Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active amisulbrom in the product Amicus Blue Fungicide

APVMA Product Number 70161

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Director Public Affairs and Communication
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604 Australia

Telephone: +61 2 6210 4988

Email: communications@apvma.gov.au

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

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PREFACE

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

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

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

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

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

About this document

This is a public release summary.

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

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

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

Making a submission

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

into consideration in determining whether the safety, efficacy or trade criteria have been met. Submissions should state the grounds on which they are based.

Submissions must be received by the APVMA by close of business on 26 July 2016 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

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

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

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

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

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

Further information

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

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: www.apvma.gov.au

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

1 INTRODUCTION

1.1 Purpose of application

Nufarm Australia Limited has applied to the APVMA for registration of the new product AMICUS BLUE FUNGICIDE containing the new active constituent amisulbrom as a suspension concentrate (SC) formulation. Amicus Blue Fungicide contains 32 g/L amisulbrom and 180 g/L copper (Cu) present as tribasic copper sulphate.

This publication provides a summary of the information reviewed and an outline of the regulatory considerations for the proposed registration of Amicus Blue Fungicide, and approval of the new active constituent, amisulbrom.

1.2 Product claims and use pattern

Amicus Blue Fungicide is intended for the control of downy mildew (*Plasmopara viticola*) in grapevines and white blister (*Albugo candid*a) and downy mildew (*Hyaloperonospora brassicae*) in brassica vegetable crops.

The proposed use of Amicus Blue Fungicide on brassica vegetable crops involves up to three foliar applications per crop at the rate of 2 L/ha (64 g amisulbrom/ha) with 7 to 10 day re-treatment intervals for consecutive applications.

Amicus Blue Fungicide is proposed for use in grapevines at a dilute spraying rate of 250 mL/100L (8 g amisulbrom/100L). The product is applied as a protectant spray to grapevines commencing after shoots are 10 cm long. Amicus Blue Fungicide is intended to be applied to grapevines with not more than two consecutive applications and a maximum of four applications per season with consecutive applications to be made 7–10 days apart. Amicus Blue Fungicide is not to be applied after E-L 31 (early bunch closure) on grapes grown for export wine production.

1.3 Mode of action

Amisulbrom, a new active to the Australian market, is an oomycete-specific fungicide which acts by inhibiting mitochondrial complex III activity through binding to the Qi centre and impairing respiration. The Fungicide Resistance Action Committee (FRAC) has categorised amisulbrom as a Quinine Insider Inhibitor (QII) based upon this mode of action. Amisulbrom has been designated as a Group 21 FUNGICIDE for resistance management purposes.

Copper (Cu) present as tribasic copper sulphate is designated as a Group M1 fungicide and acts as a multi-site activity fungicide.

For resistance management purposes, Amicus Blue Fungicide is a Group 21 and Group M1 fungicide.

1.4 Overseas registrations

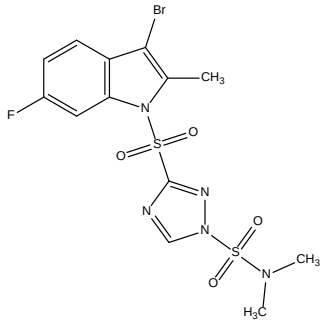
Products containing amisulbrom are currently registered overseas including in Europe, Japan, Korea, Taiwan and Vietnam. These registrations cover a range of crops including potatoes, lettuces, tomatoes, eggplants and grapes. In the USA, amisulbrom has import tolerances established for tomatoes and grapes.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

Amisulbrom is a new active constituent which belongs in the sulfonamide chemical class of fungicides.

Chemical characteristics of the active constituent:

COMMON NAME (ISO):	Amisulbrom
IUPAC NAME:	3-(3-bromo-6-fluoro-2-methylindol-1-ylsulfonyl)-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide.
CAS NAME:	3-[(3-bromo-6-fluoro-2-methyl-1H-indol-1-yl)sulfonyl]-N,N-dimethyl-1H-1,2,4-triazole-1-sulfonamide
CAS REGISTRY NUMBER:	348635-87-0
MANUFACTURER CODE:	NC-224
MINIMUM PURITY:	965 g/kg minimum
MOLECULAR FORMULA:	$C_{13}H_{13}BrFN_5O_4S_2$
MOLECULAR WEIGHT:	466.3
STRUCTURE:	
CHEMICAL FAMILY:	Sulfonamide fungicides; triazole fungicides
MODE OF ACTION:	Inhibits fungal respiration with binding to the Qi centre site on cytochrome bc1 (ubiquinone reductase) in Complex III.

Physical and chemical characteristics of amisulbrom

PHYSICAL FORM (99.8% PURITY):	Very pale yellow, odourless, crystalline solid (99.9%) Pale brown, odourless, fine powder (98.9%)
MELTING POINT:	128 ºC-130 ºC
RELATIVE DENSITY:	D420 = 1.72 (99.8% purity) D420 = 1.61 (99.1% purity)
N-OCTANOL/WATER PARTITION COEFFICIENT:	Log P_{ow} = 4.4 pH 6.4 and 25ºC
VAPOUR PRESSURE AT 25ºC:	1.8 x 10-8 Pa
SOLUBILITY IN WATER AT 20ºC:	0.11 mg/L
SOLUBILITY IN VARIOUS SOLVENTS AT 20ºC:	Acetone: >250 g/L Methanol: 10.01 g/L Dichloromethane: >250 g/L Toluene: 88.63 g/L Hexane: 0.264 g/L Ethyl acetate: >250 g/L n-Octanol: 2.6 g/L
HENRY'S LAW CONSTANT:	2.8 x 10-5 Pa m^3 mol^{-1}
UV/VIS ABSORPTION (MAX):	Neutral pH = λ_{max} 254 nm pH acidic methanol = λ_{max} 254 nm pH basic methanol = λ_{max} 222 nm pH>12 = λ_{max} 265 nm
FLAMMABILITY:	Not flammable
QUANTUM YIELD:	0.19 molecules $photon^{-1}$ at pH 4 and 25°C. Irradiation over the 48 hour test period was calculated to be equivalent to 106 hours of natural sunlight at latitude 40 °N
EXPLOSIVE PROPERTIES:	Not explosive
OXIDISING PROPERTIES:	Not oxidizing
STABILITY:	Stable for two years under ambient conditions. Stable when stored at 54°C for 14 days. Stable when stored in contact with aluminium, iron, zinc and the corresponding metal acetate salts at 54°C for 14 days

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

On the basis of the data provided, and the toxicological assessment, it is proposed that the following APVMA active constituent standard be established for amisulbrom:

APVMA CONSTITUENT STANDARD

CONSTITUENT	SPECIFICATION	LEVEL
Amisulbrom	Amisulbrom	Not less than 965 g/kg

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

2.2 Formulated product

The chemistry aspects of the product, Amicus Blue Fungicide (manufacturing process, quality control procedures, batch analysis results and analytical methods) have been evaluated by the APVMA.

The product Amicus Blue Fungicide will be packaged and marketed in 5–1000 L high density polyethylene (HDPE) containers.

Amicus blue fungicide

DISTINGUISHING NAME:	AMICUS BLUE FUNGICIDE
FORMULATION TYPE:	Suspension Concentrate (SC)
ACTIVE CONSTITUENT CONCENTRATIONS:	32 g/L Amisulbrom 180 g/L Copper (Cu) present as tribasic copper sulphate

Physical and chemical properties of formulated product

PHYSICAL FORM	Smooth blue-green homogenous suspension
PH VALUE (1% AQUEOUS):	7.15
DENSITY:	1.24–1.27 g/mL
VISCOSITY:	1500–2500 cps
PERSISTANT FOAM:	15 mL after 1 min
SUSPENSIBILITY:	102.2%
DISPERSION:	2 inversions
WET SIEVE TEST:	0.0016% retained on a 75µm sieve
PARTICLE SIZE DISTRIBUTION:	0.33 µm at d(0.1) 1.35 µm at d(0.5) 4.06 µm at d(0.9)
POURABILITY:	0.24% for rinsed residue
FLASH POINT:	Not flammable
OXIDISING PROPERTIES:	No oxidising properties
EXPLOSIVE PROPERTIES:	No explosive properties
PACK SIZES:	5–1000 L
PACKAGING MATERIAL:	HDPE containers with plastic lids
PRODUCT STABILITY:	Product is expected to remain stable over the proposed 2–year shelf life

2.3 Conclusion

The APVMA is satisfied that the chemistry and manufacture data requirements for the registration of the product Amicus Blue Fungicide and approval of the active constituent amisulbrom have been met.

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

The proposed use of Amicus Blue Fungicide containing 32 g/L amisulbrom and 180 g/L copper (Cu) present as tribasic copper sulphate is for the control of downy mildew in grapes and downy mildew and white blister in brassicas.

