Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active METRAFENONE in the Product

VIVANDO FUNGICIDE

APVMA Product Number 63487

DECEMBER 2010

This document is published by the APVMA. In referencing this document the APVMA should be cited as both author and publisher.

ISSN:

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

Comments and enquiries may be directed to:

Contact Officer

Pesticides Program

Australian Pesticides & Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604
Australia

Telephone: +61 2 6210 4748
Fax: +61 2 6210 4776
Email: AgProductscoordinator@apvma.gov.au

CONTENTS

PREFACE

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

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Ageing, Office of Chemical Safety and Environmental Health (OCSEH), Department of Environment, Water, Heritage and the Arts (DEWHA), 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 undertaken according to accepted scientific principles. Details are outlined in the APVMA's publications *Ag MORAG: Manual of Requirements and Guidelines* and *Vet MORAG: Manual of Requirements and Guidelines*.

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

About this document

This is a Public Release Summary.

It indicates that the Australian Pesticides and Veterinary Medicines Authority (APVMA) is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

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

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

Making a submission

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

Submissions must be received by the APVMA by close of business on **21/01/2011** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

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

All personal and ***confidential commercial information (CCI)***[1] material contained in submissions will be treated confidentially.

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

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:

Contact Officer, Pesticides Program

Australian Pesticides & Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604
Australia

Telephone: +61 2 6210 4748
Fax: +61 2 6210 4776
Email: pesticides@apvma.gov.au

Further information

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

Copies of full technical evaluation reports covering toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA on request.

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

1 INTRODUCTION

Applicant

BASF Australia Ltd.

Details of Product

It is proposed to register Vivando Fungicide, containing metrafenone (500 g/L) as a suspension concentrate formulation. The product is intended for use for the control of powdery mildew (*Podosphaera xanthii*) of cucurbits and powdery mildew (*Erysiphe necator*) of grapevines. Vivando Fungicide is intended to be used at a rate of 150-300mL product/ha in cucurbits and 20mL product/100L water (dilute application rate) in grapevines.

Metrafenone is a new active constituent to the Australian market. It is a fungicide which belongs to the benzophenone chemical group and represents the first commercial development from this group. The Fungicidal Mode of Action of the benzophenone group is still under evaluation and it appears to be novel and shows no sign of any cross-resistance when tested on strains of powdery mildew that have developed tolerance to other fungicide groups.

Metrafenone is currently registered for use in Europe (Table and wine grapes, various vegetables and cereal grains) and in Korea (Cucumbers and Korean melons). US import tolerances have been established for grapes.

Vivando Fungicide is new to the Australian market**.** The active metrafenone as well as the end-use product will be manufactured overseas and imported into Australia. Metrafenone is in the new group U8 (unspecified) for fungicides resistance management.

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

2 CHEMISTRY AND MANUFACTURE

2.1 Active Constituent

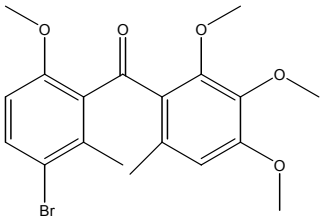
Metrafenone is a new active constituent, for use in grapevines and cucurbits for the control of powdery mildew.

Manufacturing Site

The active constituent metrafenone is manufactured by Kemfine Ltd. Kemerantie 1, KI-67701, Kokkola, Finland.

Chemical Characteristics of the Active Constituent

The chemical active constituent metrafenone has the following properties:

COMMON NAME:	Metrafenone (ISO approved)
IUPAC NAME:	3'-Bromo-2,3,4,6'-tetramethoxy-2',6-dimethylbenzophenone
CAS NAME:	(3-Bromo-6-methoxy-2-methylphenyl)(2,3,4-trimethoxy-6-methylphenyl)-methanone
CAS REGISTRY NUMBER:	220899-03-6
MANUFACTURER'S CODE:	CL 375839; BAS 560 F
MOLECULAR FORMULA:	$C_{19}H_{21}BrO_5$
MOLECULAR WEIGHT:	409.280
STRUCTURE:	
CHEMICAL FAMILY:	Aryl phenyl ketone fungicides

APVMA Active Constituent Standard for METRAFENONE Active Constituent

Constituent	Specification	Level
Metrafenone	White to beige coloured solid	Minimum 975 g/kg

Physical and Chemical Properties of Pure Active Constituent

COLOUR	White to chalky-white
PHYSICAL STATE	Solid
ODOUR	Low intensive musty smell
MELTING POINT	99.2 – 100.8 °C
VAPOUR PRESSURE AT 20°C	1.53×10^{-4} Pa (1.53×10^{-1} mbar) at 20°C 2.56×10^{-4} Pa (2.56×10^{-1} mbar) at 25°C
WATER SOLUBILITY AT 20°C	0.552 (pH 5), 0.492 (pH 7), 0.457 (pH 9) (all in mg/L).
SOLUBILITY IN ORGANIC SOLVENTS	acetone 403, acetonitrile 165, dichloromethane 1950, ethyl acetate 261, n-hexane 4.8, methanol 26.1, toluene 363 (all in g/L)
PARTITION COEFFICIENTS (N-OCTANOL/WATER)	Log K_{ow}: 4.3 (pH 4.0, 25 °C)

2.2 Product

DISTINGUISHING NAME	Vivando Fungicide
FORMULATION TYPE	Suspension concentrate (SC)
ACTIVE CONSTITUENT CONCENTRATION	Metrafenone (500 g/L)

Physical and Chemical properties of the Product

APPEARANCE	Beige suspension liquid
ODOUR	Aliphatic
ACIDITY/ALKALINITY	pH 7.2 – 7.6 (1% dilution@ 20 °C)
DENSITY	1.18 g/mL
VISCOSITY	129 mPa.s @ 20 °C
FLASH POINT	85 ± 2 °C
AUTOIGNITION	365 ± 10 °C
EXPLOSIVITY	Not explosive
OXIDISING PROPERTIES	Not oxidising
FLAMMABILITY	No evidence of flammable properties
SURFACE TENSION	At 25 °C: 41.0 mN/m - neat product: 62.4 mN/m – 0.013% aqueous solution
STORAGE STABILITY	Stability data provided by the applicant indicates that the product is expected to remain within specification for at least 2 years when stored under normal conditions in HDPE containers.
LOW TEMPERATURE STABILITY	Chemically and physically stable in HDPE packs after 12 weeks at 37 °C and following five freeze/thaw cycles at –18 °C/20 °C

Recommendation

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

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

Metrafenone is a new fungicide to the Australian market. There appeared to be an extensive body of information on the chemical 'backbone' of metrafenone. The product, VIVANDO® Fungicide, contains 500g/L of metrafenone as a suspension concentrate formulation.

Following oral administration in rats, metrafenone was well absorbed. It was poorly distributed in tissues and found mainly in the liver, kidney, muscle, fat, adrenals and blood (totalling <10%). Radio-labelled metrafenone was extensively metabolised in tissues, resulting in up to twenty or more metabolites mainly via O-dealkylation, aliphatic oxidation, debromination, ring hydroxylation and conjugation. The parent compounds were detectable in rat faeces, liver, body fat and kidney in relatively small quantities. The terminal half-life of orally administered metrafenone was 40 - 55 hours in the blood. Orally administered metrafenone was almost completely eliminated from rats within 72 h and only trace amounts left after 7 days. An *in vivo* dermal absorption study in male rats indicated that absorption of metrafenone through the skin is limited. Metrafenone has low acute oral, dermal and inhalational toxicity in rats, it is not a skin or eye irritant in rabbits and is not a skin sensitiser in guinea pigs. The formulated product, containing 500g/L metrafenone has low acute oral, dermal and inhalational toxicity in rats, it is not a skin or eye irritant in rabbits and is not a skin sensitiser in guinea pigs.

Repeat dose studies on metrafenone (active constituent) indicated that the liver is the main target organ in all the species studied. There was an increase in the liver weight as well as several incidences of centrilobular hepatocellular hypertrophy in most species studied. In addition to the liver, at higher doses increased kidney weights as well as reduced spleen and thymus weights were observed in rats. Changes in biochemical parameters were noted mostly in dogs. In rats, increased cholesterol was consistently observed in females irrespective of the study duration. In the chronic studies in mice and rats, metrafenone administration resulted in an increase in the incidence in hepatocellular adenoma in male mice and male and female rats at high dose levels (i.e. >1000 mg/kg bw/day in male mice, and at dose levels exceeding the maximum tolerated dose in rats). Metrafenone was neither a reproductive toxicant in Sprague Dawley (SD) rats nor a developmental toxicant in New Zealand White (NZW) rabbits or SD rats. It was not mutagenic or genotoxic in a series of *in vitro* tests, or genotoxic in an *in vivo* test.

Workers may be exposed to the product when opening containers, mixing/loading, application and cleaning up spills and equipment. The main route of exposure to the product/spray will be dermal and inhalation, although ocular exposure is also possible. Based on the risk assessment conducted, First Aid Instructions and Safety Directions and Re-entry statements have been recommended and shown on the product label.

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

3.2 Summary of The Evaluation of Toxicological Studies

The toxicological database for metrafenone, which consists primarily of toxicity tests conducted in laboratory animals, is quite extensive. In interpreting the data, it should be noted that toxicity tests generally use doses

that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are used to develop acceptable limits for dietary or other intakes (ADI and ARfD) at which no adverse health effects in humans would be expected.

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

Toxicokinetics and Metabolism

After oral administration, metrafenone is absorbed fairly rapidly with a T_{max} of 8-15 h following a single dose of 10 mg/kg bw. A 100 fold increase in the amount of metrafenone administered resulted in about 10 fold increase in the C_{max} in the blood and a 16 fold increase in the total blood exposure ($AUC_{0-\infty}$) to the compound. Radio-labelled metrafenone was well absorbed in rats (>88%) after oral administration. Data from bile-cannulated rats indicated that absorption was saturable, since only 15 - 17% of the dose was detected in the bile following a single oral dose of 1000 mg/kg bw compared to 85 – 90% following administration of 10 mg/kg bw. Radio-labelled metrafenone was extensively metabolised in tissues, resulting in up to twenty or more metabolites mainly via O-dealkylation, aliphatic oxidation, debromination, ring hydroxylation and conjugation. The bond between the bromophenyl ring and trimethoxyphenyl was uncleaved and the parent compounds were detectable in rat faeces, liver, body fat and kidney albeit in relatively small quantities. Metrafenone was poorly distributed in tissues. Apart from the GI and the GI tract, other tissues with appreciable levels of metrafenone (totalling <10%) were liver, kidney, muscle, fat adrenal and blood. Following a single oral administration of a single dose of 10 and 100 mg metrafenone/kg bw the plasma terminal half-life was 40 - 55 hours. In rats, orally administered metrafenone was almost completely eliminated within 72 h, with only trace amounts left after 7 days

Using a solution containing radio-labelled metrafenone at 5 mg/cm^2 or 0.0025 mg/cm^2 per animal (equivalent to about 180 and 0.1 mg/kg bw respectively) for 10 hr, the dermal absorption of metrafenone in rats, is approximately 19%.

Acute Toxicity

Metrafenone has low acute oral, dermal and inhalational toxicity in rats (LD_{50} > 5000 mg/kg bw, LD50 > 5000 mg/kg and 4-h LC_{50} > 5000 mg/m^3 respectively). The compound was not a skin or eye irritant in rabbits. Metrafenone was not a skin sensitiser in guinea pigs. Metrafenone posesses no phototoxic or photoallergenicity potential in guinea pigs. The formulated product, VIVANDO® Fungicide, has low acute oral, dermal and inhalational toxicity in rats (LD_{50} > 5000 mg/kg bw, LD_{50} > 5000 mg/kg bw and 4-h LC_{50}

>3700 mg/m^3 the highest obtainable exposure concentration, respectively). It was not a skin or eye irritant in rabbits and not a skin sensitiser in guinea pigs.

Short term and subchronic toxicity studies

Metrafenone was administered in diets at doses up to approximately 1600 mg/kg bw/d in mice, 2300 mg/kg bw/d in rats and 500 mg/kg bw/d in dogs. Studies were performed for varying lengths of time according to OECD test guidelines. The primary target organ of toxicity following repeated administration of metrafenone in these species was the liver (mainly as increased liver weight) with accompanying histopathological changes seen, such as hepatocellular hypertrophy, in some cases. In addition to effects on the liver, increased kidney weights as well as reduced spleen and thymus weights were generally observed in rats at higher doses. In addition to increased liver weights, changes in biochemical parameters were noted in dogs. In the 13-week study, an increased neutrophil count was seen in dogs at the highest dose administered. While in the 1-year study, increased neutrophil and monocyte counts were increased in dogs in the mid and high dose groups. In female rats, increased cholesterol was consistently observed across studies i.e. in short-term, subchronic and chronic studies.

