amounts. In particular the amount of the metabolite S-2188-DC continued to increase until the end of the study, reaching 20% of applied radioactivity. Most of the remaining degradates were incorporated into the soil and could not be readily identified.

Aerobic aqueous metabolism

Under aerobic conditions in water/sediment systems, fenpyrazamine is slightly-to-readily degradable, with DT_{50} values of between 18 and 68 days. As with degradation in soil there is little difference in the degradation rate between the phenyl and pyrazole labelled fenpyrazamine. SFO kinetics also provided a reasonable explanation of the degradation kinetics. Dissipation from water is slightly more rapid with DT_{50} values of 10 to 25 days. Based on the R^2 values presented by the study author, SFO kinetics appears to provide a reasonable explanation of the degradation kinetics in water and the whole system and the Department of the Environment (DotE) did not investigate this further. Fenpyrazamine dissipated from the aqueous compartment to the sediment and reached a maximum of 33% of the applied radioactivity by day 14. Two major metabolites S-2188-DC and S-2188-OH were identified but only S-2188-OH occurred in amounts greater than 10% of applied radioactivity in both systems studied. A maximum of 12% of applied radioactivity for S-2188-OH was found in the aqueous compartment near the end (day 61 of 100) of one test. By the end of the study the majority (58–62%) of the applied radioactivity could be found in the sediment.

Anaerobic aqueous metabolism

Under anaerobic conditions in water/sediment, fenpyrazamine is also regarded as readily degraded, with a DT_{50} of 19 days for the whole system, which is comparable to the aerobic degradation rate. However, the DT_{50} value needs to be treated with caution for the same reasons as the anaerobic soil study and as such

aerobic degradation pathways cannot be excluded. Again there is little difference in the degradation rate between the phenyl and pyrazole labelled fenpyrazamine. Fenpyrazamine is metabolised under anaerobic conditions mainly to S-2188-DC.

Field dissipation

Under field conditions fenpyrazamine dissipated considerably faster, with half-lives of between 0.4 and 5.3 days in the top 30 cm of soil. The degradation was best described by double first order in parallel (DFOP) kinetics, suggesting that two mechanisms of dissipation may be occurring. However, extensive leaching of fenpyrazamine did not seem to occur as only very low levels were found below the 10 cm soil horizon in sandy soils. This is consistent with what would be expected from the laboratory studies on the mobility of fenpyrazamine, discussed below. Interestingly the highest concentration in the 10–20 cm horizon was found before any rainfall occurred and the reasons for this are unknown.

Mobility

Fenpyrazamine is generally regarded as having medium mobility with a mean Koc of 310 mL/g. However, on some soils the mobility is regarded as low while on others it has high mobility, with Koc values ranging from 112 to 731 mL/g. There was some correlation of adsorption of fenpyrazamine to organic carbon in soil, but other mechanisms may predominate. The average Freundlich co-efficient was 0.91, which is slightly lower than one. This shows that as the concentration of fenpyrazamine in water increases (to the level tested), there will be a similar increase in the concentration in soil; although there is a slight trend for the proportion in water in comparison with soil to become greater, as the concentration in both increases.

Bioconcentration

The bioconcentration factor (BCF) for fenpyrazamine is between 8 and 11, which is considered slightly concentrating. The log Pow of fenpyrazamine (3.52), is indicative of low potential for bioaccumulation but is only slightly below the value of 4, which is regarded as the boundary for the potential for bioaccumulation. However, the BCF value confirms the limited potential of fenpyrazamine for bioaccumulation.

Environmental effects

Birds

Fenpyrazamine is considered to be practically non-toxic to birds based on acute oral and short term dietary toxicity studies (LC_{50} >2000 mg ac/kg bw; LC_{50} >5000 mg ac/kg feed). However, reduced body weight gain was a notable dose responsive sub-lethal effect in both species, and abnormal pathology was also observed in mallard ducks. The dietary administration of fenpyrazamine on reproduction of the bobwhite quail and mallard duck over 30 weeks produced no significant effects on the reproductive capacity or symptoms of toxicity at dose levels up to 1000 mg ac/kg feed (No Observable Effects Concentration (NOEC) = 1000 mg ac/kg feed).