In toxicokinetic studies in rats, amisulbrom oral absorption was approximately 50% at low doses (10 mg/kg bw) but much lower with high doses (5% at 1000 mg/kg bw). Amisulbrom does not accumulate in the body. It is readily excreted after single or repeat administrations to rats, with >90% eliminated primarily in faeces within 72 hours. Patterns of excretion are similar between sexes. Only small proportions (<0.5%) of administered doses are retained in tissues and carcass 120 hours after single or repeat administration, with most of the residual administered dose found in the liver, kidney, whole blood and blood cells.

Based on the findings of the acute toxicological studies evaluated, amisulbrom is of low acute oral, dermal, and inhalational toxicity in rats, and is non-irritating to the skin of rabbits and non-sensitising in guinea pigs by the Guinea Pig Maximisation Test method. Amisulbrom was considered to be a slight but persistent eye irritant in rabbits, noting the extended observation of low-level conjunctival effects in a single animal up to 22 days after treatment.

Repeat dose studies conducted with amisulbrom in rats, mice and dogs revealed treatment-related effects generally limited to non-specific toxicity (ie decreases in body weight, body weight gain, food consumption, or food conversion efficiency) and effects on the liver (e.g. serum liver enzyme changes, increased liver weights, or hepatocyte hypertrophy).

Amisulbrom was not genotoxic in several *in vitro* and *in vivo* studies.

In long-term toxicity/carcinogenicity studies with rats, mice and dogs, the target organs of toxicity were the liver and kidney. Effects observed included non-specific toxicity (i. decreased body weight gains and reduced food consumption at higher concentrations) as well as changes in the liver and kidneys, such as increased γ-glutamyl transpeptidase activity in male rats (also in females at higher doses), increased relative kidney and liver weights, increased adrenal weights in dogs, as well as histopathological changes in the liver (midzonal and centrilobular hepatocyte vacuolation) and kidney (cortical tubular pigmentation). The effects were more marked at higher doses.

In the 2–year combined chronic and carcinogenic study in rats, neoplastic changes, including higher incidences of liver hepatocellular adenoma and carcinoma, were seen at ≥ 10000 ppm (496/697 mg/kg bw/d M/F), which was considered above the maximum tolerated dose (MTD). The increased incidence of forestomach tumours in female rats were caused by local irritation of the stomach mucosa and not considered relevant to humans. In mice, a dose-related increased incidence in hepatocellular adenoma was observed in males. These neoplastic changes were noted at levels below the MTD of 8000 ppm (1035 mg/kg bw/d). Mechanistic studies submitted suggesting a carcinogenicity mode of action for amisulbrom similar to phenobarbital, a mechanism which is generally not considered relevant to humans, did not provide comprehensive evidence to eliminate the possibility of other modes of action. However, noting that the hepatocellular carcinoma findings only occurred at doses above the MTD, hepatocellular

adenomas were only observed below the MTD in male mice, and there was a lack of pre-neoplastic lesions and negative genotoxicity results, on a broader weight of evidence consideration it is unlikely that amisulbrom poses a significant carcinogenic risk.

No effect on fertility was observed in the F_0 generation in a 2–generation reproductive study in rats. However, prolonged or irregular oestrous cycles, impaired fertility and ovarian atrophy were evident in F_1 females. Fertility in F_1 males was unaffected by treatment. Mechanistic data (including an anti-oestrogenic uterotrophic assay, an anti-aromatase assay and reproductive hormone level analysis) submitted by the applicant provided evidence that impaired fertility in F_1 females was likely secondary to reduced food intake and impaired body weight gain associated with poor palatability of amisulbrom, rather than a direct amisulbrom-related effect. Therefore amisulbrom is not considered to be a reproductive toxicant.

There was no evidence of embryofoetal toxicity in developmental studies in rats and rabbits. Amisulbrom is not considered to be a developmental toxicant.

Acute and repeat-dose neurotoxicity studies conducted with amisulbrom were unremarkable.

Based on the findings of the acute toxicological studies evaluated, the product Amicus Blue Fungicide has low acute oral, dermal and inhalational toxicity. It was not a skin irritant in rabbits or a skin sensitiser in guinea pigs (Maximisation method), but slight eye irritation was seen in rabbits.

3.2 Evaluation of toxicology

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

Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available.

Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur.

Chemical class

Amisulbrom is a sulfonamide fungicide which acts by inhibiting mitochondrial complex III activity through binding to the Qi centre and impairing respiration.

Toxicokinetics and metabolism

In toxicokinetics studies, GI absorption, assessed in bile duct-cannulated rats, accounted for 49–50% or 5% of the administered dose at 10 mg/kg bw and 1000 mg/kg bw, respectively. A high proportion of the total dose (39.5–40.8%) (0–48 hr) was found in bile after 10 mg/kg bw administration.

There was a similar pattern of excretion, distribution and metabolism in single and repeat-dose studies. The highest concentrations of radioactivity were found in the liver and kidney (identified as target organs in toxicity studies). Only a small proportion of the dose was retained in tissues at 120 hrs, indicating a low potential for accumulation.

Unchanged amisulbrom in faeces accounted for 40.5–52.4% (10 mg/kg bw) or 83.2–89.3% (1000 mg/kg bw) of the administered dose. Based on the metabolic profile, the major route of metabolism for amisulbrom in rats appears to involve the initial cleavage of the sulphonylamino side chain to form IT-4 and its subsequent hydroxylation to IT-5, followed by further degradation or conjugation of these primary metabolites.

Most of the radioactivity (>90%) was eliminated in faeces and urine within 72 hrs, and there were no differences in the pattern of excretion between sexes. During observations after dosing for 120 hrs, mean urinary excretion was lower (11.5–13%) than faecal excretion (82.5–84% of dose).

Percutaneous absorption

Both *in vitro* (human and rat) and *in vivo* (human) dermal absorption studies were evaluated. Utilising the triple-pack approach, the estimated human dermal absorption factor (DAF) for a 200 g/L SC formulation of amisulbrom and a 0.067 g/L aqueous dilution were 0.62% and 11.66%, respectively.

Acute toxicity

Amisulbrom had low acute oral (LD_{50} >5000 mg/kg bw), dermal (LD_{50} >5000 mg/kg bw) and inhalational (LC_{50} >2850 mg/m^3) toxicity in rats. Amisulbrom was not a skin irritant in rabbits or a skin sensitiser in guinea pigs (maximisation test). Amisulbrom was considered to be a slight but persistent eye irritant in rabbits, noting the extended observation of low-level conjunctival effects in a single animal up to 22 days after treatment.

Amicus Blue Fungicide had low acute oral, dermal and inhalational toxicity. It was not a skin irritant in rabbits or a skin sensitiser in guinea pigs (maximisation method), but slight eye irritation was seen in rabbits.

Systemic toxicity

Repeat dose studies with amisulbrom have been conducted in rats, mice and dogs. Observations common to all species include test substance related and dose dependent reductions in food consumption, lower body weight (and decreased body weight gain), increases in liver organ weight, changes in clinical chemistry parameters (Alkaline phosphatase, Alanine aminotransferase, Gamma-glutamyl transpeptidase, triglycerides), and increased incidence and/or severity of histopathological changes (hepatocellular hypertrophy) in the liver. The liver as a main target organ is consistent with the findings in toxicokinetics studies, where high radiolabel levels were identified in the liver. The most sensitive species in repeat-dose

toxicity studies was the rat, with the lowest NOEL in this species being 11.1/14.3 mg/kg bw/day (M/F; 200 ppm), established in the 2-year chronic/carcinogenicity study.

In addition to the liver, the kidney was another target organ identified. Similar to the liver changes, a dose-dependent and time-related increase in kidney weight and incidence of histopathological changes (cortical tubular pigment, increased cortical tubular basophilia and perivascular lymphoid aggregations) were detected in repeat dose studies.

Genotoxicity and Carcinogenicity

Amisulbrom was not genotoxic in several *in vitro* and *in vivo* studies.

In the 2–year combined chronic and carcinogenic study in rats, neoplastic changes, including a higher incidence of liver hepatocellular adenoma and carcinoma, were seen at ≥ 10000 ppm (496/697 mg/kg bw/d M/F): these were considered to be above the maximum tolerated dose (MTD). The increased incidence of forestomach tumours in female rats were not considered relevant to humans and caused by local irritation of the stomach mucosa.

In mice an increased incidence in hepatocellular adenoma was observed in males which exhibited dose response. These neoplastic changes were noted at levels below the MTD of 8000 ppm (1035 mg/kg bw/d).

Mechanistic studies submitted suggesting a carcinogenicity mode of action for amisulbrom similar to phenobarbital, a mechanism which is generally not considered relevant to humans, did not provide comprehensive evidence to eliminate the possibility of other modes of action. However, noting that the hepatocellular carcinoma findings only occurred at doses above the MTD, hepatocellular adenomas were only observed below the MTD in male mice, and there was a lack of pre-neoplastic lesions and negative genotoxicity results, on a broader weight of evidence consideration it is unlikely that amisulbrom poses a significant carcinogenic risk.