Long term toxicity and carcinogenicity

In the chronic studies in mice and rats, metrafenone administration resulted in an increased incidence in hepatocellular adenoma in male mice only and male and female rats at high dose levels (i.e. at a dose >1000 mg/kg bw/d in male mice and at doses that produced a > 10% decrease in body weight gain in rats). However, these oncogenicity findings of benign tumours cannot be dismissed as, compared to controls, there was a dose related increase in liver adenomas. Furthermore, there was a dose-related increased incidence in a number of non-neoplastic histopathological changes in the liver, such as hepatocellular hypertrophy. Additional studies provided failed to pinpoint the mechanistic basis of this carcinogenic property of metrafenone (even though these were carried out using either a single dose or repeat doses over 1 or 4 weeks).

Aside the carcinogenicity findings, the data available suggests that the rat is the most sensitive species. Female rats in this 24-month study had reduced body weight gain at 5000 ppm or greater, while a significant elevation of blood cholesterol was also observed in female rats at this dose and above after 3 months. Increased gamma glutamyl transferase (GGT) activity was seen from 6 months in males at 20000 ppm, and from 50000 ppm at 24 months. Increased liver and kidney weights were seen from 12 months in both sexes at ≥5000 ppm metrafenone. Therefore, the lowest dose of 500 ppm (equivalent to 24.9 mg/kg bw/d in males) was established as the NOEL in this rat oncogenicity study (with a NOEL for carcinogenicity of 30.4 mg/kg bw/d based on hepatocellular adenomas in females).

Reproduction and Developmental Studies

In the 2-generation reproduction study, the thymus weight in both sexes of rats was significantly reduced in parental animals and pups following metrafenone administration. The reduction in the thymus weight got

progressively worse in F1 and F2 generations, with a reduction in thymus weight of approximately 50% seen in F2 females at weaning at the highest dose tested. The toxicological significance of this thymic weight reduction is unclear, since thymic involution (profound reduction in thymus size) is a natural phenomenon that occurrs with age.

Metrafenone is not a reproductive toxicant in SD rats, nor is metrafenone a developmental toxicant in NZW rabbits or SD rats. In a developmental study in rabbits the maternal and developmental NOEL were 50 and 350 mg/kg bw/d respectively. The maternal NOEL was based on decreased food consumption with attendant body weight decrease and effects on the liver at the next higher dose of 350 mg/kg bw/d. The developmental NOEL was based on decreased live foetal body weight at the highest dose as well as increased incidence of dead foetuses from dams with premature delivery at the highest dose, 700 mg/kg bw/d.

Genotoxicity Studies

Metrafenone was not mutagenic or genotoxic *in vitro,* and was not genotoxic *in vivo*.

Neurotoxicity Studies

No neurotoxicity tests were available for evaluation.

3.3 Public Health Standards

Poisons Scheduling

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

At its 58th meeting of February 2010, the NDPSC agreed that (i) the benign liver tumours in metrafenone-administered to mice and rats are unlikely be encountered in humans considering the proposed product use pattern, and (ii) metrafenone has low acute toxicity, it is non-irritating to eyes and skin, and has no skin sensitization potentials. Therefore, the Committee decided to include metrafenone in Schedule 6, with a cut-off to Schedule 5 for preparations containing 50 percent or less of metrafenone.

NOEL/ADI /ARfD

The Acceptable Daily Intake (ADI) is the quantity of an agricultural compound which can safely be ingested on a daily basis for a lifetime and is based on the NOEL for the most sensitive toxicological endpoint obtained in the most sensitive species. This NOEL is then divided by a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

The ADI for metrafenone was established at 0.25 mg/kg bw/day based on a NOEL of 24.9 mg/kg bw/day in a 24-month dietary study in rats and applying a safety factor of 100.

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

An ARfD for metrafenone has not been established and there is insufficient data to enable an ARfD to be set.

4 RESIDUES ASSESSMENT

4.1 Introduction

As part of the residues assessment for metrafenone, plant and animal metabolism studies, supervised residue trials, processing studies and trade aspects were considered. Details are provided below.

4.2 Metabolism

Metabolism studies in grapevines, cucurbits, wheat, rotational crops, rats, goats and hens have been submitted for metrafenone.

Plant Metabolism

Studies were conducted on grapevines, cucumbers, wheat, lettuce, radish and canola to determine the total radioactive residues (TRR) in these commodities after treatment with ^{14}C-labelled metrafenone.

Grape plots were treated with metrafenone labelled with ^{14}C in either the bromophenyl or trimethoxyphenyl ring. Five foliar applications were made at 10-11 day intervals at a rate of 200 g ai/ha per application. Analysis of grape extracts taken immediately after the final application showed the parent compound accounted for 53.3 and 40.7% TRR, for the bromophenyl and trimethoxyphenyl labels, respectively. Parent compound was not detected in juice samples. Residues in juice were composed primarily of multiple metabolites, none of which exceeded 4% TRR (0.003 mg mg ai equiv./kg) or 9% TRR (0.006 mg ai equiv./kg) for the respective labels. In the marc extract the parent compound was identified as the major residue component, accounting for 24.7% TRR for the bromophenyl label and 22.8% TRR for the trimethoxyphenyl label, in mature grapes. The remaining residue consisted of metabolite fractions (composed of several compounds) more polar than the parent compound, none of which exceeded 12% TRR (0.05 mg mg ai equiv./kg) or 17% TRR (0.046 mg ai equiv./kg), for the respective labels. Metabolite fractions were not characterised further as they could not be definitely identified due to low metabolite concentrations and high matrix effects.

In the cucumber metabolism study, plots were treated with two applications of ^{14}C labelled metrafenone (U-^{14}C-trimethoxyphenyl-label) at an application rate of 200 g ai/ha per application. Applications were made 17 and 3 days before harvest. Parent compound was the major residue component in cucumber leaves taken on the day of harvest being found at 95.0% TRR (6.0764 mg ai equiv./kg). In the rest of plant and peel samples taken 17 days after the first treatment, parent compound was found at 80.4% TRR (7.0837 mg ai equiv./kg) and 61.0% TRR (0.1607 mg ai equiv./kg /kg), respectively. In fruit, parent metrafenone was also the main component accounting for 0.0216 mg ai equiv./kg (42.4% TRR) and 0.0021 mg ai equiv./kg (12.6% TRR) for samples taken at 17 and 14 days after first treatment, respectively. In the sample taken at 14 days, other eluted components were below or equal to 8.9% TRR (0.0015 mg mg ai equiv./kg), while in the 17 day sample other components were each below or equal to 7.3% TRR (0.0037 mg ai equiv./kg). Parent compound in pulp was found at a level of 0.0009 mg ai equiv./kg (6.5% TRR), with other eluted components each below or equal to 12.1% TRR (0.0016 mg ai equiv./kg).

In the wheat metabolism study, plots were treated with three applications of metrafenone labelled with ^{14}C in either the bromophenyl or trimethoxyphenyl ring. Applications were made at 14 day intervals with application rates of 200 or 300 g ai/ha and a total application of 800 g ai/ha. Parent compound was the major residue component identified in the forage, hay, straw and grain. For forage collected 3 days after the first treatment, parent accounted for 64.4% TRR (5.261 mg ai equiv./kg) and 58.9% TRR (3.101 mg ai equiv./kg) for the bromophenyl and trimethoxyphenyl labels, respectively; in hay, 14 days after the second treatment, 26.0 % TRR (2.021 mg ai equiv./kg) and 12.7% TRR (1.078 mg ai equiv./kg); in straw, 35 days after the third treatment (commercial harvest), 13.6% TRR (1.215 mg ai equiv./kg) and 7.7% TRR (0.635 mg ai equiv./kg); and in grain, 35 days after the third treatment, 7.7% TRR (0.016 mg ai equiv./kg) and 3.1% TRR (0.013 mg ai equiv./kg). Other metabolites or fractions were not found at significant levels.

In the rotational crop metabolism study, metrafenone labelled with ^{14}C in either the bromophenyl or trimethoxyphenyl ring was applied to bare soil at an application rate of 625 g ai/ha (approximately 1× maximum total cucurbit crop application rate). Soil was aged for 30, 60, 90 and 365 days and cultivated to a depth of 15 cm before planting with rotational crops of lettuce, radish and canola. In lettuce TRR were <0.004-0.034 mg ai equiv./kg, in radish leaves were 0.005-0.025 mg ai equiv./kg, in radish roots were 0.004-0.023 mg ai equiv./kg, in canola straw/pods were 0.023-0.048 mg ai equiv./kg, and in canola seeds were 0.004-0.010 mg ai equiv./kg. The majority (67-89%) of TRR were extracted for all commodities except canola seeds where 44-57% of TRR were extracted.

For lettuce (at the 90 day interval), parent metrafenone consisted of 11% TRR (0.004 mg ai equiv./kg) for the bromophenyl label and <0.004 mg ai equiv./kg for the trimethoxyphenyl label. In radish leaves, parent metrafenone was found at <0.004 mg ai equiv./kg for both labels. In radish roots extractable radioactivity accounted for 62-80% TRR (0.009-0.018 mg ai equiv./kg) across the 30 and 60 day plant back interval for both labels. Metrafenone accounted for 16% TRR (0.004 mg ai equiv./kg) for the bromophenyl label and 28% TRR (0.003 mg ai equiv./kg) for the trimethoxyphenyl label (at the 30 day interval). The residue levels of metrafenone and all the metabolites found were below 0.01 mg ai equiv./kg. For canola straw samples extractable radioactivity accounted for 64-77% TRR for the bromophenyl label and 65-76 % TRR for the trimethoxyphenyl label across the different plant back intervals. All TRR values found were less than 0.05 mg ai equiv./kg. Parent metrafenone was not detected in any of the samples above a level of 0.004 mg ai equiv./kg. In canola seed, TRR were at or below 0.01 mg ai equiv./kg for all plant back intervals. Up to 62% TRR (0.004 mg ai equiv./kg) was extracted for the bromophenyl label and 86% TRR (0.004 mg ai equiv./kg) was extracted for the trimethoxyphenyl label. Significant residues are not expected in succeeding crops following application in accordance with the proposed use pattern.

A residue definition of parent compound only is supported for commodities of plant origin for both compliance and dietary risk assessment.

Animal Metabolism

Metabolism studies were conducted in rats, lactating goats and laying hens. In the rat metabolism study, animals were dosed with either bromophenyl or trimethoxyphenyl labelled metrafenone, receiving single or repeated high (1000 mg/kg bw) or low doses (10 mg/kg bw). The majority of the dose was excreted through faeces with 80.4% to 97.9% of the applied dose eliminated within 48-hours and 84.1% to 98.8% eliminated in seven days, and to a lesser degree through urine (0.7% to 6.6%). The accumulation of radioactivity in

tissues was observed mainly in GI tract and GI contents. Very little residue remained in the tissues at 168 hours post dosing.

Parent compound was the largest component identified in the fat accounting for 5.3% TRR (0.001 mg ai equiv./kg) and 6.2% TRR (0.001 mg ai equiv./kg) for the bromophenyl and trimethoxyphenyl labels, respectively. Six other metabolites were identified; however, they each accounted for less than 5% TRR. Parent compound in liver accounted for between 3.0% TRR (0.004 mg ai equiv./kg) and 7.6% TRR (0.006 mg ai equiv./kg) for the various labels and doses. Six other metabolites were also identified, accounting for between 0.4% TRR (0.000 mg ai equiv./kg) and 4.7% TRR (0.005 mg ai equiv./kg). Parent compound in kidney accounted for between 1.7% TRR (0.001 mg ai equiv./kg) and 4.7% TRR (0.023 mg ai equiv./kg) for the various labels and doses. Six other metabolites were also identified, accounting for between 0.6% TRR (0.000 mg ai equiv./kg) and 4.4% TRR (0.001 mg ai equiv./kg).

In the goat metabolism study, lactating goats were dosed orally with either bromophenyl or trimethoxyphenyl labelled metrafenone at two nominal dose levels of 10 and 70 mg/kg in the feed for 5 consecutive days. Approximately 76-86% of the total administered dose was eliminated via the urine and faeces. TRR were very low in milk at or less than 0.01 mg ai equiv./kg for both treatment levels and radiolabels, with residues plateauing after 2 to 3 days. TRR were also <0.01 mg ai equiv./kg in muscle. In liver, parent accounted for 2.7% TRR (0.035 mg ai equiv./kg) and 3.5% TRR (0.025 mg ai equiv./kg) for the bromophenyl and trimethoxyphenyl labels, respectively. In kidney, parent accounted for 4.4% TRR (0.014 mg ai equiv./kg) and 3.3% TRR (0.005 mg ai equiv./kg) for the bromophenyl and trimethoxyphenyl labels, respectively. In fat, parent was found to account for 60.0% TRR (0.009 mg ai equiv./kg) for the bromophenyl label and 85.4% TRR (0.019 mg ai equiv./kg) for the trimethoxyphenyl label.

Laying hens were dosed orally with either bromophenyl or trimethoxyphenyl labelled metrafenone for 12 consecutive days. Dose rates were at 13.87 mg/kg in the diet for the bromophenyl label and 14.19 mg/kg in the diet for the trimethoxyphenyl label. The excreted radioactivity amounted to between 85.9 and 95.1% of the total radioactivity administered for the bromophenyl and trimethoxyphenyl labels, respectively. The extractable radioactivity for the trimethoxyphenyl label ranged from 27.8% TRR (0.003 mg ai equiv./kg) in muscle to 79.8% TRR (0.079 mg ai equiv./kg) in eggs. Extractable radioactivity for the bromophenyl label ranged from 29.6% TRR (0.096 mg ai equiv./kg) in liver to 79.7% TRR (0.094 mg ai equiv./kg) in eggs. No characterisation or identification of metabolites was performed since the applied dose levels were significantly higher (~50×) than the estimated dietary exposure for poultry fed grape pomace of 0.27 mg/kg and the corrected TRR values are >0.01 mg ai equiv./kg.

