

**Public Release Summary
on**

Evaluation of the new active

AZOXYSTROBIN

in the product

AMISTAR WG FUNGICIDE

**National Registration Authority
for Agricultural and Veterinary Chemicals**

September 1999

**Canberra
Australia**

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Colin Byrnes
National Registration Authority for Agricultural and Veterinary Chemicals
PO Box E 240
KINGSTON ACT 2604

Ph: (02) 6272 4850
Fax: (02) 6272 3218

FOREWORD

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is an independent statutory authority with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the NRA works in close cooperation with advisory agencies, including the Department of Health and Family Services (Chemicals and Non-prescription Drug Branch), Environment Australia (Risk Assessment and Policy Section), the National Occupational Health and Safety Commission) and State departments of agriculture and environment.

The NRA 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 all products containing new active ingredients and for all proposed extensions of use for existing products.

The information and technical data required by the NRA 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 NRA's publications *Ag Manual: The Requirements Manual for Agricultural Chemicals* and *Ag Requirements Series*.

This Public Release Summary is intended as a brief overview of the assessment that has been completed by the NRA and 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.

More detailed technical assessment reports on all aspects of the evaluation of this chemical can be obtained by completing the order form in the back of this publication and submitting with payment to the NRA. Alternatively, the reports can be viewed at the NRA Library, Ground floor, 22 Brisbane Avenue, Barton, ACT.

The NRA welcomes comment on the usefulness of this publication and suggestions for further improvement. Comments should be submitted to the Executive Manager—Registration, National Registration Authority for Agricultural and Veterinary Chemicals, PO Box E240, Kingston ACT 2604.

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LIST OF ABBREVIATIONS AND ACRONYMS

ac	active constituent
ADI	acceptable daily intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
d	Day
EC₅₀	concentration at which 50% of the test population are immobilised
EUP	end use product
F₀	original parent generation
h	Hour
HPLC	high pressure liquid chromatography <i>or</i> high performance liquid chromatography
id	Intradermal
ip	Intraperitoneal
im	Intramuscular
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
L	Litre
LC₅₀	concentration that kills 50% of the test population of organisms
LD₅₀	dosage of chemical that kills 50% of the test population of organisms
mg	Milligram
mL	Millilitre
MRL	maximum residue limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
ng	Nanogram
NHMRC	National Health and Medical Research Council
NOHSC	National Occupational Health and Safety Commission
NOEC/NOEL	no observable effect concentration/level
po	Oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
s	Second
sc	Subcutaneous
SC	suspension concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
T-Value	a value used to determine the First Aid Instructions for chemical products that contain two or more poisons
TGAC	technical grade active constituent
WG	water dispersible granule
WHP	withholding period

SUMMARY

Azoxystrobin is a new broad spectrum fungicide which possesses a novel biochemical mode of action. Its fungicidal activity results from the inhibition of mitochondrial respiration in fungi. It is a synthetic analogue of the naturally occurring fungal metabolites strobilurins and oudemansins.

Crop Care Australasia Pty Ltd have applied for registration of the product Amistar WG Fungicide (Amistar), a water dispersible granule formulation containing 500g/kg azoxystrobin. The product will initially be marketed for the control of powdery mildew, downy mildew and Botrytis bunch rot in grapes (table, wine and dried) in all States.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Amistar WG Fungicide. Responses to this public release summary will be taken into account by the NRA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

Written comments are invited and should be submitted by **5 October 1999** to the NRA at the address shown in the Introduction.

Public health aspects

Azoxystrobin has low acute oral and dermal toxicity. It has moderate acute inhalational toxicity, and causes slight skin and eye irritation, but no skin sensitisation. The product, Amistar WG Fungicide, has low acute oral, dermal and inhalational toxicity, and causes slight skin irritation, moderate eye irritation, but no skin sensitisation.