Aquatic organisms

Effects on fish

The acute toxicity of fenpyrazamine to rainbow trout and bluegill sunfish was similar with 96 h LC_{50} values of 5.2 to 5.4 mg ac/L, indicating a moderately toxic effect. Fenpyrazamine was also determined to be moderately toxic to sheepshead minnow noting that the concentration range was inadequate to determine an LC_{50} value (LC_{50} >3.9 mg ac/L). The toxicity of fenpyrazamine in the formulated product was similar (LC_{50} = 6.5 mg ac/L). No mortality or sub-lethal effects were observed in limit studies performed with the metabolites S-2188 DC, S-2188-OH and MCNI on rainbow trout and demonstrate that these metabolites were slightly toxic to fish from acute exposure. Chronic exposure of fenpyrazamine to rainbow trout and sheepshead minnow was found to be in the range of NOEC = 0.062 to 0.37 mg ac/L, indicating slight to moderate toxicity to fish.

Effects on aquatic invertebrates

Acute toxicity studies of fenpyrazamine and the formulated product on *Daphnia magna* indicate moderate toxicity to daphnids (48 h EC_{50} = 5.5 mg ac/L and 8.3 mg ac/L, respectively) but fenpyrazamine is highly toxic to mysids (96 h LC_{50} = 0.83 mg ac/L) and eastern oysters (96 h LC_{50} = 0.66 mg ac/L). Studies performed with the metabolites show that these metabolites are considerably less toxic to daphnids compared to the parent. Chronic toxicity studies of fenpyrazamine indicate slight toxicity to *Daphnia magna* (NOEC = 0.34 mg ac/L) and with no effects to the highest concentration tested, at worst, moderate toxicity to mysids (NOEC = 0.098 mg ac/L).

Effects on algae and aquatic plants

Fenpyrazamine is moderately to very highly acutely toxic and slightly-to-highly chronically toxic to the algae species tested (Green alga, blue-green algae, freshwater and marine diatom), with ErC_{50} = 0.068-4.39 mg ac/L and NOEC = 0.0049-0.22 mg ac/L, respectively. The freshwater diatom was the most sensitive to effects on cell density with a 96 h EC_{50} of 11 µg ac/L. However, as calculated by DotE based on the applicant's primary data, the marine diatom was the most sensitive to effects on growth rate with 72 h ErC_{50} of 68 µg ac/L. The formulation was determined to be moderately toxic with acute 72 h ErC_{50} = 2.6 mg ac/L. The metabolites were at worst moderately toxic with ErC_{50} values of >45 to >94 mg ac/L. Toxic effects on algae were determined to be algistatic rather than algicidal.

Fenpyrazamine is moderately toxic to aquatic plant *Lemna gibba* with 7 d ErC_{50} of 4.9 mg ac/L with clear dose-responsive inhibition in growth rate and frond number.

Effects on sediment dwelling organisms

Water-spiked fenpyrazamine elicited no biologically significant effect to midges over their full life cycle up to the highest concentration tested (28 d NOEC = 980 µg ac/L) but significant effects on growth and reproduction were observed in estuarine amphipods (28 d NOEC = 6.6 mg ac/kg). On this basis, fenpyrazamine is slightly-to-moderately toxic to sediment dwelling organisms.

Terrestrial organisms

Effects on bees

Fenpyrazamine is only very slightly toxic to bees that have been exposed to fenpyrazamine through oral or contact applications (LD50 > 100 µg ac/bee) so no risk management instructions are required on the product label.

Effects on non-target terrestrial arthropods

No effects were observed up to 1200 g ac/ha on the predatory mite (*Typhlodromus pyri*) and parasitoid wasps (*Aphidius rhopalosiphi*) following exposure to a 50% WG formulation of fenpyrazamine.

Effects on earthworms

Fenpyrazamine had no effect on mortality up to the highest rate tested (LC_{50} >800 mg ac/kg; at worst, slightly toxic) but elicited significant dose response reductions in body weight. No adverse effects on body weight or reproduction were observed in chronic studies (56 d NOEC = 9.6 mg ac/kg soil).

Soil micro-organisms

Testing of fenpyrazamine on soil micro-organisms at 3.0 kg ac/ha revealed no significant adverse effects on soil respiration and nitrification.

Effects on terrestrial plants

The effects of the 50% WG formulation at 600 g ac/L on terrestrial vascular plants were studied.
No significant adverse effect on both seedling emergence and vegetative vigour of six plant species with 21 d NOER = 600 g ac/ha.

7.3 Risk assessment

In considering the submitted data, DotE has given particular attention to the potential risk to organisms in aquatic and terrestrial environments. Based on the submitted data, the risk to birds, mammals, plants, bees, earthworms and other non-target terrestrial invertebrates was found acceptable, and no harmful impact on soil nitrogen and carbon metabolism is expected from the proposed uses. Based on the acute and chronic aquatic toxicity studies provided, with the proposed uses the risk to aquatic and sediment-dwelling organisms from spray drift, run-off or to groundwater were found acceptable provided a downwind no-spray zone to aquatic areas of 15 m is required.