Parent metrafenone was the major component of animal metabolism. A residue definition of parent compound only is supported for commodities of animal origin for both compliance and dietary risk assessment.

The likely maximum feeding level for livestock consuming grape pomace is 0.011 mg/kg bw/day and for poultry is 0.020 mg/kg bw/day. This is significantly below the doses used in the metabolism studies. Scaling of residues in animal commodities to the expected feeding level indicates that residues are not expected in animals fed treated grape pomace. Therefore, MRLs at the LOQ are supported for milk (<0.01 mg/kg), mammalian meat and mammalian edible offal (<0.05 mg/kg), and at the LOQ of <0.05 mg/kg are supported for eggs, poultry meat and poultry edible offal.

4.3 Analytical methods

Commodities of plant and animal origin

Metrafenone residues were extracted from cucurbit samples with ethanol/water/hydrochloric acid, then liquid-liquid partitioned into cyclohexane, followed by evaporation and re-dissolution in mobile phase. A number of instruments were used for quantitation, employing LC-MS techniques. Recovery analysis and method validation was performed by the fortification of homogenised untreated samples with known levels of metrafenone. The limit of quantitation was 0.01 mg/kg.

Samples from the Australian grapevine residue trials were extracted using an acetonitrile/water extraction solvent via ultra-sonication. Quantitation was by LC-MS techniques. Final quantitation was performed via multi-point external calibration against reference standard solutions. The limit of quantitation was 0.01 mg/kg.

Grapevines samples from the European trials were extracted with n-heptane/acetone. Measurements of metrafenone were undertaken by GC-ECD. Recovery analysis was performed by the fortification of homogenised untreated grape specimens with known levels of metrafenone. The limit of quantitation was 0.05 mg/kg.

Additional methods have been validated for determining residues in barley grain, grapes, wine, milk, meat and eggs. Samples were extracted with acetone. Quantitation was by cGC-ECD for plant samples and MSD for animal commodity samples. The limit of detection was estimated to be ≤ 0.003 mg/kg for grain, grapes and wine 0.002 mg/kg for milk and 0.01 mg/kg for meat and eggs. The limit of quantitation was 0.01 mg/kg for grain, grapes, wine and milk, and 0.05 mg/kg for meat and eggs.

4.4 Residue Definition

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

COMPOUND	RESIDUE
Metrafenone	Metrafenone

4.5 Storage Stability

The stability of metrafenone in grapes and wine at <-18^{o}C was conducted over a period of 18 months. Untreated samples were homogenised and fortified at either 0.10 or 0.50 mg ai/kg. After 3, 6, 12 and 18 months of frozen storage samples were analysed for metrafenone, concurrently with one untreated blank control sample and duplicate samples freshly fortified for recovery control. Average recoveries were between 70 and 110% for grapes and wine samples at all sampling points. No significant (≤ 30%) degradation was observed during storage for a period of 18 months.

The stability of metrafenone residues in cucurbits was conducted in conjunction with the Australian cucurbit residue trials. Fortified homogenised samples were stored in the same freezer, under the same conditions and for the same duration as the field samples. Average recovery was 89.6% after a total storage time of approximately 3.5 months (104 days).

The stability of metrafenone residues in plant commodities is acceptable.

4.6 Residue Trials

In the Australian cucurbit trials, the highest metrafenone residue observed was 0.12 mg/kg in a zucchini sample taken on the day of application; in a trial conducted with one application of metrafenone at an application rate of 150 g ai/ha (1× label rate). At the proposed application rate and withholding period of 7 days, metrafenone residues in rockmelons were 0.02, 0.02 and 0.03 mg/kg, in cucumbers were 0.05 and 0.06 mg/kg, and in zucchinis were 0.06 and 0.10 mg/kg.

The highest metrafenone residue observed in the New Zealand cucurbit trials was 0.10 mg/kg in a pumpkin sample taken on the day of application; in a trial conducted with three applications of metrafenone at a rate of 300 g ai/ha per application (2× label rate). At the proposed application rate of 150 g ai/ha and withholding period of 7 days, metrafenone residues in pumpkins were 0.03 and 0.04 mg/kg and in squash were 0.01 and 0.03 mg/kg.

Residues in the submitted trials support the establishment of a MRL of 0.2 mg/kg for metrafenone in fruiting vegetables, cucurbits, with an accompanying withholding period of 7 days.

In the Australian grape trials, the highest metrafenone residue observed was 0.94 mg/kg in a grape sample taken 73 days (approximately 10 weeks) after the last application, in a trial conducted at 20 g ai/100 L (2X label rate). The highest residue in a trial conducted at 10 g ai/100 L (1× label rate) was 0.43 mg/kg in a sample taken 71 days after the last application. Only two out of the five trials had samples take at approximately the proposed withholding period of 35 days. Metrafenone residues in these samples were 0.04 and 0.08 mg/kg.

The highest metrafenone residue observed in the overseas grape trials (n=12) was 0.54 mg/kg in a sample taken just after the final application (0.7× label rate). Six of the trials were conducted with a spray interval of 7 days (as per the proposed use) and three of these trials were conducted at the maximum label application rate. Residues in samples taken at or before the proposed withholding period of 35 days, from trials conducted at the proposed label rate were 0.08, 0.13 0.28, 0.35, 0.36 and 0.38 mg/kg.

Residues in the submitted trials support the recommendation of the establishment of a MRL of 1 mg/kg for metrafenone in grapes, with an accompanying withholding period of 35 days.

It should be noted that the proposed use pattern refers to the potential use of Du Wett® low volume application spreader. The submitted studies did not indicate whether this product (or another alternative adjuvant) was used.

Processing

Six of the grape trials, conducted at between 0.7 and 2× label rate, included wine processing data. Four of the trials were conducted with a spray interval of 7 days (as per the proposed use) and two of the trials were conducted with a spray interval of 14 days. Specimens for processing were taken at 26 or 28 days after the last application. Grapes were processed according to set oenological standards and the laboratory standard operating procedures. Residues in all wine samples were <0.05 mg/kg (n=6).

Specimens for processing into raisins were left out under the sun in large trays to dry. When the grapes had dried sufficiently to become raisins they were frozen within 24 hours, remaining frozen until analysis. Residues in the raisin sample was <0.05 mg/kg (n=1). As data from only one raisin trial (1× label rate) was supplied, the proposed MRL for dried grapes of 3 mg/kg is based on an HR-P of 2.09 mg/kg (HR of 0.43 mg/kg and grape dry matter content of approximately 20%[2]).

Animal feeds

Residues in pomace were not determined in the processing study. Based on the highest residue of 0.43 mg/kg and a dry matter content of approximately 20% for grapes a MRL of 3 mg/kg is proposed for grape pomace (dry).

Crop rotation

Cucurbits are considered to be a rotational crop. Rotation crop residue studies were not provided with the application; however, a rotational crop metabolism study was submitted. The level of parent metrafenone was ≤0.004 mg/kg in all samples analysed. Therefore, residues of metrafenone are not expected to occur in rotational crops.

4.7 Animal Commodity MRLs

The dietary intake of metrafenone by cattle and poultry consuming treated grape pomace is estimated in the tables below. Grape pomace can account for 20% of livestock diet.

Cattle – 500 kg bw, 20 kg DM/day

FEED GROUP	COMMODITY	% IN DIET	FEED INTAKE	RESIDUE, MG/KG	% DM	LIVESTOCK DIETARY EXPOSURE		
						MG/ANIMAL	PPM	MG/KG BW
By-products	Grape Pomace	20	20	0.28 (STMR)	20.6	5.437	0.27	0.011

[2] Department of Community Services and Health (1991), Nutritional Values of Australian Foods, Canberra.

Poultry – 2 kg bw, 0.15 kg DM/day

FEED GROUP	COMMODITY	% IN DIET	FEED INTAKE	RESIDUE, MG/KG	% DM	LIVESTOCK DIETARY EXPOSURE		
						mg/animal	ppm	mg/kg bw
By-products	Grape Pomace	20	0.15	0.28 (STMR)	20.6	0.041	0.27	0.020

Animal feeding studies were not submitted with the application; however, metabolism studies for lactating goats and laying hens were conducted and have been used to determine expected residues in animal commodities. In the lactating goat study, goats were administered parent metrafenone at nominal dose levels of 10 and 70 mg/kg in the feed based on an average feed consumption of 2 kg per goat per day for 5 days. Goats weighed between 44.7 and 58.1 kg. Actual dose rates were at 12.6 mg/kg or 87 mg/kg feed for the bromophenyl label and 8.3 mg/kg or 60.3 mg/kg feed for the trimethoxyphenyl label. At a livestock dietary exposure of 0.27 ppm in the feed, the estimated total residue in goat muscle, fat and milk is <0.005 mg/kg, in liver is 0.003-0.007 mg/kg and in kidney is 0.001-0.007 mg/kg.

MRLs at the LOQ are supported for milk (<0.01 mg/kg), mammalian meat and mammalian edible offal (<0.05 mg/kg).

In the laying hen study, hens were administered with metrafenone for 12 consecutive days at dose rates of 13.87 mg/kg diet for the bromophenyl label (1.56 mg/animal and 1.00 mg/kg body weight) and 14.19 mg/kg diet for the trimethoxyphenyl label (1.55 mg/animal and 0.95 mg/kg body weight). At a livestock dietary exposure of 0.27 ppm in the feed, the estimated total residues in poultry eggs, muscle and skin with fat is <0.005 mg/kg, and in liver is 0.006-0.009 mg/kg.

MRLs at the LOQ of <0.05 mg/kg are supported for eggs, poultry meat and poultry edible offal.

4.8 Estimated Dietary Intake

The chronic dietary exposure to metrafenone 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[3] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for metrafenone is equivalent to 0.5% of the ADI. DIAMOND Modelling[4] of chronic dietary exposure is also performed on new chemicals, and chemicals with estimated dietary exposure greater than 90% of the ADI. The DIAMOND model estimated the chronic dietary exposure of

[3] Guidelines for predicting dietary intake of pesticide residues, WHO, 1997.
[4] DIAMOND: The Diamond Modelling Of Nutritional Data is a computer dietary modelling program based upon statistical software that is used by FSANZ.

metrafenone as 2.4% of the ADI for the general population using MRLs and 0.6% using Supervised Trial Median Residue (STMR) values.

It is concluded that the chronic dietary exposure of metrafenone is acceptable.

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

An acute reference dose has not been established for metrafenone. Therefore, the calculation of NESTIs is not required.

4.9 Bioaccumulation Potential

Metrafenone has a partition coefficient of $\log K_{ow}$ = 4.3 for n-octanol/water suggesting that it may have potential for bioaccumulation. In both the goat and hen metabolism studies higher residues were observed in the fat than in the muscle (for goats TRR were 0.015 mg/kg and 0.022 mg/kg in fat compared with 0.008 mg/kg and 0.006 mg/kg for muscle, respectively for the two radioactive metrafenone labels; and for hens TRR were 0.084 mg/kg and 0.060 mg/kg in skin with fat compared with 0.013 mg/kg and 0.010 mg/kg for muscle, respectively).

Given the relatively high $\log K_{ow}$ for metrafenone, and its tendency to partition into fat rather than muscle as shown in the metabolism studies, residues of metrafenone are designated as fat soluble. Therefore, meat MRLs should be established as in the fat.

4.10 Spray Drift

Spray drift modelling shows that with respect to no-spray zones for airblast application and ground application, with a medium droplet size as specified on the label, a no-spray zone is not required, from a residues perspective.

4.11 Recommendations

The following MRLs will be established:

Table 1

COMPOUND	FOOD	MRL (MG/KG)
ADD:		
Metrafenone		
DF 0269	Dried grapes	3
MO 0105	Edible offal (Mammalian)	*0.05

COMPOUND		FOOD	MRL (MG/KG)
PE	0112	Eggs	*0.05
VC	0045	Fruiting vegetables, cucurbits	0.2
FB	0269	Grapes	1
MM	0095	Meat (mammalian) [in the fat]	*0.05
ML	0106	Milks	*0.01
PO	0111	Poultry, edible offal	*0.05
PM	0110	Poultry meat [in the fat]	*0.05

Table 3

COMPOUND	RESIDUE
ADD:	
Metrafenone	Metrafenone

Table 4

COMPOUND		ANIMAL FEED COMMODITY	MRL (MG/KG)
ADD:			
Metrafenone			
AB	0269	Grape pomace, dry	3

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

Cucurbits: DO NOT harvest for 7 DAYS after application.

Grapes: DO NOT harvest for 5 WEEKS after application.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Commodities Exported

Grapes (including table grapes and dried grapes) and wine together with animal commodities derived from livestock that have been fed treated grape pomace are considered to be major export commodities. Cucurbits are not considered major export commodities and the overall risk to export trade is considered to be small.