Following repeated oral administration of azoxystrobin, liver toxicity was evident in rats and mice, characterised by increased liver enzymes, organ weights and increased numbers of abnormal liver cells, inflammation and necrosis at moderate to high doses. Distension and inflammation of the bile ducts were seen in rats, and increased cholesterol levels were noted in rats and dogs at similar doses. Gastrointestinal signs including diarrhoea, vomiting and fluid faeces were consistently seen in studies in mice, rats, rabbits and dogs. There was no evidence of carcinogenic potential following long-term dietary exposure to azoxystrobin in mice and rats and azoxystrobin is not likely to cause genetic damage. No effects of azoxystrobin treatment were noted on reproduction or fertility in rats, and azoxystrobin was not teratogenic in rats and rabbits. There was no evidence of neurotoxicity in rats given single high doses.

Based on an assessment of the toxicology, it was considered that there should be no adverse effects on human health from the proposed use of azoxystrobin as a component of Amistar WG Fungicide in accordance with the label directions.

Residues in food and trade aspects

Residue data were presented for trials conducted in Australia on grapes, dried grapes and wine. Overseas trial data were also provided for the same commodities. This enabled the following MRLs to be established: 2.0 mg/kg grapes, 5.0 mg/kg dried grapes. Residues in grape pomace, a potential animal feed commodity were also addressed. Grape pomace residue data, along with animal transfer studies have permitted the recommendation of animal commodity MRLs, 0.01 mg/kg in edible offal (mammalian), *0.01 mg/kg in meat(mammalian) and 0.005 mg/kg in milks; and 15 mg/kg in dry grape pomace as an animal feed commodity.

Trade aspects of exports of fresh fruit, dried fruit, wine and produce from animals which may have been fed treated material have been evaluated. Australian MRLs are generally in line with overseas levels for fresh fruit. There are no overseas tolerances for dried grapes but the NRA believes it is likely that other countries will establish a similar level. For wine, some overseas countries have set an MRL of 0.5 mg/kg while others rely on the grape MRL to cover processed commodities such as wine. It is considered that if application is not made to grapes being grown to produce wine for export after 80% capfall, no detectible residues will be present, and trade difficulties should not be encountered.

Occupational health and safety aspects

NOHSC has conducted a risk assessment on Amistar WG Fungicide and concluded that the product can be safely used by workers when handled in accordance with the control measures indicated in this assessment.

Azoxystrobin is not currently listed in the NOHSC List of Designated Hazardous Substances. NOHSC has determined azoxystrobin to be a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances. This classification is based at least on its acute inhalation toxicity. Amistar WG Fungicide was classified by Crop Care Australasia Pty. Ltd. as a hazardous substance based on its eye irritancy effects, in accordance with NOHSC criteria.

Amistar WG Fungicide will be imported fully formulated in bulk containers and re-packed in Australia. It is packed in 1 and 2 kg poly bottles (High Density Polyethylene with a neck opening of 63-72 mm), 3 kg plastic bottle with measuring cap and 2, 5 and 10 kg packs which consist of a cardboard box with a plastic liner. A maximum of 4 operators would be involved in the re-packing process. Transport, storage and retail workers will handle the packaged product, and could only become contaminated in the event of a packaging breach.

Amistar WG Fungicide has low acute oral, dermal, and inhalational toxicity. It is a slight skin irritant and moderate eye irritant, but has no skin sensitising properties.

The product is to be applied as a foliar fungicide to grapes as part of a season long spray program from early flowering to pre-harvest in rotation with products from different chemical groups. The recommended application rate is 37.5 or 50 g product/100 L with a maximum of 3 applications per season and no more than 3

consecutive sprays at 10-16 day intervals. Application will be by either boom spray equipment fitted with hydraulic nozzles or trailer mounted air blast sprayers in spray volumes of 500-1500 L/ha.

No worker exposure data were available for azoxystrobin or Amistar WG Fungicide. The occupational health and safety risk assessment was based on estimates obtained from an exposure model.

Instructions and Safety Directions are provided on the product label to minimise exposure to the product. Mixer/loaders need to elbow length PVC gloves and face shield or goggles when opening the container and preparing the spray. Additional information is available on the product material safety data sheet.