Reproductive and Development Toxicity

No effect on fertility was observed in the F_0 generation in a 2–generation reproductive study in rats. However, prolonged or irregular oestrous cycles, impaired fertility and ovarian atrophy were evident in F_1 females. Fertility in F_1 males was unaffected by treatment. Mechanistic data (including an anti-oestrogenic uterotrophic assay, an anti-aromatase assay and reproductive hormone level analysis) submitted by the applicant provided evidence that impaired fertility in F_1 females was likely secondary to reduced food intake and impaired body weight gain associated with poor palatability of amisulbrom, rather than a direct amisulbrom-related effect. Therefore amisulbrom is not considered to be a reproductive toxicant.

There was no evidence of embryofoetal toxicity in developmental studies in rats and rabbits. Amisulbrom is not considered to be a developmental toxicant.

Neurotoxicity

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

Toxicity of metabolites

The metabolite, IT-4 was moderately acutely toxic by the oral route in rats (LD_{50} >50 mg/kg bw but <300 mg/kg bw) but was not genotoxic in a bacterial mutation assay or a mouse micronucleus test.

3.3 Public health standards

Poisons scheduling

On 17 March 2016, the Delegate of the Secretary of the Department of Health published a final scheduling decision to create a new Schedule 5 entry for amisulbrom in the Standard for the Uniform Scheduling of Medicines and Poisons, with an implementation date of 1 June 2016.

ADI

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

The toxicological database for amisulbrom included several long-term oral and carcinogenicity studies in the mouse and rat, as well as a 12–month study in beagle dogs, and was considered comprehensive. Rodents were the most sensitive species to amisulbrom, with the liver (increased weights in both species; midzonal hepatocyte vacuolation, altered hepatobiliary enzymes and bile duct hyperplasia in rats; increased incidence of hepatocellular adenoma in male mice) and kidneys (increased weights, increased incidence and severity of cortical tubular pigment in rats; increased incidence of perivascular aggregations in female mice) identified as target organs for toxicity. A slight increase in cortical hypertrophy was also seen in the adrenal glands of mice following long-term treatment with amisulbrom.

The most sensitive NOEL is 11.1 mg/kg bw/d for male rats in the chronic/carcinogenicity study and 11.6 mg/kg bw/d for male mice in the carcinogenicity study. A 100–fold safety factor, consisting of a factor of 10 for each intraspecies and interspecies variation, is considered appropriate. No sensitive subpopulation groups were identified during the course of this evaluation; therefore no additional safety factor is required at this time. On this basis, the ADI for amisulbrom is established at 0.11 mg/kg bw/d.

ARfD

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

An ARfD was not established for amisulbrom, as it is of low acute oral, dermal and inhalational toxicity, and did not demonstrate evidence of a genotoxic, neurotoxic or reproductive/developmental toxicity potential from the available data.

3.4 Conclusion

After consideration of the toxicology of amisulbrom and the proposed uses of the product, the APVMA is satisfied that the approval of the active constituent amisulbrom and use of the product Amicus Blue Fungicide would not be an undue health hazard to humans and will satisfy the safety criteria stipulated in Section 5A of the Agvet Code Act (1994), when used in accordance with the label directions.

4 RESIDUES ASSESSMENT

4.1 Introduction

Amicus Blue Fungicide contains the new active constituent amisulbrom (32 g/L) and the approved active constituent copper (180 g/L Copper (Cu) present as tribasic copper sulphate). The product is proposed for use on brassica vegetables and grapes. The use of copper is registered on various fruit and vegetable crops at rates similar or higher than that proposed. Thus, residue aspects of copper are not discussed in this public release summary (PRS).

For brassicas, it is proposed that up to three foliar applications be made at the rate of 64 g amisulbrom/ha, 7–10 days apart. A harvest withholding period (WHP) of 'Not Required When Used as Directed' is proposed.

For grapes, it is proposed to apply up to 4 foliar applications per season at a spray concentration of 8 g amisulbrom/100 L, 7–10 days apart. A harvest WHP of 28 days is proposed. For grapes grown for export wine production the following statement is proposed: DO NOT apply after E-L 31 (early bunch closure) on grapes grown for export wine production.

As part of the residue assessment for amisulbrom, plant and animal metabolism studies, rotational studies, supervised residue trials and trade aspects were considered.

Metabolism

Plants

For grapes, three foliar applications of [indole-^{14}C] amisulbrom or [triazole-^{14}C] amisulbrom at ~100 g ac/ha each were made at 34, 24 and 14 days before harvest. Amisulbrom was the major radioactive residue accounting for 84.3% TRR (0.24 ppm) and 83.4% TRR (0.45 ppm) in the grapes and 58.4% TRR (3.5 ppm) and 52.1% TRR (4.8 ppm) in the foliage treated with [indole-^{14}C] amisulbrom or [triazole-^{14}C] amisulbrom, respectively, at harvest. The maximum level of the individual metabolites in the grape was ≤ 1.9% TRR (≤ 0.01 ppm).

For potatoes, four foliar applications of [indole – ^{14}C] amisulbrom or [triazole – ^{14}C] amisulbrom were made at the rate of 100g ac/ha per application at 42, 35, 28, 21 and 14 days before harvest. Amisulbrom was the major radioactive residue accounting for 74.8% TRR (2.33 ppm) and 77.9% TRR (4.70 ppm) in the foliage treated with [indole-^{14}C] amisulbrom and [triazole-^{14}C] amisulbrom, respectively, at harvest. The levels of the individual metabolites were ≤ 3.4% TRR (≤ 0.20 ppm). The total radioactive residues at 14 DALA (harvest) were 0.006 and 0.022 ppm in tubers treated with [indole-^{14}C] amisulbrom or [triazole-^{14}C] amisulbrom, respectively.

For tomatoes, three foliar applications of [indole-^{14}C] amisulbrom or [triazole-^{14}C] amisulbrom were made at the field application rate of 120 g ac/ha each at 21, 14 and 7 days before harvest. Amisulbrom was the major radioactive residue accounting for 91.3% TRR (0.22 ppm) and 91.9% TRR (0.16 ppm) in the tomatoes and 90.1% TRR (5.02 ppm) and 86.3% TRR (5.1 ppm) in the foliage treated with [indole-^{14}C] amisulbrom and [triazole-^{14}C] amisulbrom, respectively, at harvest. The maximum level of the individual metabolites in the tomato RAC was ≤ 1.1% TRR (≤ 0.002 ppm).

Animals

For lactating goats, the excretion, distribution and metabolism of amisulbrom in goats have been studied after five consecutive daily oral doses of either [indole-^{14}C] amisulbrom or [triazole-^{14}C] amisulbrom at a nominal rate of 10 ppm in the diet.

Amisulbrom residues were not found in any goat tissues or in milk. The major metabolite in liver and kidney was IT-4-N-glucuronide accounting for 17.7–17.9% TRR (0.05–0.07 ppm) and 48.2-51.4% TRR (0.13–0.18 ppm) respectively.

For laying hens, the excretion, distribution and metabolism of amisulbrom have been studied in groups of ten laying hens after fourteen daily consecutive oral doses at a nominal 10 mg/kg in the diet. Amisulbrom was labelled in both the indole and triazole rings. Amisulbrom residues ranged from 0.001–0.013 mg/kg in edible hen commodities. The major metabolite was IT-4 detected in liver, egg and fat extracts (both radiolabels) and accounted for 9.2–28.0 % TRR (0.002–0.037 mg/kg).

4.2 Analytical methods

For amisulbrom, samples were extracted using acetonitrile/water and after filtration and clean-up, residues were measured by HPLC—MS/MS. The LOQ was 0.01 mg/kg for each analyte and the recoveries in plant matrices were found to be acceptable (70–120 %, <20 % RSD).

4.3 Stability of the pesticide in stored analytical samples

In the storage stability study provided, amisulbrom was shown to be stable for a period of 12 months (≤ – 18°C) in grapes, potatoes and tomatoes and recoveries were within acceptable limits.

4.4 Residue definition

Based on the available metabolism studies (plants and animals) and analytical method, it is recommended that the residue definition in plant and animal commodities be amisulbrom (parent only) for monitoring and risk assessment.

4.5 Residue trials

Brassicas: The residues of amisulbrom (scaled) in brassicas (Brussels sprouts, broccoli, cabbage and cauliflower) following 3–4 foliar applications at 1x the maximum proposed rate, immediately after the final application were in rank order <LOD, 0.03, 0.07, 0.07, 0.08, 0.08, 0.08, 0.11, 0.11, 0.12, 0.22, 0.22, 0.31, 0.32 and 1.03 mg/kg (STMR = 0.11 mg/kg). An MRL of 2 mg/kg is considered appropriate for Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead brassicas (VB 0040) for the proposed use pattern in conjunction with a harvest WHP of 'Not Required When Used as Directed'.

Grapes: At the proposed harvest WHP of 28 days, residues of amisulbrom in grapes following 4 foliar applications made 9–11 days apart at rates ranging from ~0.7–1x the proposed application rate were in rank order 0.03, 0.03, 0.03, 0.05, 0.05, 0.06, 0.08, 0.08, 0.09, 0.09, 0.10, 0.11, 0.11, 0.12, 0.13, 0.13, 0.24 and 0.25 mg/kg. An MRL of 0.5 mg/kg is considered appropriate for grapes (FB 0269) for the proposed use pattern in conjunction with a harvest WHP of 28 days.