Destination and Value of Exports

In 2007/08, the total exports of Australian table grapes were $100.5 million, with the major export destinations generally in Asia, with Hong Kong being the most important market.

AUSTRALIAN TABLE GRAPE EXPORTS IN 2007/08

DESTINATION	VALUE, $ MILLION
Hong Kong	29.3
Indonesia	16.8
Thailand	12.6
Singapore	8.0
Malaysia	7.2
Vietnam	5.3
New Zealand	4.5
United Arab Emirates	3.7
Taiwan	3.3
Bangladesh	2.0
Sri Lanka	1.4
Other	6.3
TOTAL	100.5

Australian wine exports were 702.1 ML, worth $2.7 billion, in 2007/08, with the most important destination being the United Kingdom, where sales were worth $876.5 million. This was followed by the USA, where sales were worth $741 million and Canada at approximately $250 million. Other European countries, New Zealand, and some countries in Asia are also important markets for Australian wine.

AUSTRALIAN WINE EXPORTS IN 2007/08

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

Exports of dried vine fruit from Australia are of minor importance in comparison to wine and table grapes. Exports in 2007/08 were 4.9 kilotonnes, valued at $13 million.

AUSTRALIAN EXPORT DESTINATIONS AND VALUE OF DRIED GRAPES (RAISIN) IN 2007/08

DESTINATION	VALUE, $ MILLION
Germany	4.96
United Kingdom	2.52
New Zealand	1.63
Netherlands	1.02
Italy	0.73
Japan	0.63
Malaysia	0.28
Belgium	0.27

Canada	0.18
Fiji	0.15
TOTAL	**12.67**

Animal commodities derived from livestock fed on grape pomace are considered to be major export commodities. Based on the grape pomace MRL for metrafenone, residues are unlikely to be found in animal commodities (See Section 7).

Comparison of Australian MRLs with Codex and Overseas MRLs

Metrafenone containing products are registered for use on grapes in the USA and Europe; vegetables, wheat, barley and oats in Europe; and cucumbers and Korean melon in Korea.

The following overseas residue MRLs/tolerances have been established for metrafenone in plant commodities:

COUNTRY	PLANT COMMODITY	TOLERANCE (MG/KG)	RESIDUE DEFINITION
Australia (Proposed)	Cucurbits	0.2	Metrafenone
	Grapes	1	
Canada[5]	None established	-	-
EU[6]	Cucurbits (edible and inedible peel)	*0.05	Metrafenone
	Table grapes	0.5	
	Wine grapes	0.5	
Japan[7]	None established	-	-
Korea[8]	Korean Melon	2.0	Not specified

[5] Canada – Health Canada, List of Maximum Residue Limits Regulated Under the Pest Control Products Act (Current 26 November 2009) http://www.hc-sc.gc.ca/cps-spc/pest/index-eng.php/english/legis/maxres-e.html

[6] European Union – Regulation (EC) N°149/2008 (Updated 1 September 2008) http://ec.europa.eu/sanco_pesticides/public/index.cfm

[7] Japan – Compositional Specification for Foods (Updated 29 January 2010)

http://www.m5.ws001.squarestart.ne.jp/foundation/search.html

COUNTRY	PLANT COMMODITY	TOLERANCE (MG/KG)	RESIDUE DEFINITION
	Cucumber	0.7	
	Squash	1.0	
	Other agricultural products	0.05	
US[9]	Grape	0.6	Metrafenone

[+] Proposed Australian MRLs and Residue Definition

Note: Use pattern on grapes currently not registered in US (12 April 2010)

The following overseas animal commodity MRLs/tolerances have been established:

COUNTRY	ANIMAL COMMODITY	TOLERANCE (MG/KG)
Australia[+]	Milk	*0.01
	Meat, mammalian	*0.05
	Edible offal, mammalian [in the fat]	*0.05
	Poultry meat	*0.05
	Poultry, edible offal of	*0.05
	Eggs	*0.05
Canada	None established	-
EU	Products of animal origin-terrestrial animals[^]	*0.05
Japan	None established	-
Korea	Other agricultural products	0.05
US	None established	-

[8] Korea – Korean Food and Drug Administration, MRLs for Pesticides in Foods (updated September 2009)

http://eng.kfda.go.kr/file/PesiticideMRLs.pdf

[9] US – United States Food and Drug Administration, Code of Federal Regulations, Part 180 – Tolerances and Exemptions for Pesticide Chemical Residues in Food (Current 12 April 2010) http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=e8a13a6341e2f8110a54b023e4b44abb&rgn=div8&view=text&node=40:23.0.1.1.28.3.19.365&idno=40

[+] Proposed Australian MRLs and Residue Definition
[^] Includes meat, fat, liver, kidney, edible offal, other mammalian products, milk, cream, poultry products

Metrafenone has not considered by Codex or by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR).

Potential Risk to Trade

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

The proposed MRL of 0.2 mg/kg for cucurbits is above the European and below the Korean tolerances. However, as cucurbits are not considered major export commodities the risk to overall Australian trade posed by residues of metrafenone in cucurbits is low and acceptable.

The proposed MRL for grapes is 1 mg/kg which is higher that both the European and US tolerances of 0.5 and 0.6 mg/kg, respectively. However, the European and US tolerances are both higher than the HR of 0.43 mg/kg observed in the submitted trials. Tolerances for metrafenone have not been established for major wine export destinations including Canada, China, Hong Kong, Japan, Singapore, Switzerland and Thailand. However, as metrafenone residues are not expected in wine, the risk to trade posed by residues in wine is low and acceptable. Major export destinations of table grapes that do not currently have MRLs for grapes include Hong Kong, Indonesia, Thailand, Singapore, Malaysia, Vietnam, United Arab Emirates, Taiwan, Bangladesh and Sri Lanka. New Zealand accepts Australian MRLs under the Trans Tasman Mutual Recognition Agreement.

No information is available on the destination of Australian dried grape exports.

Therefore, there is a possible risk to Australian export trade of dried grapes and table grapes as a result of the proposed use of metrafenone on grapes.

The overall risk to export trade in animal commodities is considered to be low, as residues are not expected at the proposed GAP and the proposed MRLs are at the LOQ.

The relevant industry groups should be given the opportunity to comment on the perceived level of risk and whether any industry-initiated strategies are required to manage that risk.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Health hazards

Metrafenone has low acute oral, dermal and inhalational toxicity in SD rats. The compound is not a skin or eye irritant in rabbits and not a skin sensitiser in guinea pigs or mice. Metrafenone possesses no phototoxic or photoallergenicity potential in guinea pigs. Metrafenone is not listed on the Safe Work Australia (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2009)

The formulated product, containing 500g/L metrafenone, has low acute oral, dermal and inhalational toxicity in rats, it is not a skin or eye irritant in rabbits and is not a skin sensitiser in guinea pigs. Based on the product toxicology information and concentrations of metrafenone and other ingredients in the product, VIVANDO ® Fungicide is classified as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrases.

R40 (Carc. Cat. 3)	Limited evidence of a carcinogenic effect

Formulation, packaging, transport, storage and retailing

VIVANDO ® Fungicide will be manufactured overseas and imported into Australia as a liquid in high-density polyethylene (HDPE) cylindrical containers, with polypropylene induction screw cap. It will be available in the following pack sizes: 1L; 5 L; and 10 L. Transport workers and store persons will handle the packaged products and could only become contaminated if packaging were breached.

Use pattern

VIVANDO ® Fungicide is a new fungicidal product, which will be used for the control of powdery mildew in grapevines and cucurbit. It contains 500 g/L metrafenone and the formulation is a suspension concentrate (SC).

Exposure during use

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

There are no worker exposure studies on metrafenone or the products (VIVANDO ® Fungicide) available for assessment. In the absence of worker exposure data, the OCSEH used the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) to estimate the worker exposure during mixing/loading and application based on the maximum product use rate according to the Australian use pattern. These estimations, in conjunction with toxicology data, demonstrated that provided that workers wear a single layer cotton overall, no further PPE is required for potential repeat exposure effects when using VIVANDO ® Fungicide to treat infections in grapevines or cucurbits.

Exposure during re-entry

There is not expected to be any undue risk associated with exposure to product residues when workers re-enter treated areas.

Recommendations for safe use

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

Conclusion

The registration of VIVANDO® Fungicide, containing 500g/L of metrafenone, for control of powdery mildew in grapevines and cucurbits, is supported.

VIVANDO® 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 MSDS.

7 ENVIRONMENTAL ASSESSMENT

BASF Australia Limited has applied for registration of the new agricultural product VIVANDO® Fungicide (containing 500 g/L of the new active constituent metrafenone) to complement current fungal control programs in grapevine and cucurbit crops for powdery mildew control. A comprehensive data package was provided for assessment with the data provided considered to adequate to allow a full environmental assessment of the application.

Metrafenone is a benzophenone fungicide with protectant and curative properties. Although the mode of action of metrafenone has not been determined, it appears that the fungicide inhibits the growth of mycelium on the leaf surface, leaf penetration, formation of haustoria (that part of the parasitic fungus which invades the host's tissue .

7.1 Environmental fate summary

Metrafenone was stable to hydrolysis at pH 4, 7 and 9 over a 5 day period at 50°C where less than 10% of test substance was hydrolysed. Consequently, metrafenone is not expected to undergo hydrolysis in the environment.

Based on two laboratory studies under continuous light conditions using sterile water (pH 7) and a natural water (pH 7.7), metrafenone can be classified as readily photodegradable. The chemical was rapidly degraded in sterile water under photolytic conditions with a half-life of 3.1 days of continuous irradiation, while environmental half-lives were calculated as being from 12.3 (Summer, 40°N latitude) to 128 days (Winter 50°N latitude). The primary identified photoproduct in the sterile water study was carbon dioxide, which reached levels of approximately 24 to 26% of the applied radioactivity after 15 days of continuous irradiation. A large number of degradation products, none of which was more than 10% of the applied radioactivity and mostly polar, were formed via phototransformation. Studies in natural water showed that the chemical rapidly degraded under continuous photolytic conditions with a DT50 of 2.6 days. Multiple minor metabolites were formed, among which CL 377160, CL 377095, CL 377096, CL 4084564, and CL 375816 were identified. None of the metabolites exceeded 10% of the applied radioactivity at any time during the study. Formation of CO_2 at up to 5% of the applied radioactivity indicated metrafenone would be ultimately mineralised under such photolytic conditions. Aqueous photolysis of metrafenone is expected to be a significant route of degradation in the aquatic environment.

Metrafenone is expected to undergo photolysis on soil. Under continuous irradiation with a light intensity equivalent to mid-autumn sunlight in New Jersey, USA, the measured photolysis DT50 of the chemical was approximately 15.5 days. The major photodegradate was identified as CL 377160, the demethylated parent compound, which maximized at 19% by day 14, and then decreased to 6.4% by day 30. CL 377160 was not formed in the dark control. Other minor photoproducts were detected, none of which was present at a level above 10% of the applied radioactivity. There were no major degradation products observed in the dark control samples. Approximately 2 to 3% of the applied radioactivity was evolved as carbon dioxide.

Based on reactions of metrafenone with hydroxy radicals in the troposphere, the atmospheric photodegradation half-life of metrafenone was calculated to be 0.63 hours. Although metrafenone is expected to be only slightly volatile, any reaching the troposphere would undergo very fast degradation by

photochemical processes and long range atmospheric transportation of metrafenone is not expected to be of significance.

Three aerobic soil studies were presented. In all these studies, the calculated DT50s were greater than the respective study durations so that they must be treated with caution. In the first study, metrafenone degraded slowly in a silty loam soil under aerobic laboratory conditions at 20°C, in darkness, with a DT50 value of approximately 250 days. A DT90 value of approximately 850 days was extrapolated. After 210 days, the study's end, carbon dioxide made up approximately 3% of the applied radioactivity. No other degradation product was determined to be present in excess of 0.2% of the applied radioactivity. Bound residues made up approximately 13 to 14% of the applied radioactivity after some 60 days and approximately 28 to 29% at study's end, at which time some 55-57% of the applied radioactivity was still present as metrafenone.

In the second study, metrafenone degradation in a loamy sand, a sandy loam and a clay loam, again at 20°C, was found to be slow over the 120 days of the study with between 56 to 69% of the applied radioactivity remaining at the study's end. The DT50 values for the degradation of metrafenone ranged from 182 to 365 days. DT90 values were between 600 and 1250 days. Only one extractable degradate or fraction of degradates was found but as this was in amounts below 1% of the applied radioactivity no attempt was made to identify it. Carbon dioxide the final degradation product and was found in amounts of up to approximately 5% at the study's end. These two studies showed that the primary route of degradation was conversion to residues that could not be extracted from the soil and that could eventually mineralise to carbon dioxide. The third aerobic soil study was conducted at a lower temperature (10 rather than 20°C) on a loamy sand soil. After 120 days, metrafenone still made up 82% of the applied radioactivity with no other defined peak or metabolite fraction was observed at any sampling time. Bound residues made up to 8.2% of the applied radioactivity at the end of the study, while carbon dioxide accounted for 1.4% of the applied radioactivity at that time. The calculated DT50 and DT90 were, respectively, 693 and 2303 days. Aerobic soil degradation of metrafenone is seen to be slow with lengthy soil lifetimes expected.