Environmental aspects

In regard to environmental assessments, azoxystrobin is expected to have widespread use in viticulture around Australia. Following application, any azoxystrobin not captured by the crop is expected to mainly become associated with the soil compartment, either directly beneath the crop or in smaller concentrations at off-target locations receiving spray drift deposits. Further movement may occur in the sorbed state if soil particles are transported in erosive runoff events. Persistence under field conditions is low, with photodegradation an important route for primary degradation. Further metabolism in soils means that degradation products also do not persist. Azoxystrobin has low mobility under field conditions.

Laboratory testing indicates that azoxystrobin is practically nontoxic to birds. Toxicity to fish is moderate to high, and to invertebrates and algae moderate to very high. Slight to very slight toxicity was apparent in laboratory testing with bees and earthworms, but the effects were not ecologically significant. Similarly, some effects were seen in testing with predators and parasites, but effects were not expected to harm populations. Toxicity to terrestrial plants is low.

Assessment indicates that there may be a slight hazard to sensitive aquatic invertebrates inhabiting shallow water if high rates of drift occur from applications at the upper end of the proposed range. Note that this assessment includes a number of conservative assumptions, and it is not expected that any small and isolated invertebrate impacts from use of azoxystrobin would be ecologically significant.

Efficacy and crop safety aspects

In regard to the efficacy of the product, the claims made in the submission are for the control of powdery mildew, downy mildew and Botrytis bunch rot using Amistar at the rate of 37.5 or 50g of product /100L water.

The results presented show that 6 to 7 applications of Amistar at 37.5 or 50 g/100L controls powdery mildew, downy mildew and Botrytis bunch rot to levels that are as good as or better than the standard fungicide programme.

In order to reduce the development of resistance, the Avcare Fungicide Resistance Action Committee strategies recommend avoidance of application of fungicides from only one activity group for long periods. It is therefore now proposed that a maximum of 3 applications of Amistar occur in any one season, with an alternative chemical from another activity group to be used if required. This program is considered likely to be effective in managing the diseases whilst reducing the onset of fungicide resistance.

In two experiments, slight interveinal chlorosis developed on leaves sprayed with high rates of Amistar. The phytotoxicity was not permanent, only developed early in the season and did not appear to adversely affect yield. Nevertheless, some caution as to the possibility of mild phytotoxicity should be mentioned on the label as concentrate sprays may be used in commercial situations.

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Amistar WG Fungicide, which contains the new active constituent azoxystrobin.

Responses to this public release summary will be considered prior to registration of the product. They will be taken into account by the NRA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

Written comments are invited and should be submitted by **5 October 1999**, addressed to:

Colin Byrnes
AgVet Chemicals Evaluation Section
National Registration Authority
PO Box E240
KINGSTON ACT 2604

Phone 02 6722 4850

Fax 02 6272 3218

Applicant:

Crop Care Australasia Pty Ltd

Product details:

Amistar WG Fungicide is a water dispersible granule formulation containing 500g/kg azoxystrobin. Azoxystrobin is a new broad spectrum fungicide which possesses a novel biochemical mode of action. Its fungicidal activity results from the inhibition of mitochondrial respiration in fungi. It is a synthetic analogue of the naturally occurring fungal metabolites strobilurins and oudemansins.

The active constituent is manufactured by Zeneca Agrochemicals in the United Kingdom, and the product will be formulated by that company, also in the UK.

The product is proposed to be registered for control of downy mildew, powdery mildew and Botrytis bunch rot in grapes in all States.

Wettable granule and suspension concentrate formulations of azoxystrobin are registered in 25 countries under a variety of tradenames. The first registration occurred in Germany in 1996 for use in cereal crops. The active is now registered for use in the USA and many parts of Europe and Latin America.