8 EFFICACY AND CROP SAFETY ASSESSMENT

Sumitomo Chemical Australia Pty Ltd has applied to the Australian Pesticides and Veterinary Medicines Authority (APVMA) for the registration of the product Prolectus Fungicide containing a new active constituent fenpyrazamine (400 g/L). Prolectus Fungicide is a suspension concentrate (SC) formulation proposed for the control of grey mould (*Botrytis cinerea*) in table and wine grapes.

8.1 Proposed product use pattern

The use of Prolectus Fungicide will be restricted to ground application and will involve a spray concentration of 100 mL product (40 g ac)/100 L, with recommended spray volumes of 500–1000 L/ha for wine grapes and 1000–1500 L/ha for table grapes (a maximum application rate for any use of 1.5 L product/ha (600 g ac/ha)). The maximum number of applications is two with a minimum interval of 14 days between applications.

For wine grapes, application will occur between 10% flowering (E-L 20) and just prior to bunch closure (E-L 31). For table grapes, application will occur between 10% flowering (E0L 20) and prior to harvest (E-L 38)[8].

8.2 Assessment of study/trial data

The results of 16 trials on the efficacy and crop safety of Prolectus Fungicide were presented. The trials were carried out under commercial conditions in vineyards in major wine growing areas around Australia (Tasmania, Western Australia, South Australia, Victoria and Queensland).

All trials were randomised complete block design with 3 or 4 replicates and un-treated controls. Statistical analyses were carried out on all trials.

Application was by spray until the point of run-off. Several different spray programmes were used starting at different stages in the development of the grapes. While there were 4 applications in most trials, in two trials there were three applications and in 4 trials there were two applications.

The rates tested ranged from 30 g ac/100L to 60 g ac/100L. The proposed rate for Prolectus Fungicide is 100mL/100L which equates to 40 g ac/100L. In many of the trials, the surfactant, Maxx was added. The addition of Maxx at 30 mL/100L is recommended on the proposed label to improve efficacy.

The trials assessed efficacy [incidence (% bunch infected) and severity (% bunch area infected)] in general and under different spray programme and phytotoxicity to riesling, chardonnay and sauvignon blanc wine grape varieties and on red gobe, white muscat, crimson seedless and Thompson seedless table grapes.

[8] Note that the EL growth stage of grapes is explained here: www.awri.com.au/wp-content/uploads/grapegrowth.pdf

The trial results showed that overall treatment with Prolectus Fungicide was effective in reducing the incidence and severity of grey mould disease in wine and table grapes. The addition of Maxx surfactant generally increased efficacy, however the degree of efficacy depended on the spray programmed being followed. In general, spray programmes that had the first application early in the development of the grapes were more effective than those that began later. In all the trials efficacy of Prolectus Fungicide was equivalent to, or better than, the industry standards tested.

It is concluded from the trial results presented, that treatment with Prolectus Fungicide according to the proposed label directions, will be effective in controlling grey mould (*Botrytis cinerea*) disease in wine and table grapes.

Crop safety

No phytotoxic effects were observed at any rate or any application. Trial results showed that fenpyrazamine is safe to use on wine and table grapes at rates up to 60 g ac/ha.

The information and data presented indicate that Prolectus Fungicide is safe to use on wine and table grapes when used as directed.

Resistance management

Fenpyrazamine is a pyrazole fungicide that presents its fungicidal activity through inhibition of germ tube elongation and mycelium elongation.

The Fungicide Resistance Action Committee (FRAC), a specialist technical group of CropLife International, has designated fenpyrazamine as a Group 17 fungicide. The proposed use of Prolectus Fungicide is subject to a CropLife Australia Fungicide Resistance Management Strategy which limits the total number and consecutive number of applications of the product.

8.3 Conclusion

The claims on the proposed label that Prolectus Fungicide provides acceptable control of grey mould (*Botrytis cinerea*) disease in wine and table grapes when used as directed is supported by the results from the Australian trials.

Acceptable crop safety is expected when the product is used as directed. The directions for use are appropriate and consistent with fungicide use in commercial agriculture in Australia.

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

9 LABELLING REQUIREMENTS

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Prolectus®

Fungicide

ACTIVE CONSTITUENT: 400 g/L FENPYRAZAMINE

GROUP	17	FUNGICIDE

For the Control of Grey mould in Grapes, as specified in the Directions for Use Table.