An aerobic soil metabolism in three soils (a silty clay loam, a loamy sand and a sandy loam) at 20°C with metrafenone metabolite CL 377160 (formed by soil photodegradation) was conducted over a 120 day period. There was a rapid disappearance of the metabolite (from 84 to 109% of the applied radioactivity at day 0 to between approximately 5 and 6% by day 7 and 0.5 to 2% at day 120. Carbon dioxide made up between 0.5 and 1.3% of the applied radioactivity after 120 days. At that time, bound residues made up some 63 to 74% of the applied radioactivity. Characterisation of bound residues from the 7 and 120 day samples showed most of the radioactivity in the bound residues remained in the humin fraction. A kinetics analysis could not be performed as the CL 377160 declined to 5-6% of the applied radioactivity at the first sampling point after 7 days of incubation. The DT50 and DT90 for the aerobic soil dissipation/degradation of CL 377160 were each less than 7 days and CL 377160 is not expected to persist in aerobic soils.

In two anaerobic soil studies, metrafenone was demonstrated to degrade rapidly in soil under anaerobic conditions to multiple minor degradation products and polar components that were incorporated into the soil matrix (i.e. high amounts of bound residues). A majority of these polar components could be released from the soil matrix by acid/base treatments, but are not believed to be bioavailable. The degradation products included CL 377160, CL 434223, CL 377096, CL 307468 and CL 375816. A small amount of $^{14}CO_2$ formation indicated an ultimate (if slow) mineralisation of metrafenone. The DT50 values reported in the two studies of about 8 and 15 days indicate metrafenone is not expected to persist in soil under anaerobic

conditions, where it undergoes demethylation or debromination to form hydroxylated metabolites along with the metrafenone and/or its metabolites also degrading via cleavage at the carbonyl moiety to form smaller molecules, such as the bromobenzoic acid metabolite, CL 375816, and trimethoxytoluene.

The distribution and degradation of metrafenone, radiolabelled in either the bromobenzyl or trimethoxybenzyl rings of the metrafenone, was studied in two natural systems of water and sediment (a river and a pond) under dark conditions with aerobic conditions maintained in the water columns. Over a period of 100 days, the applied radioactivity dissipated steadily from the water to the sediment. The radioactivity in the water layer decreased to less than 35% (28.2 to 28.6%) of applied radioactivity within 7 days in both systems. After 100 days of incubation 8.3 to 12.3% of the applied radioactivity remained in the water phase for the river system and 11.5 to 28.7% the pond system. In the sediment a corresponding increase in radioactive residues was seen, which accounted for 60.0 to 79.1% of the applied radioactivity at the end of the incubation period for both systems. Mineralisation was observed in both systems with evolved carbon dioxide accounting for 2.6 and 7.1% of the applied radioactivity in the river system and 6.6 and 12.4% pond system. No other volatile degradates were detected. High amounts of bound residues were formed in the sediment, which accounted for up to 26.4% applied in the river system and up to 20.4% in the pond system.

More than 20 minor degradation products were detected. Two metabolites, CL375816 (bromobenzoic acid metabolite) and CL377160 (3-hydroxy metabolite), were identified. Four other minor degradates, CL377095 (2-hydroxy metabolite), CL377096 (2,3-dihydroxy metabolite), CL375228 (desbromo metabolite) and CL4084564 (hydroxylated desbromo metabolite) were also characterised. The metabolites were mainly found in the sediment. The maximum amounts of CL375816 and CL377160 were, respectively, 8.5 and 6.5% of the applied radioactivity at, again respectively, 100 and 14 days. None of the other metabolites exceeded 5% of the applied radioactivity except for an unidentified polar metabolite (11.3% of the applied radioactivity at day 28) which was shown to be composed of two to three components. The estimated DT50 values for metrafenone ranged from 3.0 to 4.7 days in the water columns, 3.5 to 4.5 days in the sediments and 8.5 to 10.0 days in the total systems. The DT90 value for metrafenone was 10.1 to 15.6 days in the water phase, 11.5 to 15.0 days in the sediment phase, and 28.1 to 33.1 days in the water-sediment total systems. The study results predict that metrafenone will be degraded in water/sediment systems and not be persistent in the aquatic environment.

In a ready biodegradability study with radio-labelled metrafenone using the Modified Sturm Test no significant carbon dioxide or mineralisation occurred. Carbon dioxide production reached 0.13% of the applied radioactivity at study termination (28 days) compared to the 60% or greater level required to meet the ready biodegradability criterion. Consequently, metrafenone is not classed as readily biodegradable.

The results of the adsorption/desorption studies with metrafenone and five different soils (two sandy loams, two silt loams and a loam) and with the metrafenone metabolite CL 377160 (with different five soils, a clay loam, a loam, a loamy sand, a silt loam and a silty clay loam) show that metrafenone and its main metabolite CL 377160 adsorbs to soil particles with Koc values ranging from 1592 to 5556 for metrafenone and 2199 to 21649 for the metabolite. Qualitatively, these values represent low (Koc = 500-2000), through slight soil mobility (Koc = 2000-5000) to immobility (Koc >5000) for metrafenone. Mobility of metrafenone or its metabolite CL 377160 and leaching to groundwater is not expected on the basis of these results.

Field dissipation studies were conducted at four sites in Europe (in the United Kingdom with a loam soil, in France with a silt soil, in Denmark with a loam soil and in Germany with a silt loam) using a single application

of a 200 g metrafenone/ha SC formulation applied to bare ground at ~400 g metrafenone/ha. Soils were sampled for between 482 and 495 days after treatment with metrafenone residues found only in the 0-10 cm soil profile. No measurable levels of the metrafenone metabolite CL 377160 were found in any of the studies. Degradation in the Danish, French and German soils were adequately described by biphasic first order degradation kinetics with respective DT50 values of 53.7, 31.6 and 124 days and DT90 values of >1000, 493 and 637 days reported. The degradation seen in the United Kingdom soil were not adequately modelled by either simple first-order or biphasic first-order kinetics and the simple first-order derived DT50 and DT90 values of 149 and 495 days are unreliable. In the French, German and United Kingdom soils, residues had significantly declined by the ends of the sampling periods. In contrast, the degradation in the Danish soil had essentially ceased by approximately 100 days leaving about 35-40% remaining. Considered with the high Koc values seen for metrafenone, the field dissipation DT50 values show that metrafenone is expected to have slight soil mobility or be immobile in soil where it will be moderately persistent.

In view of the lengthy soil DT90 laboratory results residue field accumulation studies were conducted from 1999 to 2005 in Italy, Germany (two studies) and Spain. Soil types at the respective study sites were clay, silt loam, silt loam and a sandy loam. The Italian and Spanish studies involved application to bare soils using a European grapevine use pattern rate of 800 g metrafenone/ha per year (8 x 100 g metrafenone/ha) with a spray interval of 14 days. In the German grapevine study, eight treatments of metrafenone using a 500 g/L SC were applied to vines each year. The dose rates ranged from 59 to 170 g metrafenone/ha (the rates increasing over the season to correspond to the increase in the size of the growing grapevines) with spray intervals of 14 days. A total of 48 applications were made in each of these three studies. The second German study used applications of metrafenone to cereals at a rate of 200 g metrafenone/ha/year with two applications/year with a total of twelve applications made. Residues of metrafenone were determined in the soil profiles at intervals before and after each application of metrafenone and were found primarily in the 0-10 cm soil profile. No quantifiable residues of metabolite CL 377160 were detected in any of the soils even after multiple years of application.

In the Italian bare soil study, the maximum metrafenone residue concentrations occurred at the 24th application (the third year of metrafenone application) where residues were 0.66 and 0.69 mg metrafenone/kg before and after that application and, taking the subsequent concentrations of metrafenone in the soil into account, soil concentrations of metrafenone reached a plateau level in the fifth year of application. Consequently, accumulation of metrafenone in the soil was not expected. In the German grapevine study, the maximum metrafenone soil concentrations were seen at the 44th application (0.36 and 0.38 mg metrafenone/kg before and after the application respectively) or in the fifth year of the study. While subsequent soil concentrations were below these values, there was insufficient evidence to show that the clearly increasing trend in soil concentrations seen from the commencement of the study to its sixth year would have continued or not. This study did not show a plateau with respect to metrafenone levels in the soil has been reached and accumulation of metrafenone has not been excluded by it. In the German cereal study, the maximum metrafenone soil concentration was 0.245 mg metrafenone/kg which was found after the 11th application (the concentration before the 11th application was 0.065 mg metrafenone/kg). While the level in the soil after the 12^{th} and last application was 0.206 mg metrafenone/kg, no further applications were made and it was not possible to conclude that the increasing trend in soil residues seen from the start of this study had or would reach a plateau. After 6 years of successive applications, the field accumulation studies had to be discontinued because of technical problems. The maximum metrafenone soil concentration in the Spanish bare soil study was 0.19 mg metrafenone/kg which occurred on two occasions, after treatments 32 and 40 (in the fourth and fifth years of application) and it was concluded that the data showed that residues

in the soil then stabilised, indicating plateau concentrations had been reached by about the sixth year, a result indicating that metrafenone would not be expected to accumulate in the soil.

As a result, to assure certainty in the long-term exposure assessment the measured soil concentrations were compared to accumulation modelling results using worst case laboratory soil half-lives. When comparison of the predicted (modelled) soil concentrations of metrafenone with those found in the field accumulation studies were made the following conclusions were reached. In the Italian bare field study, measured values were generally of the same order as modelled values, with the latter supporting the contention that plateau concentrations had been reached in the Italian field trial. In the Spanish grape study, both measured and modelled results indicated that plateau concentrations had been reached before the study's end and that continued accumulation of metrafenone in the soil was not expected to occur.

The modelled German grapevine results indicated that soil concentrations had not reached a plateau level by the time of the study's end, with this being consistent with the results from the field study. For the German cereal trial, the modelled data show that plateau concentrations of levels of metrafenone in the soil had not occurred during the study period. Again, this is consistent with field results where no plateau level was reached. Modelling data presented in the data package showed that the modelled results from the second year of application always exceeded the measured results and the modelled results appear to be reaching a plateau after some 6 or 7 years.

The Italian and Spanish data best predict the ultimate attainment of a plateau with respect to metrafenone levels in the soil, and the proposed Australian use pattern for Vivando on grapevines is not expected to result in continually increasing levels of metrafenone in the soil. Given the equivalent use rates are proposed for the use of Vivando on cucurbits, there is a similar expectation with respect to soil accumulation of metrafenone following treatment of these crops.

The bioaccumulation in fish of metrafenone, radio-labelled in either the bromophenyl or trimethoxyphenyl rings, was investigated using the bluegill sunfish (*Lepomis macrochirus*) in a flow-through test system at test concentrations of 5 and 50 µg metrafenone/L. The 28 day exposure phase was followed by a 14 day depuration period. The total radioactivity residues (TRR) and the amount of metrafenone in whole fish each reached a steady-state plateau by day 14 of the uptake period after exposure to the radio-labelled metrafenone. The highest residues of total radioactivity were observed in the viscera. The parent compound was a major component of the residues in whole fish making up a reported 18.5–28.5% of the TRR during the steady state period (day 14–day 28). The three metabolites CL 434223, CL 1500699 and CL 377160 accounted for 4.5–39.5, 6.9-47.7 and 0.8–13.4% of the TRR respectively. All other metabolites were present at <10% of the TRR in whole fish. In the aquarium water, the parent compound accounted for 50.8-59.7% of the TRR and the metabolites CL 434223, CL 1500699 and CL 377160 accounted for 6.7–22.9, 0-15.8 and 0–7.9% respectively. All other metabolites were present at <10% of the TRR. The depuration half-life for metrafenone in whole fish was 0.55-0.64 and 0.63-0.65 days for the 4.4-4.5 µg/L and 43-46 µg/L exposure levels, respectively and the time to reach 95% clearance (t95) was 2.3-2.7 days for both exposure levels. Bioconcentration factors obtained by kinetic modelling were in the range of 140-180 for whole fish while the lipid content corrected BCF value was 2400-2700 based on metrafenone and, based on total radioactive residues, respectively 460 to 530 and 6800 to 8500. As metrafenone was readily metabolised and depurated, bioconcentration is not expected to be of significance.

7.2 Environmental toxicity summary

Acute oral and dietary studies were conducted on the mallard duck and the Northern bobwhite quail. Metrafenone was practically non-toxic to mallard ducks and bobwhite quail with respect to acute oral toxicity (i.e. the LD50 is greater than 2000 mg active constituent/kg body weight). In the dietary studies, the LC50 for both bird species was >5314 ppm, classifying metrafenone as practically non-toxic to birds via the dietary exposure route. A 22 week subchronic reproduction study with the bobwhite quail reported a NOEC of 1350 ppm and found that there were no observed adverse effects on adult health or survival or on any reproductive parameter that could be related to the metrafenone exposure.