The predominant crops it is registered for use on are cereals, bananas, tomatoes, cucumbers and grapes. It is currently registered in 19 countries and Europe for use on

grapes (USA, South Africa, Europe, Austria, Bulgaria, Croatia, Czech Republic, France, Hungary, Italy, Romania, Serbia, Slovakia, Slovenia, Spain, Switzerland, Turkey, Japan, Taiwan and Thailand), and is currently being considered for registration in grapes in a further four countries (Canada, Australia, New Zealand and Germany).

CHEMISTRY AND MANUFACTURE

The product proposed for registration in Australia is a water dispersible granule formulation under the trade name Amistar WG Fungicide.

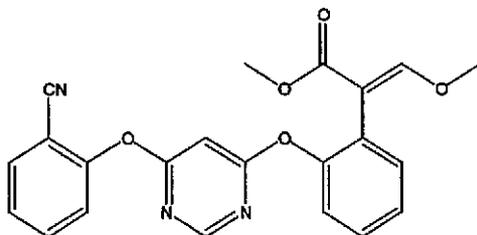
The formulation storage stability and the physical and chemical properties of the formulated product and active constituent have been evaluated by the NRA and are considered acceptable.

The source of Technical Grade Active Constituent to be used in the product has been approved by the NRA (Approval No 44444).

Active constituent

The active constituent azoxystrobin in Amistar has the following properties:

Common name (ISO):	Azoxystrobin
Chemical name:	Methyl (E)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
CAS Registry Number:	131860-33-8
Empirical formula:	C ₂₂ H ₁₇ N ₃ O ₅
Molecular weight:	403.40
Structural formula:	



Physical form:	powdery solid
Colour:	pale brown
Melting point:	114-116°C
Density:	1.34g/cm ³ at 20°C
Vapour pressure at 25°C:	1.1x10 ⁻¹³ kPa at 20°C
Water Solubility:	6.7 mg/L (pH 5.2), 6.7 mg/L (pH 7), 5.9 mg/L (pH 9.2)
Partition Coefficient:	logP = 2.5 (n-octanol/water)
Dissociation Constant:	No readily dissociable groups are present.

TGAC approval number: 44444

Manufacturer: Zeneca Agrochemicals, UK

Formulated product

Product Name: AMISTAR WG FUNGICIDE

Formulation type: Water dispersible granule

Level of active constituent: 500g/kg

Colour: Beige

Density: 0.54 to 0.58 g/cm³

Vapour pressure: 1.1×10^{-13} kPa at 20°C

TOXICOLOGICAL ASSESSMENT

The toxicological database for azoxystrobin, which consists primarily of toxicity tests conducted using animals, is extensive. In interpreting the data, it should be noted that toxicity tests generally use doses which are high compared to 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 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 at which no adverse health effects in humans would be expected.

Toxicokinetics and Metabolism

Azoxystrobin administered to rats is well absorbed from the gastrointestinal tract and rapidly eliminated primarily in the faeces with the balance in the urine. Azoxystrobin is extensively metabolised to a number of derivatives of the parent compound. There was no evidence to indicate accumulation of azoxystrobin in tissues (such as after repeated dosing with azoxystrobin).

Acute Studies

Azoxystrobin exhibits low acute oral toxicity in mice and rats ($LD_{50} > 5000$ mg/kg) and low dermal toxicity in rats ($LD_{50} > 2000$ mg/kg). Acute inhalation toxicity was moderate in rats with LC_{50} values of 962 mg/m³ in males and 698 mg/m³ in females. Both skin and eye irritation were slight in rabbits while skin sensitisation was not noted in guinea-pigs.

Amistar WG Fungicide (containing 500 g/kg azoxystrobin) had low oral ($LD_{50} > 5000$ mg/kg), dermal ($LD_{50} > 2000$ mg/kg) and inhalation ($LC_{50} > 4670$ mg/m³) toxicity in rats. Irritation potential was slight in rabbit skin and moderate in rabbit eye. Skin sensitisation was not observed in guinea-pigs.

Short-Term Studies

In rats administered azoxystrobin dermally at doses of 0, 200 or 1000 mg/kg on 21 days out of a 30 day period, there was no evidence for either systemic toxicity or dermal irritation at any dose.