IMPORTANT: READ THE ATTACHED BOOKLET BEFORE USING THIS PRODUCT.

CONTENTS: 5 L, 20 L

SUMITOMO CHEMICAL

Sumitomo Chemical Australia Pty Ltd
204 Beecroft Road
Epping NSW 2121
Tel: 02 8752 9000
A.B.N. 21 081 096 255

® Registered Trademark of Sumitomo Chemical Co., Japan

DIRECTIONS FOR USE:

RESTRAINTS:

DO NOT apply if heavy rain has been forecast over the next 72 hours.
DO NOT apply more than two sprays per season with a minimum interval of 14 days as over-use may lead to development of resistance.
DO NOT apply with aircraft.

SPRAY DRIFT RESTRAINTS:

DO NOT apply when wind speed is less than 3 or more than 20 kilometres per hour.
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.
DO NOT apply if there are aquatic and wetland areas including aquacultural ponds, surface streams and rivers within 15 metres downwind from the application area.

CROP	PEST	RATE	CRITICAL COMMENTS
Wine grapes	Grey mould *(Botrytis cinerea)*	100 mL/100L **Dilute spraying** Water rate should be adjusted to growth stage and size of foliage to give good coverage. Generally between 500 and 1000 L/ha **Concentrate spraying** Refer to the **Application** section	Apply as part of a botrytis control spray program between 10 % flowering (E-L 20) and berries pea size – just prior to bunch closure (E-L 31). **DO NOT** apply after E-L 31. **DO NOT** apply more than 2 sprays of PROLECTUS in any one season, with a minimum 14 day interval. Apply by dilute or concentrate spraying equipment but ensure that sufficient water is used and the sprayers are directed to get good penetration of the canopy and coverage of flowers or bunches. Maxx organosilicone surfactant is recommended at 30mL/100L as this provides increased penetration of flowers and bunches and so improves the result.
Table grapes	Grey mould *(Botrytis cinerea)*	100 mL/100L **Dilute spraying** Water rate should be adjusted to growth stage and size of foliage to give good coverage. Generally between 1000 and 1500 L/ha **Concentrate spraying** Refer to the **Application** section	Apply as part of a botrytis control spray program between 10 % flowering (E-L 20) and 7 days prior to harvest (E-L 38). **DO NOT** apply more than 2 sprays of PROLECTUS in any one season, with a minimum 14 day interval. Apply by dilute or concentrate spraying equipment but ensure that sufficient water is used and the sprayers are directed to get good penetration of the canopy and coverage of flowers or bunches. Maxx organosilicone surfactant is recommended at 30 mL/100L as this provides increased penetration of bunches and will improve the result.

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

WITHHOLDING PERIODS:

WINE GRAPES:	**NOT REQUIRED WHEN USED AS DIRECTED**
TABLE GRAPES:	**DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION**
GRAZING:	**DO NOT GRAZE LIVESTOCK IN TREATED VINEYARDS**

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

GENERAL INSTRUCTIONS

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

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

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. Avoid excessive run-off.
- The required water volume may be determined by applying different test volumes, using different settings on the sprayer, from industry guidelines or expert advice.
- Add the amount of product specified in the Directions for Use table for each 100 L of water. Spray to the point of run-off.
- The required dilute spray volume will change and the sprayer set up and operation may also need to be changed, as the crop grows.

Concentrate Spraying: DO NOT use less than 1000 L per hectare of water once vines reach full size (2.5 m high).
- Use a sprayer designed and set up for concentrate spraying (that is a sprayer which 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 (for vines which have not yet reached full size):
1. Dilute spray volume as determined above: **for example** 1000 L/ha
2. Your chosen concentrate spray volume: **for example** 500 L/ha
3. The concentration factor in this example is: **for example** 2X (that is, 1000 L ÷ 500 L = 2)
4. If the dilute label rate is 40 g/100 L, then the concentrate rate becomes 2 X 40, that is, 80 g/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.

Wetting Agent

Add MAXX Organosilicone Surfactant at the rate of 30 mL/100 L of spray. Do not exceed this rate.
FUNGICIDE RESISTANCE WARNING:

GROUP	17	FUNGICIDE

PROLECTUS Fungicide is a member of the hydroxyanilide group of fungicides. For fungicide resistance management PROLECTUS Fungicide is a Group 17 fungicide. Some naturally occurring individual fungi resistant to the product and other Group 17 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungal population if these fungicides are used repeatedly. These resistant fungi will not be controlled by this product and other Group 17 fungicides, thus resulting in a reduction in efficacy and possible yield loss. Since the occurrence of resistant fungi is difficult to detect prior to use, Sumitomo Chemical Australia Pty Ltd accepts no liability for any losses that result from failure of this product to control resistant fungi.