When trout and bluegill sunfish were exposed to metrafenone for 96 hours under flow-through conditions, there were 10% mortalities at the two highest exposure concentrations for the trout and 15% mortality at the highest exposure concentration for the bluegill sunfish. The 96-hour LC50 was >0.82 mg metrafenone/L (the highest concentration tested) for trout and >0.87 mg metrafenone/L (again the highest concentration tested) for the bluegill sunfish and metrafenone is, at worst, highly toxic to fish (0.1 mg/L < LC50 ≤ 1 mg/L). When rainbow trout were exposed to a 500 g metrafenone/L formulation (similar to that proposed for use in Australia) at 13 to 104 mg formulation/L for 96 hours under static conditions, no mortalities or overt signs of toxicity were recorded. The 96 hour LC50 was set at >104 mg formulation/L (the highest concentration measured).

No mortalities or sublethal effects in rainbow trout exposed to the aquatic metrafenone metabolite, CL 375816 or 3-bromo-6-methoxy-2-methylbenzoic acid for 96 hours under static conditions at 100 mg/L and the 96 hour LC50 was >99 mg/L. With rainbow trout exposed for 96 hours under static conditions to the aquatic metrafenone metabolite CL 4084564 or (3-hydroxy-6-methoxy-2-methylphenyl)(2, 3, 4-trimethoxy-6-methylphenyl) methanone at 5 to 100 mg/L there was 80% mortality at 50 mg/L and 100% mortality at 100 mg/L. The 96 hour LC50 was set at 18 mg CL 4084564/L and this metabolite is slightly toxic to fish (10 > LC50 ≤ 100 mg/L).

When fathead minnows (*Pimephales promelas*) were exposed to metrafenone at a concentration of 0 to 835 µg metrafenone/L for 28 days there was a statistically significant reduction in post-hatch survival at the highest exposure concentration. A statistically significant reduction in total length and wet weight was observed at 419 µg metrafenone/L (the second highest concentration tested). The NOEC for growth was 228 µg metrafenone/L based on the observed weight loss and metrafenone is slightly chronically toxic to fish (100 < NOEC ≤ 1000 µg metrafenone/L).

Exposure of *Daphnia magna* for 48 hours 0 to 0.92 mg metrafenone/L resulted in no mortality/immobility or overt signs of sublethal toxicity observed in any treatment during the test and the 48 hour EC50 was >0.92 mg metrafenone/L. Metrafenone is, at worst, highly toxic to *Daphnia magna* (0.1≥ EC50 ≤1 mg/L). Following exposure of *Daphnia magna* to 0 to 1979 µg/L of a 500 g metrafenone/L SC formulation similar to that proposed for Australian use for 48 hours, there was 5% mortality in the highest concentration but no dead or immobile daphnids in any of the remaining treatments. The 48-hour EC50 value was >1.98 mg formulation/L. In daphnia exposed to 0 to 100 mg CL 375816/L for 48 hours, no significant mortality was observed at any test concentration and the 48 hour EC50 was >100 mg CL 375816/L and this metabolite is practically non-toxic to daphnia (EC50 > 100 mg/L). Exposure of daphnia to mean measured concentrations of 0 to 66.5 mg CL 4084564/L for 48 hours resulted in no loss of mobility at concentrations up to 12.5 mg/L

and 55 and 65% immobility at 49.6 and 66.5 mg CL 4084564/L respectively. The 48 hour EC50 was set at 47.3 mg/L and the metabolite is slightly toxic to daphnia (10 < EC50 ≤ 100 mg/L).

Daphnia magna were exposed to metrafenone at mean measured concentrations of 54 to 881 µg metrafenone/L for 21 days during a life-cycle toxicity test. There were no statistically significant differences in survival of parent *Daphnia magna* in any metrafenone exposed group as compared to the controls, but *Daphnia* exposed to 881 µg metrafenone/L had statistically significant reduced reproduction (mean live young) and mean dry weights in comparison to pooled controls. *Daphnia magna* exposed to 462 and 881 µg metrafenone/L had statistically significantly reduced lengths in comparison to the pooled controls. The NOEC for this study was 225 µg metrafenone/L (based on reduction in mean length of the parent daphnids after 21 days exposure) and metrafenone is rated as slightly chronically toxic to aquatic invertebrates (100 < NOEC ≤ 1000 µg/L).

The effects of prolonged exposure of metrafenone to the sediment dwelling larvae of the freshwater dipteran *Chironomus riparius* under static test conditions were studied for a period of 40 days using a spiked water water/sediment system with concentrations of 0 (control and solvent control) to 1000 µg metrafenone/L. All comparisons were made between solvent control and treatment groups because of a solvent effect observed in the untreated controls. In the metrafenone exposed midge, the numbers of male and female midges which emerged was not statistically different from the control means. Exposure to metrafenone did not show any consistent dose effect on development time or upon emergence rates All emerged midges appeared normal. However, the occurrence of statistically significant results in the mean development rates of three of the five test concentrations and the greater than 10% deviations from the solvent control mean in four of the five test concentrations, taken with the failure of the negative control to achieve at least 70% emergence, have resulted in SEWPAC setting the NOEC for development rate as less than <63 µg metrafenone/L.

To determine the effects of metrafenone on the growth of four algal species (*Pseudokirchneriella subcapitata* (*Selenastrum capricornutum*), *Anabaena flos-aquae, Navicula pelliculosa* and *Skeletonema costatum*) under static conditions, the algae were exposed to nominal concentrations of 63 to 1000 µg metrafenone/L (nominal) for periods of 72 to 96 hours. Based on measured concentrations of metrafenone, the 72 and 96 hour ErC50 (rate) values ranged from 670 (*Skeletonema costatum*) to >910 (*Navicula pelliculosa*) µg metrafenone/L. The 72 and 96 hour EbC50 value for biomass were 470 (*Skeletonema costatum*) to >910 µg metrafenone/L (*Navicula pelliculosa*). Metrafenone is classed as, at worst, highly toxic to algae (100 µg/L ≥ ErC50 ≤ 1000 µg/L). No noticeable changes in cell colour, size or morphology, no visual evidence of adherence of cells to the test chambers, flocculation of cells or aggregation of cells attributable to metrafenone were seen in any of the algal species tested.

When *Pseudokirchneriella subcapitata* were exposed to a 500 g metrafenone/L SC formulation similar to that proposed for use in Australia for 72 at nominal concentrations of 31 to 1000 µg metrafenone/L for 72 hours, the 72 hour ErC50 and EbC50 values were both >971 µg metrafenone/L (>2248 µg formulation), based on day 0 measured concentrations. After 72 hours of exposure, however, growth rate and biomass were significantly reduced in the 245, 480 and 971 µg metrafenone/L treatment groups in comparison to the negative control, resulting in the 72 hour NOECs for growth rate and biomass were both set at 127 µg metrafenone/L (294 µg formulation/L). The percentage inhibition at those concentrations were, respectively, 4.6, 5.6 and 11% for average specific growth rate and 20, 21 and 42% for mean biomass. After 72 hours, there were no noticeable changes in cell colour, size or morphology at any concentration tested, and there

was no visual evidence of adherence of cells to the test chambers, flocculation of cells or aggregation of cells.

When the alga *Pseudokirchneriella subcapitata* was exposed to the metrafenone metabolite, CL 4084564 for 72 hours at nominal concentration of 3.1 to 100 mg/L (3.2 to 58 mg/L, mean measured concentration), adverse effects on cell morphology and cell aggregation were not observed. The 72 hour ErC50 and EbC50 values were, respectively, 38.7 and 27.8 mg CL 4084564 mg/L, showing this metabolite to slightly toxic to algae (10 mg/L < EC50 ≤ 100 mg/L). The 72 h EbC10 and 72 h EbC10 values (NOEC surrogates) were, respectively, 18.3 and 20.3 mg CL 4085464/L as mean measured concentrations. A similar study with the metabolite CL 375816 using nominal test concentrations of 0.6 to 100 mg metabolite/L resulted in no reported adverse effects on the exposed *Pseudokirchneriella subcapitata* and the 72 h EbC50 and ErC50 were both reported as >100 mg CL 375816/L based on nominal concentrations over the 72 hour period. The metabolite CL 375816 is practically non-toxic to algae (EC50 > 100 mg/L). The 72 hour NOECs for cell density, biomass and growth rate were all set as 100 mg CL 375816/L.

In a seven day static renewal test, duckweed were exposed to nominal metrafenone concentrations of 0.063 to 1.0 mg/L. No dead or chlorotic fronds were observed over the exposure period. While necrotic effects occurred at all concentrations at days 5 and 7, the percentages of fronds affected were small (≤2.5%) and no dose response was present. Based on mean, measured concentrations, the 7 day EC50 values for frond number, biomass and growth rate were each >0.76 mg metrafenone/L, the highest concentration tested. The NOEC for frond number and final biomass was 0.41 mg metrafenone/L. Based on the 7 day EC50 for frond number, biomass and growth rate all being >0.76 mg metrafenone/L, metrafenone is classed as, at worst, highly toxic to duckweed (0.1 mg/L > EC50 ≤ 1 mg/L).

In a honey bee oral and contact toxicity study with metrafenone, bees were exposed to a nominal 100 µg metrafenone/bee via their diet or direct dorsal application over a 48 hour period. In the oral toxicity test after 48 hours, the average mortality seen in the metrafenone treated group was 2% with no bees affected (i.e. moribund and disoriented bees but not dead) at that time. There were no mortalities or adverse effects in bees exposed to metrafenone via the contact route over the 48 hours. The 48 hour LD50s of metrafenone technical by oral and contact exposure were respectively >114.0 µg and >100 µg metrafenone/bee and metrafenone is, at worst, very slightly toxic to the honeybee via the oral and contact routes (LC50 > 100 µg/bee). In a second study, the acute contact and oral toxicity of metrafenone as a 500 g/L SC formulation (similar to that to be used in Australia) to honey bees were determined. Bees were exposed to a nominal 100 µg metrafenone/bee via their diet or direct dorsal application over a 48 hour period. At test termination (48 h), the average mortality observed for the formulation treated group was 2% (oral toxicity) and 4% (contact toxicity). No formulation affected bees were seen at 48 hours in either the oral or contact toxicity study. The 48 hour LD50s by oral or contact exposure are > 119.2 or >100 µg formulation/bee and metrafenone, as a formulated material, is rated as very slightly toxic to the honeybee via the oral and contact routes (LC50 > 100 µg/bee).

When earthworms were exposed to a 1000 mg metrafenone/kg soil (dry weight) for 14 days there were no mortalities in either the metrafenone exposed or the control earthworms. There was a 10% mortality in the acetone controls. The 14-day LC50 of metrafenone in earthworms was estimated to be >1000 mg metrafenone/kg dry substrate showing metrafenone is very slightly toxic to the earthworm (LC50 > 1000 mg/kg dry soil). Exposure of earthworms to 1000 mg of a 500 g metrafenone/L formulation similar to that to be used in Australia for 14 days resulted in no earthworm mortality in either the water control or formulation

treatment. The day 14 NOEC set at <1000 mg formulation/kg dry substrate as a result of the statistically significant weight change as seen in the earthworms exposed to the formulation. Metrafenone, formulated as 500 g/L SC material, is very slightly toxic to the earthworm (LC50 > 1000 mg/kg dry soil). There were no mortalities or adverse behavioural effects in earthworms exposed to the metrafenone metabolite CL 377160 for 14 days at concentrations of 198 to 1000 mg/kg artificial soil and the 14 day LC50 was set at >1000 mg CL 377160/kg soil dry weight and the NOECs for mortality, biomass and behaviour each at 1000 mg CL 377160/kg soil dry weight. CL 377160 as very slightly toxic to earthworms (LC50 > 1000 mg/kg dry soil).

Assessment of the potential sub-lethal effects of a 300 g metrafenone/L formulation, BAS 560 00 F, as a 300 g/L SC formulation to earthworms in an artificial soil was determined by evaluation of adult worm mortality, their biomass development and their reproduction rate are evaluated over 8 weeks. The 28 day LC50 for earthworms was >5.0 L formulation/ha (>6 mg metrafenone/kg test soil), the day 28 NOEC for mortality and biomass development was 5.0 L formulation/ha. However, on the basis of the consistent reduction in numbers of juvenile earthworms seen at concentrations greater than 0.25 L formulation/ha, the 56 d NOEC for reproduction is set at 0.25 L formulation/ha, equivalent to 75 g metrafenone/ha or 0.30 mg/kg soil.

In a second earthworm reproduction study, the potential sub-lethal effects of the proposed 500 g metrafenone/L SC formulation to earthworms were evaluated over 8 weeks. The formulation was applied at nominal rates of 0.1 L/ha to 4.0 L/ha. The parent earthworm mortality LC50 (28 d) was >4.0 L/ha and the 28 d NOECs for biomass development and for juvenile reproduction were both set at 2.0 L formulation/ha or 1000 g metrafenone/ha.