Azoxystrobin was given in the diet of rats at doses of 0, 12, 58, 328 and 1004 mg/kg for males and 0, 11, 53, 308 and 846 mg/kg for females for 28 days. At the highest dose anaemia, increased serum enzymes indicative of liver damage, triglycerides and

cholesterol were observed. Other evidence for liver toxicity included increased organ weights in all male groups and, increased organ weight, increased numbers of liver cells, inflammation and necrosis in females at 328 and 1004 mg/kg.

In dogs given 100, 150 or 200 mg/kg/day azoxystrobin by capsule for 6 weeks, salivation and fluid faeces were observed at all doses. Body weight gain and increased liver weight were seen at 200 mg/kg, but there were no associated pathological changes.

Sub-Chronic Studies

In mice given azoxystrobin in the diet at doses of 0, 17, 188, 569 and 1280 mg/kg/day for males and 0, 21, 227, 675 and 1468 mg/kg/day for females for 13 weeks, food consumption and bodyweight gain were severely reduced from 188 mg/kg/day in males and 227 mg/kg/day in females, resulting in suspension of the treatment in week 3. Increased liver weight and liver damage was shown in females at 227 and 675 mg/kg/day. The NOEL for this study was 17 and 21 mg/kg/day in males and females respectively.

Rats given azoxystrobin in the diet at doses of 0, 20, 211 and 444 mg/kg/day in males and 0, 22, 223 and 449 mg/kg/day in females for 13 weeks, showed distended abdomen and had reduced food consumption and body weight gain at 211 and 444 mg/kg/day in males and 223 and 449 mg/kg/day in females. Evidence of liver damage included elevated serum liver enzymes and increased liver weight at the two higher doses, with proliferation and inflammation of bile ducts and increased numbers of liver cells at the highest dose. The NOEL for this study was 20 and 22 mg/kg/day in males and females respectively.

Dogs administered 0, 10, 50 or 250 mg/kg/day azoxystrobin in capsules for 13 weeks showed increased salivation, regurgitation of capsules, fluid faeces and depressed body weight gain at 50 and 250 mg/kg. There were also elevations in triglycerides, cholesterol and liver enzymes in serum at 250 mg/kg, and liver weight was increased at 50 and 250 mg/kg but with no pathological changes evident. The NOEL was 10 mg/kg/day.

Chronic Studies

In mice administered azoxystrobin in the diet for 104 weeks at doses of 0, 6, 38 and 272 mg/kg for males and 0, 9, 51 and 363 mg/kg for females, body weight gain was depressed at 272 and 363 mg/kg for males and females respectively, and liver weights were increased at the highest dose in both sexes. Azoxystrobin was not carcinogenic in mice. The NOEL was 37.5 mg/kg in males and 51 mg/kg in females.

Rats fed diets containing azoxystrobin for 104 weeks at doses of 0, 4, 18 and 117 mg/kg/day in males and 0, 4.5, 22 and 117 mg/kg in females showed increased mortality, abdominal distension, reduced food intake and body weight gain, and bright yellow urine at 117 mg/kg, resulting in a reduction of the dose to 82 mg/kg/day from week 53. Bile duct obstruction was found only in males at 117 mg/kg/day and resulted in distension and inflammation of the bile duct and increased numbers of

epithelial cells or ulceration of the liver. Azoxystrobin did not increase tumour incidences. The NOEL was 18 and 22 mg/kg/day in males and females respectively.

In dogs administered azoxystrobin orally in capsules daily for one year at doses of 0, 3, 25 or 200 mg/kg/day, fluid faeces was seen at 200 mg/kg especially in males and regurgitation/vomiting were seen in both males and females at the same dose. Increased serum triglycerides, cholesterol, liver enzymes and liver weight were suggestive of an effect on the liver, but no liver pathology was noted. The NOEL was 3 mg/kg/day.