Following application according to the proposed use for wine grapes (2 applications made 7 days apart, growth stages ranging from E-L 19-31 (at or prior to early bunch closure)), residues of amisulbrom in grapes at commercial harvest were <LOD (0.008 mg/kg, n=4) and <LOQ (0.01 mg/kg). Following 4 applications residues of amisulbrom were <LOD (0.008 mg/kg), 0.01, 0.01, 0.02, 0.03, 0.04, 0.05, 0.14 and 0.21 mg/kg.

Treated grapes were processed to various end products including juice, raisins, wine and pomace. Based on the median processing factor of 2.4 to raisins, the HR-P is estimated to be 0.6 mg/kg. A Table 1 MRL of 1 mg/kg for DF 0269 Dried grapes (sultanas, currants, raisins) is recommended. Residues in wine were <LOQ following the proposed use.

The median processing factor to grape pomace (dry) was 7 and the estimated residues (HR-P) in dried pomace is 1.75 mg/kg. It is recommended that an MRL for AB 0269 Grape pomace, dry be established at 3 mg/kg.

4.6 Animal commodity MRLs

Residues of metabolites or the parent amisulbrom above the limit of quantification (0.01 mg/kg) are not expected in edible animal (cattle and poultry) commodities following the proposed use. Thus, permanent MRLs of *0.01 mg/kg for cattle (edible offal, meat and milks) and poultry (edible offal, meat and eggs) commodities are considered appropriate.

4.7 Estimated dietary intake

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

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived primarily from the 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 (ARfD) has not been established in Australia for amisulbrom.

4.8 Bioaccumulation potential

The partition coefficient (Log Pow) for amisulbrom is 4.4 (pH 6.4 and 40 °C) (99.8 % pure) which suggests it is fat soluble. Amisulbrom residues in fat tissue were below the LOQ where metabolism studies analysed in goat or hen.

4.9 Spray drift

Aerial application is not proposed for the use of Amicus Blue Fungicide and the following Restraint is included on the label: ‘DO NOT apply by aircraft’.

Based on the proposed use, residues of amisulbrom above the LOQ (0.01 mg/kg) are not expected in animal commodities, therefore a spray drift assessment is not considered necessary.

4.10 Residues in rotational crops

For rotational crops, wheat, lettuce and carrot were tested. A mixture of [indole-^{14}C] amisulbrom and [triazole-^{14}C] amisulbrom was applied to the soil surface at 600 g ac/ha. After ageing the soil for 30, 120 and 365 days, wheat, lettuce and carrot seeds were sown. Samples taken from 30 and 120 days were analysed for residues. Amisulbrom was not detected in any crop matrices and no metabolites were present at levels of >0.01 ppm.

4.11 Recommendations

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

Table 1

COMPOUND		FOOD	MRL (mg/kg)
ADD:			
Amisulbrom			
VB	0040	Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead brassicas	2
DF	0269	Dried grapes (=Currants, Raisins and Sultanas)	1
MO	0105	Edible offal (Mammalian)	*0.01
PE	0112	Eggs	*0.01
FB	0269	Grapes	0.5
MM	0095	Meat [mammalian]	*0.01
ML	0106	Milks	*0.01
PO	0111	Poultry, Edible offal of	*0.01
PM	0110	Poultry meat	*0.01

Table 3

COMPOUND	RESIDUE
ADD:	
Amisulbrom	Amisulbrom

Table 4

COMPOUND		ANIMAL FEED COMMODITY	MRL (mg/kg)
ADD:			
Amisulbrom			
AB	0269	Grape pomace (dry)	3

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

Brassicas: Not required when used as directed.

Grapes: Do not harvest for 28 days after application.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Grapes (including dried grapes) and wine are considered to be major export commodities[2], as are commodities of animal origin, such as meat, offal and dairy products, which may be derived from livestock fed feeds produced from food commodities treated with amisulbrom.

Residues in these commodities resulting from the use of Amicus Blue Fungicide may have the potential to unduly prejudice trade.

5.2 Destination of exports

Australian exports of wine were forecast to be worth $2068 million during 2015–2016[3] financial year. The major export markets are Hong Kong, China, New Zealand, Canada, United Kingdom and the United States.

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

5.3 Proposed use pattern

Amicus Blue Fungicide (180 g/L Copper (Cu) present as tribasic copper sulphate and 32 g/L Amisulbrom)

CROP	DISEASE	RATE	CRITICAL COMMENTS
Brassica vegetables	White Blister (Albugo candida) Downy mildew (Hyaloperonospora brassicae)	2.0 L/ha (64 g amisulbrom /ha and 360 g tri basic copper sulphate/ha)	Apply in a protectant spray program. Ensure thorough coverage of the crop, spray volume should be increased as the crop canopy expands DO NOT apply more than three applications per crop. Consecutive spray applications should be made at 7 to 10 day intervals. Avoid application to brassica crops when frosts are possible as crop damage may result.

[2] APVMA Regulatory Guidelines—Data Guidelines: Agricultural - Overseas trade (Part 5B)

[3] (Agricultural commodities, ABARES September Quarter 2015)

CROP	DISEASE	RATE	CRITICAL COMMENTS
Grapevines	Downy mildew (Plasmopara viticola)	Dilute spraying 250 mL/100 L (8 g amisulbrom /100 L and 45g tri basic copper sulphate/100 L Concentrate spraying Refer to the Application section	Apply as a protectant spray to grapevines commencing after shoots are 10 cm long. DO NOT apply more than two consecutive applications and do not apply more than four applications per season. If consecutive applications are made they should be 7 to 10 days apart and followed by two applications with an alternative mode of action before resuming Amicus Blue applications. DO NOT apply after E-L 31 (early bunch closure) on grapes grown for export wine production.

Harvest Withholding Periods:

Brassicas: NOT REQUIRED WHEN USED AS DIRECTED

Grapevines: DO NOT HARVEST FOR 28 DAYS AFTER APPLICATION

5.4 Overseas registration and approved label instructions

Amisulbrom is registered in Europe, Japan, Korea, Taiwan and Vietnam on various commodities including brassica and grapes. In the USA, amisulbrom has import tolerances established for tomatoes and grapes.

5.5 Comparison of Australian MRLs with Codex and International MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods. Amisulbrom has not been considered by Codex. The following relevant international CXLs have been established for amisulbrom:

Current and proposed Australian and overseas MRLs/tolerances for amisulbrom

COUNTRY/STATUS	RESIDUE DEFINITION	COMMODITY	TOLERANCE, mg/kg
Australia (proposed)	Amisulbrom	Grapes	0.5
		Dried grapes	1
EU [4]	Amisulbrom[5] (plants)	Grapes (Table and wine)	0.5
Japan [6]	Amisulbrom (plants)	Grapes	5
USA [7]	Amisulbrom (plants)	Grape	0.4
		Grape, raisin	1.0

5.6 Potential risk to trade

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

For grapes and dried grapes (raisins), MRLs of 0.5 mg/kg and 1 mg/kg respectively are proposed.

While Codex has not established MRLs for amisulbrom, the EU and Japan have established MRLs of 0.5 mg/kg and 5 mg/kg respectively for grapes. The US has established grape and raisin MRLs at 0.4 mg/kg and 1.0 mg/kg respectively. The proposed MRL of 0.5 mg/kg for grapes is in line with the EU MRL of 0.5 mg/kg, only slightly higher than the US MRL of 0.4 mg/kg and significantly lower than that established by Japan.

Based on a processing study, residues of amisulbrom in wine are not expected to be above the LOQ (0.01 mg/kg) following the proposed use, thus potential risk to trade in wine is considered to be low. In edible

[4] http://ec.europa.eu/sanco_pesticides/public/?event=homepage&CFID=954987&CFTOKEN=20996516&jsessionid=0904385fe316baf7c7521a536e71452824f4TR

[5] EU has established provisional residue definition for animal commodities based on metabolites and established MRLs at LOQ for parent for animal commodities.

[6] www.m5.ws001.squarestart.ne.jp/foundation/search.html

[7] www.ecfr.gov/cgi-bin/text-idx?c=ecfr&sid=1c8c528c83ba8b0f0d1cb05cb5060737&tpl=/ecfrbrowse/Title40/40cfr180_main_02.tpl

animal commodities, as residues of amisulbrom are not expected to be above the LOQ following the proposed use, thus potential risk to trade in animal commodities is considered to be low.

Comment is invited on the potential for the proposed use of Amicus Blue Fungicide to unduly prejudice Australian export trade.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Summary

Amicus Blue Fungicide will be used by farmers and their employees, as well as contract sprayers. Users may be exposed to the product when opening containers, mixing/loading/application, cleaning up spills, maintaining equipment and entering treated crops. The main routes of exposure to the product/spray will be dermal and inhalation, and ocular exposure is also possible.