The median lethal application rate (LR50) for nymphs of the predatory mite *Typhlodromus pyri* exposed for 7 days to metrafenone on glass plates to a 500 g/L SC formulation equivalent to that to be used in Australia in the laboratory was greater than 500 g metrafenone/ha, the highest rate tested in the study. Significant differences in fecundity (as mean numbers of eggs/female at days) were detected following 400 and 500 g metrafenone/ha treatments. Mites exposed to 400 g metrafenone/ha had 33% reductions in the total mean number of eggs/female compared to the control (untreated) value and 47% following exposure at 500 g metrafenone/ha.

In a second study, the median lethal application rate (LR50) with *T. pyri* nymphs exposed for 7 days to metrafenone in a 300 g/L SC formulation, on dried residues on glass plates, was determined to be greater than 300 g metrafenone/ha, the highest rate tested. A significant difference in fecundity (as mean numbers of eggs/female) over the study period was detected between the control treatment and the 150 and 300 g metrafenone/L treatments at days 10 and 12 for both test concentrations but not at day 14 after treatment in either test concentration. Mites exposed to metrafenone showed 38 (150 g metrafenone/ha) and 43% (300 g metrafenone/ha) reductions in the total mean number of eggs/female compared to the control (untreated) value.

The median lethal application rate (LR50) for adults of the parasitic wasp *Aphidius rhopalosiphi* exposed for 48 hours to metrafenone in a 500 g/L SC formulation, equivalent to that to be used in Australia on dried residues on glass plates, was determined to be greater than 300 g metrafenone/ha, the highest rate tested in the study. Fecundity was determined by parasitisation of cereal aphids by the surviving female wasps. A significant difference in fecundity (as mean numbers of mummies/female over the study period) was detected between the control treatment and the 300 g metrafenone/L treatment and the EC50, the concentration causing a greater than 50% reduction in this parameter, is set as >150 g metrafenone/ha. The mean

numbers of mummies in the control and 100, 150 and 300 g metrafenone/ha treatments were 5.3, 3.1, 5.0 and 1.1 with the last value representing 21% of the control value.

In a second laboratory study with adult *Aphidius rhopalosiphi* and a 300 g/L metrafenone formulation, the median lethal application rate (LR50) after 48 hours exposure to the dried formulation, was determined to be greater than 300 g metrafenone/ha, the highest rate tested in the study. With respect to fecundity (measured again as the mean numbers of mummies/female over the study period), the mean numbers in the control, 150 and 300 g metrafenone/ha treatments were, respectively, approximately 5.3, 1.1 and 2.6 with the latter two values representing 21 and 49% of the control value. As a result, the EC50 for this parameter, mean numbers of mummies/female, is set as <150 g metrafenone/ha.

To determine the acute toxicity of a 300 g metrafenone/L formulation on the lacewing larvae *Chrysoperla carnea* Steph. in the laboratory, lacewing larvae were exposed to 150 and 300 g metrafenone/ha as the formulated material. After exposure, pupae were transferred to Petri dishes for development of adults. The reproduction performance, i.e. egg deposition and hatching rate, was determined using hatched females. Mortality in the controls was 4.0% and corrected mortalities in the 150 and 300 g metrafenone/ha groups, respectively, 0.0 and 2.1%. The numbers of eggs/female/day were 30.7, 29.8 and 31.1 in the control, 150 and 300 g metrafenone/ha groups respectively and the equivalent hatching rates, 84.3, 86.43 and 81.9%. Under laboratory conditions, metrafenone as a 300 g/L formulation, caused no adverse effects on mortality and reproduction of the foliage dwelling predator *Chysoperla carnea* up to an application rate of 300 g metrafenone/ha.

Male and female carabid beetles, *Poecilus cupreus*, were exposed to concentrations of 300 g metrafenone/ha (as either a 300 or the proposed 500 g metrafenone/L formulation) and effects on mortality and behavioural impacts (e.g. food uptake) measured over a period of 14 days. In both cases there were no control or metrafenone exposed beetle deaths and no statistically significant difference between the number of consumed pupae/beetle for the control and metrafenone exposed beetles.

Metrafenone, as a 300 g/L formulation, applied to soil at 150 g and 1.5 kg metrafenone/ha did not have prolonged effects upon the short-term respiration or nitrogen mineralisation capacity of soi1 microflora with the trigger value of 25% from the control not being exceed at any time. The proposed 500 g metrafenone/L formulation applied to soil at 0.067 and 0.536 mg metrafenone/kg dry soil (reflecting multiple applications over time) had no effects on short-term respiration and no lasting effects on nitrification processes in soi1 at the concentrations tested. CL 377160, a soi1 photolysis metabolite of metrafenone, at worst case soil concentrations of 0.031 and 0.31 mg metrafenone/kg dry soi1, resulted in deviations from the control values for carbon mineralisation and nitrogen turnover of less than 25% on all occasions and CL 377160 had no effects on either of these soil microflora dependent processes.

When the proposed 500 g metrafenone/L SC formulation was sprayed onto one to three week old seedlings of ten plant species at rates equivalent to 100 and 300 g metrafenone/ha, there was an absence of any significant effects on mortality and the other growth parameters in the exposed plants and a vegetative vigour NOEC of 300 g metrafenone/ha was set. In a seedling emergence study with ten plant species, application of the proposed 500 g metrafenone/L formulation at 100 and 300 g metrafenone/ha had no significant effect on seedling emergence, seedling survival and day 21 plant height. There were, however, biologically significant effects in the day 21 plant dry weight and day 21 phytotoxicity results at the 300 g metrafenone/ha level and the day 21 NOEC for these parameters is set at 100 g metrafenone/ha.

7.3 Risk Assessment

Exposure to birds (and small mammals) to metrafenone residues would primarily be via the eating of grapes on the treated vines or insects that were in the vines or cucurbits and sprayed with the formulated material. Based on the estimated dietary intakes of metrafenone by birds (and small mammals) following single and multiple applications of Vivando® Fungicide at the maximum use rate of 150 g a.i. metrafenone/ha and comparison of such values with the relevant subchronic dietary LC50 or NOECs, risk to birds (and small mammals) through eating of metrafenone contaminated feed has been shown to be acceptable.

Risk assessment based on a direct overspray of waterbody indicated marginally unacceptable risk for aquatic species from exposure to metrafenone. A refinement of the risk assessment based on a 10% spraydrift event showed acute aquatic risk was acceptable to all trophic levels. The 10% spraydrift scenario risk assessment also showed that aquatic risk is acceptable following the maximum proposed four applications of Vivando® Fungicide. Because the acute and chronic aquatic risks from single or multiple applications of Vivando Fungicide are acceptable in all cases, no need exists for the establishment of down-wind no-spray zones. Aquatic risk from runoff of metrafenone was modelled taking into account field runoff, water solubility, foliar interception and binding of metrafenone to soils/sediments. This modelling indicated that the acute and chronic risk to aquatic ecosystems from the run-off of metrafenone in the runoff water and in the sediment washed from treated crops is acceptable.

Risk to honeybees from metrafenone applied at the maximum proposed use rate is indicated as acceptable. Risk assessment based on the predicted environmental concentration and either the earthworm LC50 or NOEC values showed that the proposed use of Vivando® Fungicide on cucurbits and grapevines is not expected to cause unacceptable risk to earthworms. Risk quotients based on the relationship of the in-field exposure of non-target or beneficial arthropods (predatory mite and parasitic wasp) showed that, following exposure to metrafenone levels at and exceeding the maximum proposed Australian use rate of 150 g a.i./ha were acceptable with respect to mortality but the laboratory studies indicated that significant adverse effects on fecundity occurred. As these could be expected to also take place in the field, there is a possibility of adverse impact on integrated pest management practices. Consequently, because of the absence of field studies, an integrated pest management statement advising that Vivando Fungicide may have an adverse effect on non-target beneficial insects where IPM is practised is recommended.

Metrafenone was shown to have no adverse effects on the survival of lacewing larvae and carabid ground beetles following exposure to levels of metrafenone equal to or exceeding the proposed Australian use rate. The effects of metrafenone as either a 300 or 500 g metrafenone/L formulation, upon the rate of short-term respiration (carbon utilisation) and on the nitrification capacity of soi1 microflora under aerobic conditions were within 25% of the control values over the 28 day period of the 300 g/L study and at 42 days in the 500 g/L study. Exposure rates were equivalent to the proposed maximum Australian use rate of 150 g a.i. metrafenone/ha and ten times that rate. Lasting effects on carbon and nitrification processes in soil are not expected to occur with the proposed Vivando® Fungicide use pattern.

Risk assessment showed risk to off-field non-target terrestrial plants as a result of use of the proposed Australian Vivando Fungicide use patterns from a single and multiple applications is acceptable.

Because Vivando® Fungicide is manufactured and formulated overseas, these processes will not cause harm to the Australian environment. Risk from spills is expected to be controlled on the basis of label and safety data sheet information.

8 EFFICACY AND SAFETY ASSESSMENT

The applicant, BASF Australia Ltd, seeks registration of the proposed new product, VIVANDO® FUNGICIDE, for the control of powdery mildew (*Podosphaera xanthii*) of cucurbits and powdery mildew (*Erysiphe necator*) of grapevines. The product is a suspension concentrate formulation containing 500 g/L metrafenone.

8.1 Proposed use pattern

VIVANDO® FUNGICIDE is intended to be used at a rate of 150-300mL product/ha in cucurbits and 20mL product/100L water (dilute application rate) in grapevines. Use is proposed in all Australian states and territories.

8.2 Summary of Evaluation of Efficacy and Crop safety

VIVANDO® FUNGICIDE is a suspension concentrate containing 500 g/L metrafenone. Metrafenone is a new active constituent to the Australian market. It is a fungicide which belongs to the benzophenone chemical group and represents the first commercial development from this group. The Fungicidal Mode of Action of the benzophenone group is still under evaluation - it appears to be novel and to date has not demonstrated any cross-resistance when tested on strains of powdery mildew that have developed tolerance to other fungicide groups. Whilst the Mode of Action of metrafenone is not fully understood, it has been shown to have local systemic activity with some eradicative action, however the product is to be used primarily as a protectant.

A total of 16 field trials on cucurbits and grapevines were established mainly in Western Australia, with one cucurbit trial in Queensland, one grapevine trial in South Australia and one in Victoria. Sites were selected in areas where the crops are commercially grown and where the target disease, Powdery Mildew, is likely to occur.

Trial design was suitable in all instances. Data were analysed using standard ANOVA and Fischer's least significance test was used for comparing treatment means at the 5% level of significance. Data were well presented. The efficacy trials provided demonstrated satisfactory efficacy at the proposed label rates of 150-300mL product/ha in cucurbits and 20mL product/100L water (dilute application rate) in grapevines. The product will be applied to cucurbits by boom equipment using spray volumes between 250 to 500 L/ha and to grapevines by dilute or concentrate spraying methods. Addition of a wetter such as Du-Wett® Low Volume Application Spreader is recommended particularly where reduced spray volumes are used.

The information provided showed that VIVANDO® FUNGICIDE has good efficacy in control of powdery mildew of cucurbits and grapevines, and demonstrates acceptable crop safety, when used as directed.

Assessment of study/trial data

Field trials were located at sites where there was a history of regular occurrence of the target diseases (powdery mildew (*Podosphaera xanthii*) of cucurbits and powdery mildew (*Erysiphe necator*) of grapevines). Weather conditions at most of the sites were suitable to ensure that the development of the disease

progressed to levels suitable for efficacy evaluation. Application of trial fungicide treatments in the cucurbit trials commenced when powdery mildew was either just starting to appear or was at a very low level. This is consistent with the fact that the action of metrafenone is primarily that of a protectant, although it also has some eradicative properties. Application of the trial fungicide treatments on grapevines was either at early flowering (W.A. trials) or at late flowering (Victorian and S.A. trials), well before any symptoms of powdery mildew were evident.

In the cucurbit trials, application was done with either a gas-pressurised knapsack sprayer fitted with a boom containing the appropriate spray nozzles at 10 to 12.5 cm spacing, or with a small-plot sprayer fitted with a boom and suitable nozzles. With the grapevine trials, fungicide was applied to the canopy using a hand lance fitted with appropriate solid cone nozzles, and motor-pressurised.

Spray application of VIVANDO® FUNGICIDE was assessed for efficacy compared with industry standard fungicide(s) currently recommended for control of the nominated diseases and an untreated control.

Results in the cucurbit trials indicate that VIVANDO® FUNGICIDE, when applied as directed, gave a reduction in disease severity which varied between 80% and 86% which was at least equal to, or better than the industry standards.

Results in the grapevine trials indicate that when VIVANDO® FUNGICIDE was applied as directed, the severity of powdery mildew leaf infection was reduced from between 58% and 100%, and severity of bunch infection from between 70% and 99%. In addition, powdery mildew infection of grape berry rachis in one trial was completely controlled by application of the product. Disease control on grapevines was comparable to that obtained using registered industry standards.

Results in all trials indicated that use of VIVANDO® FUNGICIDE at recommended maximum label rates did not result in any evidence of phytotoxicity in the target crop.

Integrated pest management (IPM)

A statement has been included on the label warning that VIVANDO® FUNGICIDE may have an adverse effect on non-target beneficial predatory mites and parasitoid wasps in target crops where IPM is practised.