Reproduction Study

In rats administered azoxystrobin in the diet for 2 generations at doses of 0 - 168 mg/kg for males and 0 - 180 mg/kg for females, except during the early post natal period when doses were 0-386 mg/kg, abdominal distension and an increase in bile duct inflammation was observed in some males in each generation at 168 mg/kg, with bile duct distension confirmed at *post mortem*. Body weights and food consumption were depressed at the highest dose in males and females and liver weights were increased in both sexes at the same dose. There were no changes on the reproductive system and fertility. During lactation, reduced body weight gain and liver weight increases were evident in both male and female pups at the highest dose. The NOEL was 32 mg/kg/day during the premating period.

Developmental Studies

In two developmental studies, mated female rabbits were administered azoxystrobin orally at doses of 0, 25, 40 and 150 mg/kg/day and 0, 50, 150 and 500 mg/kg/day respectively on days 8 - 20 of gestation (i.e. during the period of foetal organ development). There were no maternal deaths. Diarrhoea was evident at all treatment doses in both studies and staining of the genital area at all doses in the second study. Decreased bodyweight gains were observed at 40 and 150 mg/kg/day in the first study, whereas significant decreases in bodyweight were seen in animals treated at 500 mg/kg/day in the second study, and were reversible when treatment ended, and slight reductions in bodyweight gains were observed in rabbits at 50 and 150 mg/kg for a short period early in treatment. There were no effects on maternal pathology nor on foetal growth and development. The NOEL was 25 mg/kg/day.

Pregnant rats were administered oral doses of 0, 25, 100 or 300 mg/kg/day azoxystrobin through days 7 - 16 of gestation. The 300 mg/kg dose group was suspended due to a high rate of mortality, and significant incidence of diarrhoea, urinary incontinence and weight loss. At 100 mg/kg/day, bodyweight gains and food consumption were decreased, together with some diarrhoea, urinary incontinence and gastrointestinal and stomach damage. There were no effects on growth and development of the foetus at any dose. Azoxystrobin was not teratogenic in rats. The NOEL for maternal toxicity in the rat was 25 mg/kg/day.

Genotoxicity

Azoxystrobin was non-genotoxic in two *in vitro* bacterial mutagenicity studies (*S. typhimurium* and *E. coli*). It was positive in two mammalian cell systems *in vitro*

(mouse lymphoma mutation test and human lymphocyte chromosome aberration), but was negative in two *in vivo* studies (mouse micronucleus and rat hepatocyte DNA repair). On balance, these studies do not indicate that azoxystrobin is a mutagenic risk to humans.

Neurotoxicity

In acute and subchronic tests, azoxystrobin was found to be non-neurotoxic at doses up to 2000 mg/kg and 160 and 200 mg/kg/day in males and females respectively.

PUBLIC HEALTH STANDARDS

Poisons Scheduling

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

The NDPSC recommended that azoxystrobin be placed in Schedule 5 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). There are provisions for appropriate warning statements and first-aid directions on the product label.

NOEL/ADI

The most sensitive species tested was the dog with a NOEL of 10 mg/kg/day in a 3 month dog toxicity study. In order to calculate an Acceptable Daily Intake (ADI) for humans, a safety factor is applied to the NOEL in the most sensitive species. The magnitude of the safety factor is selected to account for uncertainties in extrapolation from animal data to humans, variation within the human population, the quality of the experimental data, and the nature of the potential hazards. Using a safety factor of 100, an ADI of 0.1 mg/kg bw/day was established for azoxystrobin.

METABOLISM AND TOXICOKINETICS ASSESSMENT

Plant metabolism

The metabolism of azoxystrobin in grapes, winter wheat and peanuts is very similar in terms of the degradative pathways which the parent follows. Cleavage of the phenylacrylate ring to give a hydroxypyrimidinyl cyanophenyl ether followed by further cleavage of the pyrimidinyl substituent to 2-hydroxy-cyanobenzene is the most significant metabolic pathway common to all three plant species. The next most significant pathways are photolytic isomerism to give the *cis*-isomer and of the parent, and hydrolysis of the methyl ester group of the parent to give the corresponding acid. The metabolic route which results in overall replacement of the acrylate moiety of the parent with a carboxylic acid group is also common to all three plant species. Peanuts differ to grapes and wheat grain in that the parent undergoes ready conversion to fatty acids and sugars in the nut. These routes of conversion were not observed in grapes or wheat.