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

Based on the risk assessment, first aid instructions, safety directions and re-entry statements have been recommended for the product label.

6.2 Health hazards

Amisulbrom (CAS: 348635-87-0) is not listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2016). With the available toxicology information, amisulbrom is not classified as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

Tribasic copper sulphate (CAS 1332-14-5) is not listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2016).

Based on the product toxicology information and concentrations of the active constituents amisulbrom and copper (Cu) present as tribasic copper sulphate, Amicus Blue Fungicide is not classified as a hazardous substance in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

6.3 Formulation, packaging, transport, storage and retailing

Amicus Blue Fungicide will be marketed in 5–1000 L rigid HDPE bottles.

6.4 Use pattern

Amicus Blue Fungicide is proposed to be used for the control of downy mildew in grapes and white blister and downy mildew in brassicas. The applicant indicated that Amicus Blue Fungicide will likely be applied 4–8 days per year to grapevines and 3–6 days per year to brassicas.

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

- Do not apply by aircraft.
- Do not apply more than three applications per crop. Consecutive spray applications should be made at 7 to 10 day intervals (brassicas).

- Do not apply more than two consecutive applications and do not apply more than four applications per season. If consecutive applications are made they should be 7 to 10 days apart and followed by two applications with an alternative mode of action before resuming Amicus Blue applications (grapevines).

Amicus Blue Fungicide is likely to be applied to grapevines and brassicas using airblast and vehicle-mounted spray tanks and by equipment worn on the back of the user. Amicus Blue Fungicide may also be applied to brassicas via ground boom equipment.

The draft product label specifies a harvesting withholding period (WHP) of 28 days for grapevines, and states that a WHP is not required when used as intended on brassicas.

6.5 Exposure during use

Users may be exposed to the product when opening containers, using the product, cleaning up spills, maintaining equipment and entering treated areas. The main routes of potential exposure to the product will be dermal, inhalational and ocular.

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

The toxic endpoint of concern and identified NOEL for risk assessment is derived from a repeat dose study in animals, and in this instance a margin of exposure (MOE) of 100 or above is considered acceptable. The MOE takes into account both potential inter-species extrapolation and intra-species variability. Based on the risk assessment, risks associated with exposure to the product when preparing and using the product were at an acceptable level when a single layer of personal protective equipment (PPE) is used by workers, except when applied by spraying equipment carried on the back of the user, where a second layer of clothing with gloves is required.

6.6 Exposure during re-entry

The OCS notes that the re-entry risks associated with conducting activities in areas where the product has been applied are expected to be by the dermal route, and that exposure to amisulbrom is expected to occur at specific periods of time after application to a crop. As the Margins of Exposure (MOEs) after very high exposure activities in brassicas are acceptable (MOE >100) on day zero after application, the OCS considers that the risks associated with re-entry activities is low after the spray has dried, and the following standard re-entry statement is recommended:

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

As the MOEs after very high exposure activities in vineyards are not acceptable (MOE <100) until five days after application, the OCS considers that the risks associated with re-entry activities is low after five days, and the following re-entry statement is recommended:

Do not enter treated areas in vineyards for 5 days to perform very high exposure activities such as tying/training/leaf pulling unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

6.7 Recommendations for safe use

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

6.8 Conclusion

The APVMA is satisfied that the proposed use of Amicus Blue Fungicide, containing 32 g/L amisulbrom and 160 g/L copper (Cu) present as tri basic copper sulphate, would not be an undue hazard to the safety of people exposed to it during its handling and use, and will satisfy the safety criteria stipulated in Section 5A of the Agvet Code Act (1994), when used in accordance with the label directions.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

The environmental assessment considered the proposed use of Amicus Blue Fungicide as detailed on the proposed draft label.

Environmental fate and effects studies were provided in support of the application. These were sufficient to undertake the environmental risk assessment as outlined below.

7.2 Environmental fate

Hydrolysis

For both [indole-^{14}C] and [triazole–^{14}C] forms of amisulbrom, half-life values (DT_{50}) at 25 ^{o}C for the hydrolysis of amisulbrom were similar at pH 4 (DT_{50} = 78.5 days) and pH 7 (DT50 = 76.5 days), but was lower at pH 9 (DT_{50} = 5.0 days). Therefore, the rate of hydrolysis of amisulbrom was shown to be dependent on pH and is considered to be fairly hydrolysing at pH 9 but slightly hydrolysing at pH 4 and 7. The major metabolite identified was IT-4 (17.8%) over the incubation period of 30 days.

Photolysis

Aqueous photolysis

Amisulbrom was degraded in irradiated sterile pH 4 buffer solutions at 25ºC under simulated sunlight with continuous irradiation. The photolysis half-life of amisulbrom in sterile buffer was 6.1 h under continuous irradiation. Amisulbrom degrades to several major metabolites identified as T-1, T-7, I-2, I-8 and I-9. The DT_{50} of the irradiated test systems over 48 h was calculated to be 106 h of natural summer sunlight at latitude 40 ºN. In sterile natural water (pH 7.6), one major degradation product identified was I-2 derived from [indole-^{14}C] amisulbrom and several major metabolites T-1, T-3 and T-4 derived from [triazole-5-^{14}C] amisulbrom were identified. In sterile natural water, the photolytic half-life of amisulbrom was up to 4.4 h under continuous irradiation. The natural light equivalent at 35 ^{o}N is DT_{50} = 0.8 d (Spring).

Soil photolysis

Amisulbrom degraded at approximately similar rates following exposure to irradiation or incubation in the dark with DT_{50} values of 12.5 and 10.9 days respectively. The DT_{50} in the dark was shorter than in the irradiated soil therefore it is expected that photolysis will not be a significant factor in the degradation of amisulbrom in the field.

IT-4 was the major degradate detected in irradiated or dark control soils (maximum 35.9% of applied radioactivity, AR) and was considered to result from aerobic soil metabolism rather than photolytic degradation. All other metabolites were present at low levels with IT-2, IT-5, IT-14 (dark control only) and two unidentified degradates present at ≤0.9% AR.

Biodegradation

Aerobic soil metabolism

The aerobic route of degradation of amisulbrom using [indole-^{14}C] and [triazole-^{14}C] labelled amisulbrom was studied in a sandy loam soil at 20 ºC. The results indicate that little mineralisation of amisulbrom was evident, with ≤0.9% of AR recovered in the trapping solutions. The quantity of radioactivity extracted from the soil decreased over the period of the study as the quantity of soil bound residues increased up to 26.4% of AR at 120 days. The soil bound residues were shown to be associated with humic acid and humin fractions. Levels of amisulbrom declined to approximately 46% over the 120 day duration of the study. The major metabolite, IT-4, increased to a maximum of 21% after ~ 90 days. All other metabolites, IT-2, IT-5, IT-9, IT-11, IT-14 and one unidentified metabolite, were present at lower levels (≤2.8% of AR).

The rate of degradation of amisulbrom was conducted at various pH levels using triazole-labelled amisulbrom in clay loam, silty clay loam and an acidic sandy loam (all 3 soils at 20 ºC) and in sandy loam at 10 ºC. The results indicated that amisulbrom was degraded under aerobic conditions and that the rate of degradation is dependent on soil pH with DT50s in the range of 22 to 348 days. The rate of degradation was fastest in the soil with the highest pH and slowest with the lowest pH. IT-4 was shown to degrade relatively rapidly in the clay loam (20 ºC), silty clay loam (20 ºC) and sandy loam (10 ºC) with DT_{50}s found in the range of 36–49 days.

The rate of degradation of IT-4 was conducted in three soils: clay, sandy loam and acidic sandy loam at 20ºC over an incubation period of 120 days. It was found that IT-4 degraded fastest (DT50 = 68.5 days) in the clay soil and slowest (DT_{50} = 114 days) in the sandy loam (acidic) soil.

Anaerobic soil metabolism

The fate of degradation of amisulbrom in an anaerobic soil/water system was conducted in a UK sandy loam soil at 20 ºC. The results indicate that amisulbrom was partitioned from aqueous phase relatively quickly with a DT_{50} = 7 days. Once in the anaerobic soil phase amisulbrom degrades with a DT_{50} = 45 days [DT_{50} (total system) = 27 d]. Two major metabolites IT-4 and IT-15 were identified over the incubation period of 120 days. IT-4 has a DT_{50} = 7 days in the aqueous phase and 47 days in the total soil/water system. IT-15 degradation was shown to have a DT_{50} = 16 days in the total water/soil system.

Aerobic aqueous metabolism

The fate of amisulbrom was studied in two disparate natural water/sediment systems incubated at 20ºC under aerobic conditions: clay loam sediment (water: pH 5.9 and sediment: pH 6.7) and clay sediment (water: pH 6.5 and sediment: pH 8.0). In both test systems, amisulbrom partitioned from the water into the sediment phase (max 29%) and underwent further degradation in the sediment phase.

The dissipation of amisulbrom from the aqueous phase ranged from 6–7 days for both systems. The DT_{50}s were determined to be ranged from 40–80 days in the total system for both systems.