Crop safety

The information and data presented indicate that VIVANDO® FUNGICIDE is safe to use on cucurbits and grapevines when used as directed. No adverse symptoms were apparent in any crop at the recommended label application rates.

Resistance management

The new active constituent metrafenone has been included in the new group U8 (unspecified) resistance grouping. Metrafenone is in Group U8 for Fungicides Resistance Management. The Fungicidal Mode of Action of the benzophenone group is still under evaluation - it appears to be novel and to date has not demonstrated any cross-resistance when tested on strains of powdery mildew that have developed tolerance to other fungicide groups.

9 CONCLUSION

The claims on the proposed product label that the product VIVANDO® FUNGICIDE provides acceptable control of powdery mildew of both cucurbits and grapevines when used as directed, are supported by the results from the Australian trials. Acceptable crop safety is also to be expected when the product is used as directed. The Directions for Use are appropriate and consistent with fungicide use in commercial agricultural production in these crops in Australia. The label Restraints, Critical Comments, General Instructions (IPM warning), Withholding Periods, Fungicides Resistance statements and Application Instructions are consistent with Australian Good Agricultural Practice (GAP) and other risk assessments conducted for the product.

The application by BASF Australia Ltd for the registration of VIVANDO® FUNGICIDE is supported on efficacy and crop safety grounds when used in accordance with the proposed label instructions and Good Agricultural Practice (GAP).

10 LABELLING REQUIREMENTS

CAUTION

KEEP OUT OF REACH OF CHILDREN

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

VIVANDO® FUNGICIDE

ACTIVE CONSTITUENT: 500 g/L METRAFENONE

GROUP	**U8**	FUNGICIDE

For the control of powdery mildew in cucurbits and grapes as per the Directions for Use Table.

CONTENTS: 1 – 20 L

BASF Australia Ltd ABN 62 008 437 867
Level 12, 28 Freshwater Place Southbank VICTORIA 3006

APVMA Approval No.: 63487/XXXXX

STORAGE AND DISPOSAL

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

Triple or preferably pressure rinse containers before disposal. Add rinsings to 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, triple rinse, break, crush or puncture and deliver empty packaging for appropriate disposal at 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. Empty containers and product must not be burnt.

SAFETY DIRECTIONS

When opening the container and preparing spray, wear elbow length PVC gloves. After each day's use, wash gloves. Wash hands after use.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126.

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet.

CONDITIONS OF SALE

All conditions and warranties rights and remedies implied by law or arising in contract or tort whether due to the negligence of BASF Australia Ltd or otherwise are hereby expressly excluded so far as the same may legally be done provided however that any rights of the Buyer pursuant to non- excludable conditions or warranties of the Trade Practices Act 1974 or any relevant legislation of any State are expressly preserved but the liability of BASF Australia Ltd or any intermediate Seller pursuant thereto shall be limited if so permitted by the said legislation to the replacement of the goods sold or the supply of equivalent goods and all liability for indirect or consequential loss or damage of whatsoever nature is expressly excluded. This product must be used or applied strictly in accordance with the instructions appearing hereon. This product is solely sold for use in Australia and must not be exported without the prior written consent of BASF Australia Ltd.

APVMA Approval No: 63487/XXXXX

Batch No:
Date of Manufacture:

BASF Australia Ltd
ABN 62 008 437 867
Level 12, 28 Freshwater Place
Southbank VICTORIA 3006

FOR SPECIALIST ADVICE IN AN EMERGENCY ONLY PHONE 1800 803 440 TOLL FREE-ALL HOURS-AUSTRALIA WIDE

CAUTION

KEEP OUT OF REACH OF CHILDREN

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

VIVANDO® FUNGICIDE

ACTIVE CONSTITUENT: 500 g/L METRAFENONE

GROUP	U8	FUNGICIDE

For the control of powdery mildew in cucurbits and grapes as per the Directions for Use Table.

CONTENTS: 1 – 20 L

BASF Australia Ltd ABN 62 008 437 867
Level 12, 28 Freshwater Place Southbank VICTORIA 3006

APVMA Approval No.: 63487/XXXXX

DIRECTIONS FOR USE

RESTRAINTS
DO NOT apply with aircraft.

SPRAY DRIFT RESTRAINTS
DO NOT apply with spray droplets smaller than a MEDIUM spray droplet size category according to nozzle manufacturer specifications that refer to the ASAE S572 Standard or the BCPC Guideline.
DO NOT apply when wind speed is less than 3 or more than 20 kilometres per hour as measured at the application site.
DO NOT apply in vineyards when the wind speed is less than 3 or more than 20 kilometres per hour as measured 15 metres outside of the vineyard on the upwind side.
DO NOT 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 during surface temperature inversion conditions at the application site.
Mandatory No Spray Zones for livestock, pasture or any land that is producing feed for livestock downwind from the application area are not required when used as directed.
Users of this product MUST make an accurate written record of the details of each spray application within 24 hours following application and KEEP this record for a minimum of 2 years. The spray application details that must be recorded are: 1) date with start and finish times of application; 2) location address and paddock/s sprayed; 3) full name of this product; 4) amount of product used per hectare and number of hectares applied to; 5) crop/situation and weed/pest; 6) wind speed and direction during application; 7) air temperature and relative humidity during application; 8) nozzle brand, type, spray angle, nozzle capacity and spray system pressure measured during application; 9 name and address of person applying this product. (Additional record details may be required by the state or territory where this product is used.)

CROP	DISEASE	RATE	WHP	CRITICAL COMMENTS
Cucurbits	Powdery mildew (*Podosphaera xanthii*)	150 – 300 mL/ha	7 days	Apply two consecutive VIVANDO spray applications 7 to 10 days apart commencing before powdery mildew becomes established. VIVANDO should only be applied as a protectant spray. Applications beginning before disease is evident on the undersides of the older leaves are recommended. A second block of two VIVANDO sprays may be applied if required providing that it is preceded and followed by at least two applications of fungicides from a different fungicide Group (e.g. Colliss® Fungicide) for resistance management. As a precaution, DO NOT apply more than four applications of VIVANDO per crop and DO NOT exceed more than one third of the total powdery spray program with VIVANDO. Refer to the Application directions below for information on the use of Du Wett® Low Volume Application Spreader with VIVANDO.

CROP	DISEASE	RATE	WHP	CRITICAL COMMENTS
Grapevines	Powdery mildew (*Erysiphe necator*)	Dilute spray 20 mL/100L Concentrate spray Refer to the application section.	5 weeks	Apply as part of a protectant spray program commencing when shoots are 10 cm in length. DO NOT apply more than two consecutive applications of VIVANDO 7 to 10 days apart before changing to an alternative fungicide group for powdery mildew control (e.g. Cabrio® Fungicide). DO NOT apply more than four applications of VIVANDO per crop. Apply by dilute or concentrate spraying equipment. Apply the same amount of total product to the target crop whether applying this product by dilute or concentrate spraying methods. The addition of Du Wett® will assist spray coverage on leaves and bunches especially if spray volumes are less than dilute.

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

WITHHOLDING PERIODS:

Cucurbits: DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION.
Grapes: DO NOT HARVEST FOR 5 WEEKS AFTER APPLICATION.

GENERAL INSTRUCTIONS

VIVANDO Fungicide may have an adverse effect on non-target beneficial predatory mites and parasitoid wasps where IPM is practiced.

FUNGICIDE RESISTANCE WARNING

GROUP U8 FUNIGICIDE

VIVANDO Fungicide is a member of the unspecified group of fungicides. For fungicide resistance management VIVANDO is a Group U8 fungicide. Some naturally occurring individual fungi resistant to VIVANDO and other Group U8 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungi population if these fungicides are used repeatedly. These resistant fungi will not be controlled by VIVANDO and other Group U8 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, BASF Australia Limited accepts no liability for any losses that may result from the failure of VIVANDO to control resistant fungi.

MIXING

To ensure even mixing, half-fill the spray tank with clean water and add the required amount of product. If required, add compatible products and agitate thoroughly, then add the remainder of the water. Agitate again before spraying commences.

APPLICATION

Apply to cucurbits by boom equipment using spray volumes between 250 to 500 L/ha. Du-Wett® Low Volume Application Spreader will assist the performance of VIVANDO at all spray volumes but is especially recommended when reduced water volumes are used.

Dilute Spraying

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

Concentrate Spraying (Grapevines ONLY)

♦ Use a sprayer designed and set up for concentrate spraying (that is a sprayer which applies spray volumes less than those required to reach the point of run-off) and matched to the crop being sprayed.
♦ Set up and operate the sprayer to achieve even coverage throughout the crop canopy using your chosen spray volume.
♦ Determine an appropriate dilute spray volume (See Dilute Spraying above) for the crop canopy. This is needed to calculate the concentrate mixing rate.
♦ The mixing rate for concentrate spraying can then be calculated in the following way:
EXAMPLE ONLY
1. Dilute spray volume as determined above: For example 1500 L/ha
2. Your chosen concentrate spray volume: For example 500 L/ha
3. The concentration factor in this example is: 3 X (i.e. 1500 L ÷ 500 L = 3)
4. If the dilute label rate is 20 mL/100 L, then the concentrate rate becomes 3 x 20 (that is 60 mL of product per 100 L water for concentrate spraying).
♦ The chosen spray volume, amount of product per 100 L of water, and the sprayer set up and operation may need to be changed as the crop grows.
♦ For further information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow industry Best Practices.

COMPATIBILITY

For information on compatibility please contact your local industry representative.

EXPORT OF TREATED FRUIT OR WINE

Growers should note MRLs or import tolerances do not exist in all markets for fruit treated with VIVANDO Fungicide. If you are growing fruit for export (either fresh, dried or for wine production), please check with your industry representative or the Australian Wine Research Institute (AWRI) http://www.awri.com.au// for the latest information on MRLs and import tolerances BEFORE using VIVANDO.

RE-ENTRY PERIOD

DO NOT allow entry into treated areas until the spray has dried. When prior entry is necessary, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

DO NOT apply under weather conditions or from spraying equipment which could be expected to cause spray drift. Very toxic to aquatic plants and moderately toxic to aquatic invertebrates. DO NOT contaminate streams, rivers or waterways with the chemical or used containers.

STORAGE AND DISPOSAL

Store in the closed, original container in a cool, well-ventilated area. DO NOT store for prolonged periods in direct sunlight.
Triple or preferably pressure rinse containers before disposal. Add rinsings to 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, triple rinse, break, crush or puncture and deliver empty packaging for appropriate disposal at 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. Empty containers and product must not be burnt.

SAFETY DIRECTIONS

When opening the container and preparing spray, wear elbow length PVC gloves. After each day's use, wash gloves. Wash hands after use.

FIRST AID

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

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet.

CONDITIONS OF SALE

All conditions and warranties rights and remedies implied by law or arising in contract or tort whether due to the negligence of BASF Australia Ltd or otherwise are hereby expressly excluded so far as the same may legally be done provided however that any rights of the Buyer pursuant to non- excludable conditions or warranties of the Trade Practices Act 1974 or any relevant legislation of any State are expressly preserved but the liability of BASF Australia Ltd or any intermediate Seller pursuant thereto shall be limited if so permitted by the said legislation to the replacement of the goods sold or the supply of equivalent goods and all liability for indirect or consequential loss or damage of whatsoever nature is expressly excluded. This product must be used or applied strictly in accordance with the instructions appearing hereon. This product is solely sold for use in Australia and must not be exported without the prior written consent of BASF Australia Ltd.

APVMA Approval No: 63487/XXXXX
Batch No:
Date of Manufacture:

® = Registered trademark of BASF

BASF
The Chemical Company

BASF Australia Ltd
ABN 62 008 437 867
Level 12, 28 Freshwater Place
Southbank VICTORIA 3006

FOR SPECIALIST ADVICE IN AN EMERGENCY ONLY PHONE 1800 803 440 TOLL FREE-ALL HOURS-AUSTRALIA WIDE

ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute Reference Dose (human)
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EUP	End Use Product
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Heamatocrit
Hg	Haemoglobin

HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
K_{ow}	Octanol/water partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NOAEL	No Obsevable Adverse Effect Level
NOEC/NOEL	No Observable Effect Concentration/Level

OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
STMR	Supervised Trial Median Residue
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
TRR	Total Radioactive Residues
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter
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.
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of an absorbed material from a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	Water repelling
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octonol water partitioning co-efficient
Metabolism	The conversion of food into energy
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

Felton, J.C., Oomen, P.A. & Stevenson, J.H. 1986, 'Toxicity and hazard of pesticides to honeybees: harmonisation of test methods', *Bee World*, vol. 67, no. 3, pp. 114-24.

Goring, C.A.I. et al. 1975, 'Principles of pesticide degradation in soil', in *Environmental Dynamics of Pesticides*, edited by R. Haque and V.H. Freed, Plenum Press, New York, pp 135-72.

Matthews, G.A. 1992, *Pesticide Application Methods*, 2nd ed., Longman, London.

Australian Pesticides and Veterinary Medicines Authority 2008, *Ag MORAG: Manual of Requirements and Guidelines*, APVMA, Canberra.

Australian Pesticides and Veterinary Medicines Authority 2008, *Vet MORAG: Manual of Requirements and Guidelines*, APVMA, Canberra.