Rotational crop metabolism studies revealed the presence of many conjugated metabolites which resulted from uptake of already partially metabolised parent which was present in the soil and further metabolism.

Animal metabolism

Animal metabolism in general indicated that azoxystrobin was rapidly eliminated in the excreta. The target tissues for the residual radioactivity were the liver and kidney, the kidney showing highest residues in rats and the liver doing so in goats. The parent compound was a principal component in the overall radioactive residue for rats and goats. In hens, radioactivity was also largely eliminated in the excreta. Liver was the main target tissue for residual radioactivity, however a large portion of the retained radioactivity was found in egg yolk where it was found as fatty acids. Extended feeding studies (up to 14 days in the rat and 7 days in goats) showed that the majority of administered radioactivity is eliminated within 96 hrs and that tissue residues, including those in kidney and liver, at that time are very low.

RESIDUES ASSESSMENT

Residues in food commodities

Residue data were presented for trials conducted in Australia on grapes, dried grapes and wine. Overseas trial data were also provided for the same commodities. Residues in grape pomace, a potential animal feed commodity were also addressed. Grape pomace residue data, along with animal transfer studies have permitted the recommendation of animal commodity MRLs.

Grapes

Data from 11 Australian trials were presented. From 4 to 11 applications of azoxystrobin were made at 0.75x, 1x and 2x the recommended rate (25 g a.i./100 L). Residues in grapes ranged from 0.64 – 0.95 mg/kg after the 0.75 x treatments, 0.11 – 2.2 mg/kg after the 1 x treatments, and 1.0 – 4.8 mg/kg after the 2 x treatments, at a sampling interval of 14 – 21 days. The residue of 2.2 mg/kg observed in a South Australian trial after treatment at the 1x rate is considered an anomalously high result, possibly due to application of a much higher spray-volume than other crops treated at the 1x rate. The proposed label use-pattern permits a maximum of 3 sprays at a minimum retreatment interval of 10 days. A withholding period of 14 days has been recommended. A MRL of 2 mg/kg is recommended for grapes, in accordance with the proposed use-pattern in Australia.

Dried grapes

A single Australian trial addressed azoxystrobin residues in dried grapes. Between 4 and 10 applications were made at the label rate. Dried grape residues ranged from 0.41 – 3.1 mg/kg at sampling intervals ranging from 1 hr to 47 days. The highest residue, 3.1 mg/kg, was observed 3 days after the 8th application. Drying grapes has the effect of concentrating the residues present so that the commodity produced contains residues much higher than the fresh fruit. The processing factors for drying calculated from this study range from 0.47 – 2.38 for seven samples taken between 1 hr and 47 DAT. The majority of the samples showed the processing factor to be reproducibly between 1.27 and 1.36.

Further processing data from overseas trials was made available. The general trend observed upon drying of fresh grapes was a concentration of residues. An MRL of 5 mg/kg has been recommended for dried grapes.

Wine

Seven Australian trials were conducted to analyse for azoxystrobin residues in wine from treated grapes. Between 5 and 11 applications were made at 0.75x, 1x and 2x the label rate. Residues in wine ranged from 0.09 to 1.4 mg/kg after the 1x treatment, and from 0.23 to 5.7 mg/kg after the 2x treatment. The sampling intervals for the treated grapes ranged from 14 to 43 days after the final application of azoxystrobin. A separate MRL has not been recommended for wine. The MRL of 2 mg/kg for grapes will adequately cover wine.

Wine data from overseas trials was also supplied. Most of this data indicates a significant decrease of fresh fruit residues upon processing to wine. This trend is not reflected in the Australian trials where residues in grapes are largely unaffected by wine-making.