Resistance management strategy:
DO NOT apply PROLECTUS Fungicide more than two times per season, with a minimum 14 day interval.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Very toxic to aquatic life. **DO NOT** contaminate streams, rivers or waterways with the product or used containers.
DO NOT apply PROLECTUS Fungicide if wind is likely to cause drift onto natural and impounded lakes, waterways, streams or rivers.

STORAGE AND DISPOSAL:

Store in the closed original container in a well-ventilated area, as cool as possible, although avoid freezing. Do not store for prolonged periods in direct sunlight.

Triple or preferably pressure rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point.

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

SAFETY DIRECTIONS:

When opening the container and preparing spray wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length chemical resistant gloves.

When using the prepared spray wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and a washable hat.

Wash hands after use. After each day's use wash contaminated clothing.

RE-ENTRY:
Do not allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

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

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

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

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

APVMA Approval No.:

Batch No:

Date of Manufacture:

ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
BBCH	**B**iologische **B**undesanstalt, Bundessortenamt and **CH**emical industry
BCF	Bio-concentration Factor
bw	bodyweight
^{o}C	Degrees Centigrade
^{14}C	Carbon 14
CXL	Codex MRL
d	day
cm	Centimetre
DotE	Department of the Environment
DFOP	Double first order in parallel
DT_{50}	Time taken for 50% of the concentration to dissipate
EC_{50}	concentration at which 50% of the test population are immobilised
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
F_1	First Generation
F_2	Second generation
FRAC	Fungicide Resistance Action Committee
g	gram
GAP	Good Agricultural Practice
GLP	Good Laboratory Practice
GPMT	Guinea Pig Maximisation Test
h	hour
ha	hectare

HDPE	High Density Polyethylene
HR	Highest residue
HR-P	HR corrected for processing
id	intradermal
im	intramuscular
pH	Potential of hydrogen
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
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—Mass Spectrometry/Mass Spectrometry
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
LOQ	Limit of Quantitation – level at which residues can be quantified
$MgSO_4$	Magnesium Sulphate
mg	milligram
mL	millilitre
MOE	Margin of Exposure
MRL	Maximum Residue Limit
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram

NaCl	Sodium Chloride
NOEC/NOEL	No Observable Effect Concentration/Level
OC	Organic Carbon
OCS	Office of Chemical Safety (in the Department of Health)
OM	Organic Matter
P	Parental
PF	Processing Factor
PHED	Pesticide Handler Exposure Database
po	oral
PPE	Personal Protective Equipment
ppm	parts per million
QuEChERS	Quick Easy Cheap Effective Rugged Safe
s	second
sc	subcutaneous
SC	Suspension Concentrate
SDS	Safety Data Sheet
SFO	Single-phase first order
STMR	Supervised Trials Medium Residues
STMR-P	STMR corrected for processing
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGAC	Technical grade active constituent
TSH	Thyroid-stimulating hormone
TTR	Total Radioactive Residue
µg	microgram
WG	Water Dispersible Granule
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.
Algicidal	Having the property of killing algae
Algistatic	Having the property of inhibiting algal growth
Bio-concentration Factor (BCF)	The concentration of a contaminant in an organism compared to the surrounding ambient environment
Carcinogenicity	The ability to cause cancer
Central Tendency	In statistics, a central tendency is a central or typical value for probability distribution
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Chronic	Of long duration
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
Guinea Pig Maximisation Test (GPMT)	Is an in vivo test to screen for substances that cause human skin sensitisation (i.e. allergens)
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Mean	In statistics, mean refers to the mean or average that is used to derive the central tendency of the data in question. It is determined by adding all the data points in a population and then dividing the total number by the number of points.
Metabolism	The chemical processes that maintain living organisms
pH	A figure expressing the acidity or alkalinity of a solution on a logarithmic scale on which 7 is neutral, lower values are more acid and higher values more alkaline. The pH is equal $-\log_{10} [H^+]$ where $[H^+]$ is the hydrogen ion concentration in moles per litre
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
S-2188	The manufacturers code for fenpyrazamine
S-2188-DC, S-2188-OH	Metabolites of S-2188 (fenpyrazamine)

and MCNI	
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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