Field dissipation

Field dissipation studies for amisulbrom were conducted on bare soil in France, Germany, Spain and UK. They were used to determine the rate of degradation of amisulbrom and its metabolite IT-4. Amisulbrom was applied at the nominal rates of 600 g ac/ha over a period of up to 269 days following application where soil samples were taken to a depth of 30 cm. Amisulbrom and its metabolite were confined to the upper soil segment (0–10 cm).

Single first order kinetics was the best fit model for the degradation data. Amisulbrom residues were observed to degrade in the field dissipation trials with DT_{50} values of 2.8 to 12.6 days, indicating that amisulbrom is readily degradable in soil. An estimated DT_{50} of 60 days was determined for IT-4 using a sandy loam soil.

Mobility

The Freundlich adsorption coefficients (Kf_{ads}) for amisulbrom ranged from 147 to 378. Freundlich adsorption coefficients adjusted for soil organic carbon content ($Kfoc_{ads}$) ranged from 8156 to 44231 in sandy loam, loam, loamy sand, clay loam and clay. Amisulbrom was therefore classified as immobile in all soils. This lack of mobility was confirmed in the field dissipation studies where amisulbrom was confined to upper soil segment (0–10 cm).

The Freundlich adsorption coefficients (Kf_{ads}) for IT-4 ranged from 25.5 to 107.8 with Freundlich adsorption coefficients ($Kfoc_{ads}$) adjusted for soil organic carbon content, in the range 821 to 11402. IT-4 is classed as having low mobility in the clay loam and sandy loam soils, with slight mobility in the loam soil and is immobile in the loamy sand soil.

Bioaccumulation

Amisulbrom has a log P_{ow} of 4.4 (pH 7) suggesting that it has a potential for bioconcentration. A bluegill sunfish bioconcentration study showed a worst case BCF value of 176 for the non-edible tissue of fish. No radioactivity was detected in the extractable fraction of the edible tissues. The BCF values are <500 and therefore amisulbrom does not have a potential to bioconcentrate. Amisulbrom was readily metabolised by the fish. During the depuration phase its concentration in fish declined rapidly so that within 3 days it was found to be below 1% of the concentration at the end of the uptake phase.

IT-4 was identified as the major metabolite in the study. However, given that it is structurally similar to the parent compound and has a log K_{ow} (3.3) lower than the parent, it is unlikely to be more bioaccumulative than its parent compound.

7.3 Environmental effects

Birds

Amisulbrom is practically non-toxic to both bobwhite quail and mallard duck via the acute oral exposure route. Five days dietary toxicity studies in which bobwhite quail and mallard ducks were exposed to

amisulbrom via their diet identified no amisulbrom treatment-related deaths. Amisulbrom was practically non-toxic with 5 d LC_{50} >5000 mg ac/kg feed for both bobwhite quail and mallard duck. A 22 weeks feeding/reproduction study with the Japanese quail and mallard duck identified no dose responsive adverse effects on either adults or reproductive success. The 22 weeks NOEC was determined to be 400 mg ac/kg feed for both mallard duck and bobwhite quail.

Mammals

Based on mammalian toxicity studies presented amisulbrom is practically non-toxic to small mammals from acute oral and contact exposure and moderately toxic from chronic exposure.

Aquatic organisms

Effects on fish

In acute fish toxicity studies conducted in carp, rainbow trout, three-spined stickleback, fathead minnow, zebra fish and bluegill sunfish were exposed to amisulbrom for 96 h under flow-through conditions. The 96 h LC_{50} values ranged from 22.9–170 µg ac/L, indicating amisulbrom is highly toxic to very highly toxic to fish.

The acute toxicity of metabolites (IT-4 and IT-15) to carp was investigated in semi-static exposure studies. The 96 h LC_{50} values were determined to be 0.232 and 11 mg/L for IT-4 and IT-15, respectively, indicating the metabolites are slightly to highly toxic to fish. The formulation is moderately toxic to fish with 96 h LC_{50} = 2.3 mg product/L (47 µg ac/L).

In a 28 d juvenile growth test, fathead minnow were exposed to amisulbrom and IT-4 under flow-through conditions. The NOEC was 37 µg ac/L for amisulbrom indicating it is chronically moderately toxic to fish. The NOEC was 160 µg ac/L for IT-4, indicating it is chronically slightly toxic to fish.

Effects on aquatic invertebrates

The acute toxicity study of amisulbrom on *Daphnia magna* (48 h EC_{50} = 36.8 µg ac/L) indicates that amisulbrom is very highly toxic to daphnids. The metabolites IT-4 and IT-15 are considered to be slightly to moderately toxic to daphnids. A chronic study on *Daphnia magna* (21 d NOEC = 19.7 µg ac/L) indicates that amisulbrom is moderately toxic to daphnids.

Amisulbrom is at worst, highly toxic to *Chironomous riparius* (EC_{50}>111.4 µg ac/L) and chronically slightly toxic (NOEC =111.4 µg ac/L). Spiked sediment studies indicated that the metabolites IT-4 and IT-15, are not very toxic to chironomids.

Effects on algae and aquatic plants

Based on a 96 h ErC_{50} = 57 µg ac/L, amisulbrom is considered to be very highly toxic to green algae (*Raphidocelis subcapitata*).The toxicities of metabolites IT-4 and IT-15 and the formulated product were determined to be moderately to slightly toxic to green algae based on the 72 h ErC_{50}s ranging from 1.59 to

24.9 mg test item/L. Amisulbrom is also, at worst, very highly toxic to duckweed with 7 d EC_{50} >0.0819 mg ac/L.

Terrestrial organisms

Effects on bees

Amisulbrom is, at worst, very slightly toxic to honey bees with both acute oral and contact toxicity (48 h LD_{50} >100 µg/bee).

Effects on non-target terrestrial arthropods

Terrestrial arthropods, both parasitic wasps and predatory mite, were insensitive to amisulbrom based on LR50 >1000 g ac/ha.

Effects on earthworms

Amisulbrom and its metabolite IT-4 are, at worst, very slightly toxic to earthworms with 14 d LC_{50} >1000 mg/kg soil. The chronic 56 d NOEC = 93.7 mg ac/kg soil and 16 mg IT-4/kg soil indicate no adverse effects to earthworms at these soil concentrations.

Soil micro-organisms

No significant effects were observed on soil micro-organisms at the soil concentrations up to of 1.6—mg ac/kg soil and 0.45 mg ac/kg soil for amisulbrom and IT-4, respectively, for an exposure period of 28 days.

Effects on terrestrial plants

No herbicidal activity was observed at the proposed application rate.

7.4 Risk assessment

In considering the submitted data, particular attention was given to the potential risk to organisms in aquatic and terrestrial environment. The environmental risk assessment has determined that the risk to birds, mammals, terrestrial plants, honeybees, earthworms and non-target arthropods was found to be acceptable and no adverse effects on soil nitrogen and carbon metabolism is expected from the proposed uses. The risks to aquatic and sediment dwelling organisms from spray drift, runoff or groundwater were found to be acceptable based on the proposed use pattern subject to label protection statements and a downwind buffer zone of 10m for protection of the aquatic environment.

7.5 Conclusion

The APVMA is satisfied that the proposed use of Amicus Blue Fungicide, when used according to the product label instructions, would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment and will satisfy the safety criteria stipulated in Section 5A of the Agvet Code Act (1994), when used in accordance with the label directions.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed product use pattern

Amicus Blue Fungicide (containing 32 g/L amisulbrom and 180 g/L copper (Cu) present as tribasic copper sulphate) is intended for the control of downy mildew in grapevines and white blister and downy mildew in brassica vegetable crops.

The proposed use of Amicus Blue Fungicide on brassica vegetable crops involves up to three foliar applications per crop at the rate of 2 L/ha (64 g amisulbrom/ha) with 7 to 10 day re-treatment intervals for consecutive applications.

Amicus Blue Fungicide will be used in grapevines at a dilute spraying rate of 250 mL/100 L (8 g amisulbrom/100 L). The product is applied as a protectant spray to grapevines commencing after shoots are 10 cm long. Amicus Blue Fungicide is intended to be applied to grapevines with not more than two consecutive applications, and a maximum of four applications per season with consecutive applications to be made 7–10 days apart. Amicus Blue Fungicide is not to be applied after E-L 31 (early bunch closure) on grapes grown for export wine production.

8.2 Assessment of study/trial data

Formulations tested are detailed below:

- NC-224 or NUL-1955—amisulbrom
- TBB—Copper (Cu) present as tribasic copper sulphate
- NC-224 or NUL-1955 plus TBB—tank mix equivalent to Amicus Blue Fungicide
- NUL-2584—Amicus Blue Fungicide.

The submission provided data from over 5 seasons in grapevines and 4 seasons in brassicas to assess the efficacy and crop safety in these crops. All trials contained an untreated control (UTC) as a reference for disease levels.

All field studies were undertaken under commercial conditions of use. All of the studies in both grapevines and brassicas were conducted using randomised complete block trial design with adequate plot sizes and replication. Assessments for crop safety and disease control were undertaken.

Statistical analysis was undertaken using an analysis of variance (ANOVA) on either untransformed or transformed data where appropriate.

The initial trial results demonstrated bioequivalence between Amicus Blue Fungicide (NUL-2584) and the tank mix NC-224 and TBB for the control of downy mildew in grapevines and white blister in broccoli. In the final series of trials the commercial formulation Amicus Blue Fungicide (NUL-2584) was applied at a range of rates.

Grapevines:

Nineteen small plot replicated trials were conducted in commercial vineyards in Australia in a range of grape cultivars targeting downy mildew (*Plasmopara viticola*). The trials confirmed amisulbrom activity against downy mildew with NC-224/NUL-1955 reducing downy mildew incidence and severity on grapevines leaves and bunches. The addition of TBB to amisulbrom improved efficacy at some of the trial sites.

Amicus Blue Fungicide provided a significant reduction in the severity of downy mildew infection on leaves and on bunches compared to the untreated control. Data presented in the series of trials is supportive of the registration of Amicus Blue Fungicide at a dilute application rate of 250 mL/100 L for control of downy mildew in grapevines and demonstrates that it performed as well as or in some cases better than industry standards.

Brassicas:

A series of trials were conducted to support the proposed white blister label claim in brassicas, comprising 9 field trials and 1 glass house trial. Broccoli was used as the brassica test crop due to its susceptibility to white blister (*Albugo candida*). Additional trials were conducted on cauliflower which confirmed efficacy against white blister.

Amicus Blue Fungicide was applied at the rates of 1, 2, 3 & 4 L/ha for the control of white blister. The data showed that 1 L/ha was statistically less efficacious than 2 L/ha and increasing the rate to 3 L/ha did not provide any additional statistically significant levels of disease control. The data shows that the application of Amicus Blue Fungicide provided very good control of white blister and downy mildew in brassica trials at the proposed label rate of 2 L/ha.

Two of the Tasmanian efficacy trials evaluated Amicus Blue Fungicide and/or NC-224/NUL-1955 for control of downy mildew (*Hyaloperonospora brassicae*) in broccoli. Both NC-224/NUL-1955 and Amicus Blue Fungicide treatments significantly reduced downy mildew infection on broccoli heads. The results from these trials support the use of Amicus Blue Fungicide for the control of downy mildew in brassicas.

Crop safety

Crop safety data was determined from a series of trials in grapevines with 4 to 7 applications at label rates (1X) and in some trials, double (2X) label rates. Data demonstrated that Amicus Blue Fungicide was safe to grapevines.

Crop safety data was obtained from 24 trials in a range of brassica crops at 1 to 5 L/ha with 3 to 7 applications occurring from 6 leaf to harvest. Crop safety was determined at label rates (1X) and double (2X) label rates. The data showed no adverse effects on marketable produce in any of the trials.

Resistance management

Amisulbrom is an oomycete-specific fungicide which acts by inhibiting mitochondrial respiration.
The Fungicide Resistance Action Committee (FRAC) has categorised amisulbrom as a Quinine Insider Inhibitor (QII) based upon this mode of action. Amisulbrom has been designated as a Group 21 FUNGICIDE

for resistance management purposes. Copper (Cu) present as tribasic copper sulphate is designated as a Group M1 fungicide and acts as a multi-site activity fungicide.

For resistance management purposes, Amicus Blue Fungicide is a Group 21 and Group M1 fungicide.

8.3 Conclusion

The claims on the proposed label that Amicus Blue Fungicide provides acceptable control of downy mildew in grapevines and white blister and downy mildew in brassica vegetable crops when used as directed is supported by the results from the Australian trials.

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

The application by Nufarm Australia Limited for the registration of Amicus Blue Fungicide in grapevines and brassica vegetables is supported on efficacy and crop safety grounds when used in accordance with label instructions.

9 LABELLING REQUIREMENTS

POISON

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

Amicus Blue®

Fungicide

ACTIVE CONSTITUENTS: 180g/L COPPER (Cu) present as TRIBASIC COPPER SULPHATE
32g/L AMISULBROM

GROUP	21 M1	FUNGICIDE

For control of downy mildew in grapes and white blister and downy mildew in brassicas as per the Directions for Use Table.

IMPORTANT: READ THE ATTACHED LEAFLET BEFORE USING THIS PRODUCT

® Amicus Blue is a registered trademark of Nufarm Australia Limited

Nufarm Australia Limited
ACN 004 377 780
103-105 Pipe Road
Laverton North Victoria 3026
Tel: (03) 9282 1000
Fax: (03) 9282 1001

Contents: 5 - 1000 Litres

APVMA Approval No.: 70161/62643

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, break, crush, or puncture and bury empty containers in a local authority landfill. If no landfill is available, bury the containers below 500mm 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 should NOT be burnt.
Refillable containers
Store in the closed, original container in a cool, well ventilated area. DO NOT store for prolonged periods in direct sunlight. Empty contents fully into application equipment. Close all valves and return to point of supply for refill or storage.

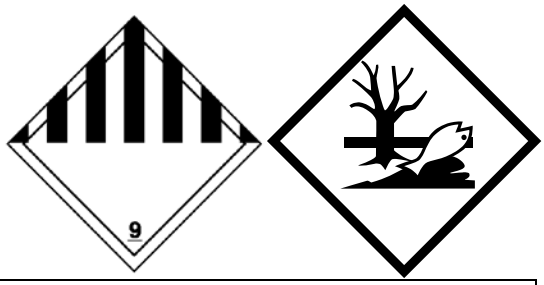
SAFETY DIRECTIONS
May irritate the eyes. Avoid contact with eyes and skin. When preparing product for use and using the prepared product, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing). If applying by spraying equipment carried on the back of the user, wear cotton overalls, over normal clothing, buttoned to the neck and wrist and elbow-length chemical resistant gloves. If product on skin, immediately wash area with soap and water. Wash hands after use. After each day's use wash gloves and contaminated clothing.

FIRST AID
If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126. If skin contact occurs, remove contaminated clothing and wash skin thoroughly. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

MATERIAL SAFETY DATA SHEET
For further information refer to the Material Safety Data Sheet (MSDS), which can be obtained from your supplier or from the Nufarm website – www.nufarm.com.au

In case of emergency: Phone 1800 033 498 Ask for shift supervisor. Toll free 24 hours.

CONDITIONS OF SALE
"Any provisions or rights under the Competition and Consumer Act 2010 or relevant state legislation which cannot be excluded by those statutes or by law are not intended to be excluded by these conditions of sale. Subject to the foregoing, all warranties, conditions, rights and remedies, expressed or implied under common law, statute or otherwise, in relation to the sale, supply, use or application of this product, are excluded. Nufarm Australia Limited and/or its affiliates ("Nufarm") shall not accept any liability whatsoever (including consequential loss), or howsoever arising (including negligence) for any damage, injury or death connected with the sale, supply, use or application of this product except for liability which cannot be excluded by statute."
BN / DOM / Barcode / DrumMuster



ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (CONTAINS COPPER PRESENT AS TRIBASIC COPPER SULPHATE)
UN No: 3082
PACKING GROUP: III
HAZCHEM: 2Z
IN AN EMERGENCY DIAL: 000 POLICE OR FIRE BRIGADE
IN AN EMERGENCY, SPECIALIST ADVICE NUFARM AUSTRALIA LIMITED 1800 033 498

POISON

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

Amicus Blue®

Fungicide

ACTIVE CONSTITUENTS: 180g/L COPPER (Cu) present as TRIBASIC COPPER SULPHATE
32g/L AMISULBROM

GROUP	21 M1	FUNGICIDE

For control of downy mildew in grapes and white blister and downy mildew in brassicas as per the Directions for Use Table.

IMPORTANT: READ THE ATTACHED LEAFLET BEFORE USING THIS PRODUCT

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nufarm.com.au

APVMA Approval No. 70161/62643

DIRECTIONS FOR USE

Restraints

DO NOT apply by aircraft.
DO NOT apply during the hottest part of the day when temperatures exceed 35°C.
DO NOT apply when slow drying conditions prevail.
DO NOT apply to copper-shy crops or cultivars.
DO NOT apply if it is likely to rain before the spray is dry.
DO NOT apply to wet crops.
DO NOT use in spray solutions less than pH 6.5.

SPRAY DRIFT RESTRAINTS

DO NOT apply if there are aquatic and wetland areas including aquacultural ponds within 10 meters downwind from the application area.
DO NOT apply during surface temperature inversion conditions at the application site.
DO NOT direct the spray above vines during airblast applications. Turn off outward pointing nozzles at row ends and outer rows during airblast applications.

CROP	DISEASE	RATE	CRITICAL COMMENTS
Brassica vegetable crops Broccoli Cauliflower Cabbage Brussels sprouts	White Blister (*Albugo candida*) Downy mildew (*Hyaloperonospora brassicae*)	2 L/ha	Apply in a protectant spray program. Ensure thorough coverage of the crop, spray volume should be increased as the crop canopy expands DO NOT apply more than three applications per crop. Consecutive spray applications should be made at 7 to 10 day intervals. Avoid application to brassica crops when frosts are possible as crop damage may result.
Grapevines	Downy mildew *(Plasmopara viticola)*	Dilute spraying 250mL/100L Concentrate spraying Refer to the Application section	Apply as a protectant spray to grapevines commencing after shoots are 10 cm long. DO NOT apply more than two consecutive applications and do not apply more than four applications per season. If consecutive applications are made they should be 7 to 10 days apart and followed by two applications with an alternative mode of action before resuming Amicus Blue applications. DO NOT apply after E-L 31 (early bunch closure) on grapes grown for export wine production.

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

WITHHOLDING PERIODS

BRASSICAS: NOT REQUIRED WHEN USED AS DIRECTED.
GRAPEVINES: DO NOT HARVEST FOR 28 DAYS AFTER APPLICATION.

GENERAL INSTRUCTIONS

MIXING/APPLICATION

Partly fill the spray tank with water and add the required amount of product while stirring. If required, add compatible products and agitate thoroughly. Continue agitation as filling of the tank is completed. Agitate again before spraying commences. If tank mixing with other water dispersible granule (WG) or wettable powder (WP) formulations, ensure they are mixed in well before adding emulsifiable concentrate (EC) or suspension concentrate (SC) products. WP formulations should be pre-mixed separately prior to adding to the spray tank.

WETTING AGENTS

A wetting agent is not required when used as directed but may be used if required for a tank mix partner.

COMPATIBILITY
Amicus Blue is generally compatible with other agricultural pesticides but should be tested locally on a small scale prior to widespread use.

GRAPEVINES
Apply sufficient volume to wet all leaf surfaces up to the point of run-off. Apply using MEDIUM spray droplets. Air-blast sprayers are recommended for application to vines with very dense foliage.

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

CONCENTRATE SPRAYING
Use a sprayer designed and set up for concentrate spraying (i.e. a sprayer which applies water volumes less than those required to reach the point of run-off) and matched to the crop being sprayed. Set up and operate the sprayer to achieve even coverage throughout the crop canopy using your chosen water volume. Determine an appropriate dilute spray volume (See Dilute Spraying above) for the crop canopy. This is needed to calculate the concentrate mixing rate. The mixing rate for concentrate can then be calculated in the following way:
EXAMPLE ONLY

1. Dilute spray volume as determined above: For example 1500L/ha
2. Your chosen concentrate spray volume: For example 500L/ha
3. The concentration factor in this example is: 3X (i.e. 1500L÷500L=3)
4. If the dilute label rate is 10mL/100L, then the concentrate rate becomes 3 x 10, i.e. 30mL/100Lof concentrate spray.

The chosen spray volume, amount of product per 100L 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.

BRASSICA VEGETABLE CROPS
Thorough coverage of the plants is essential for maximum effectiveness. To achieve thorough coverage:
1. Spray volumes need to be increased as the plants grow.
2. The configuration of the sprayer may need to be altered as the plants grow and change shape. The coverage provided by the sprayer should be checked prior to each application and adjusted if necessary. This should only be done with water plus any required wetting agents.

APPLICATION BY GROUND-RIG
Apply as a MEDIUM spray in a minimum of 250 litres of water per hectare using a low mounted boom adjusted to the nozzle manufacturer's specifications. May be applied with hydraulic nozzles or fan-assisted rotary atomizers. Avoid application in very windy conditions or when the temperature and humidity cause rapid drying.

FUNGICIDE RESISTANCE WARNING

GROUP	21	M1	FUNGICIDE

For fungicide resistance management Amicus Blue Fungicide is a Group 21 and M1 fungicide. Some naturally-occurring individual fungi resistant to Amicus Blue Fungicide and other Group 21 and M1 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. The resistant fungi will not be controlled by Amicus Blue Fungicide and other Group 21 and M1 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, Nufarm Australia Limited accepts no liability for any losses that may result from the failure of Amicus Blue Fungicide to control resistant fungi.

Re-entry Statement
Do not enter treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.
Do not enter treated areas in vineyards for 5 days to perform very high exposure activities such as tying/training/leaf pulling unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

PROTECTION OF CROPS, NATIVE AND OTHER NONTARGET PLANTS
DO NOT apply under weather conditions, or from spraying equipment, that may cause spray to drift onto nearby susceptible plants/crops, cropping lands or pastures.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product or used containers.

STORAGE AND DISPOSAL
Store in the closed, original container in a cool, well-ventilated area. DO NOT store for prolonged periods in direct sunlight. Triple or preferably pressure rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on-site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and bury empty containers in a local

authority landfill. If no landfill is available, bury the containers below 500 mm 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 should NOT be burnt.

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Nufarm Australia Limited ACN 004 377 780
103-105 Pipe Road, Laverton North Victoria 3026
Tel: (03) 9282 1000, Fax: (03) 9282 1001

ABBREVIATIONS

λ_{max}	Maximum wavelength
AC/ac	active constituent
ACCS	Advisory Committee on Chemicals Scheduling
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ANOVA	Analysis of variance
APVMA	Australian Pesticides and Veterinary Medicines Authority
AR	Applied radioactivity
ARfD	Acute Reference Dose
BCF	Bioconcentration factor
bw	bodyweight
^{14}C	radiocarbon
^{o}C	Degrees Centigrade
Croplife	Croplife Australia
cm	centimetre
cps	centiPoise
Cu	Copper
CXL	Codex Maximum Residue Limits
d	day
DAF	Dermal absorption factor
DALA	Days After Last Application
DAT	Days After Treatment
DofE	Department of Environment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
EC_{50}	concentration at which 50% of the test population are immobilised

E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
ESI	Export Slaughter Interval
EU	European Union
EUP	End Use Product
Fo	original parent generation
F_1	First generation
FRAC	Fungicides Resistance Action Committee
g	gram
GAP	Good Agricultural Practice
GI	Gastro Intestinal
GLP	Good Laboratory Practice
h	hour
ha	hectare
Hb	Haemoglobin
Hct	Heamatocrit
Hg	Haemoglobin
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HR	highest residue
HR-P	Calculated highest residue—processed commodity
HSIS	Hazardous Substance Information System
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
JMPR	Joint FAO/WHO Meetings on Pesticide Residues
Kf_{ads}	Freundlich adsorption coefficients
Kfoc $_{ads}$	Freundlich adsorption coefficients adjusted for soil organic carbon content
kg	kilogram
K_{oc}	Organic carbon 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
logKow	Octanol-Water Partition Coefficient
LOQ	Limit of Quantitation – level at which residues can be quantified
LR_{50}	Application rate that kills 50% of the test population of organisms
m	metre
mg	milligram
mL	millilitre
MoA	Mode of Action
MOE	Margin of Exposure
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
MS/MS	Mass Spectrometry/Mass Spectrometry
MTD	Maximum tolerated dose
ND	Not Detectable
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake

NESTI	National Estimated Short Term Intake
ng	Nanogram
nm	nanometres
NOEC/NOEL	No Observable Effect Concentration/Level
NOHSC	National Occupational Health and Safety Commission
NOER	No Observable Effect Rate
OC	Organic Carbon
OCS	Office of Chemical Safety (Department of Health and Ageing)
OM	Organic Matter
Pa	Pascals
ppb	parts per billion
PHED	Pesticide Handler Exposure Database
PPE	Personal Protective Equipment
ppm	parts per million
PRS	Public release summary
QII	Quinine Insider Inhibitor
Q-value	Quotient-value
RAC	Confined Rotational Crop
RBC	Red Blood Cell Count
RSD	Relative Standard Deviation
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
STMR	Supervised Trials Median Residue
SWA	Safe Work Australia
T1/2	Elimination Half-Life

TBB	Tribasic copper sulphate
TGAC	Technical grade active constituent
Tmax	Time to achieve maximum concentration
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
TRR	Total Radioactive Residue
UTC	Untreated control
µg	microgram
UV/VIS	Ultra Violet/Visible Light
W	Body weight (grams live weight)
WG	Water Dispersible Granule
WHP	Withholding Period
WHO	World Health Organisation

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.
Bioaccumulation	When an organism absorbs a toxic substance at a greater rate than the rate of loss
Bio-concentration Factor (BCF)	The concentration of a contaminant in an organism compared to surrounding ambient environment
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	repels water
IT-4	Amisulbrom metabolite
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
NC-224	Manufacturers code for amisulbrom
Mean	In statistics, mean refers to the mean or average that is used to derive the central tendency of the data in question. It is determined by adding all the data points in a population and then dividing the total number by the number of points.
Metabolism	The chemical processes that maintain living organisms
Mutagenicity	The ability to produce permanent changes in genetic material
pH	A figure expressing the acidity or alkalinity of a solution on a logarithmic scale on which 7 is neutral, lower values are more acid and higher values more alkaline. The pH is equal –log10 [H+] where [H+] is the hydrogen ion concentration in moles per litre
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body

Toxicology	The study of the nature and effects of poisons

REFERENCES

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