Animal commodities

Animal transfer studies revealed that nil residues can be expected in meat and the meat (mammalian) MRL of *0.01 mg/kg proposed by the Applicant is supported. The same animal transfer study indicated higher residues in offal. Assuming a 100% intake of grape pomace in a cattle diet results in a MRL of 0.01 mg/kg for offal. Finite residues were detected in cow's milk up to 0.003 mg/kg for animals fed at 5.0 mg/kg azoxystrobin in the diet, the proposed MRL of 0.005 mg/kg for milk of cattle, goats and sheep is therefore recommended.

Animal transfer studies

Animal transfer studies were conducted in dairy cattle. Lactating cows were treated with doses of 0.18 to 9.1 mg/kg bw/day for up to thirty consecutive days. The animals were milked twice daily to give a single daily sample. At the end of the treatment period the cows were slaughtered and tissue samples collected for residue analysis. No detectable residues in meat were observed at all treatment rates. Maximum tissue residues were 0.05 mg/kg observed in the liver for the 2.7 mg/kg bw/day rate and 0.07 mg/kg in liver at the 9.1 mg/kg bw/day dose rate. Milk residues were generally low, the only anomaly in these results being that the maximum residue observed in milk from the 9.1 mg/kg bw/day dose group was higher (0.006 mg/kg) than that observed in milk from the 2.7 mg/kg bw/day dose group (0.004 mg/kg).

Skimmed milk and cream were generated from milk samples obtained on days 21 – 23. No detectable residues were observed in both commodities from the 0.18 and 9.1 mg/kg bw/day dose groups. Skimmed milk contained maximum residues of 0.001 and 0.003 mg/kg from the 2.7 and 9.1 mg/kg bw/day dose groups, respectively. Cream residues were higher, the maximum residues observed being 0.02 and 0.04 mg/kg from the 2.7 and 9.1 mg/kg bw/day dose groups, respectively.

The proposed MRL of 0.005 mg/kg in milk is supported provided that azoxystrobin does not exceed 5.0 mg/kg in the diet of the animal. The applicant argues that grape pomace will be the sole source of azoxystrobin in animal diets and that this is unlikely to be fed at a rate exceeding 25% of the total diet. The recommended maximum residue level in this commodity is 15 mg/kg, and so it is calculated that dietary intake should not exceed 3.75 mg/kg in the total diet.

Should grape pomace containing no more than 15 mg/kg of azoxystrobin constitute 100% of the beef cattle diet for a period up to 30 days, the maximum residues expected in liver and kidney are 0.01 and <0.01 mg/kg respectively. Analysis of offal residues in liver indicates that feeding at 15 mg/kg would lead to maximum residues of 0.01 mg/kg, and so feeding at this higher rate impacts on the proposed MRL for offal of *0.01 mg/kg. Since finite residues may be expected under drought feeding situations, the recommended offal MRL is 0.01 mg/kg.

MRL Standard

The following additions to the *MRL Standard* have been recommended:

Table 1

Compound	Food	MRL (mg/kg)
Azoxystrobin		
ADD:		
FB 0269	Grapes	2.0
DF 0269	Dried grapes	5.0
MO 0105	Edible Offal (mammalian)	0.01
MM 0095	Meat (mammalian)	*0.01
ML 0106	Milks	0.005

Table 3

Compound	Residue
ADD:	
Azoxystrobin	Azoxystrobin

Table 4

Compound	Food	MRL (mg/kg)
Azoxystrobin		
ADD:		
AB 0269	Grape pomace, dry	15.0

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Commodities exported

Grape commodities exported are fresh (table) grapes, dried grapes and wine. Of these three export commodities, wine is the most significant contributor to export earnings. Wine exports for the 1996/7 period totalled \$584M, and the industry projects that this will increase to \$1 billion over the next few years.

Over 1992-3 dried vine fruit exports totalled 53,000 tonne/\$95M. Sultanas accounted for the majority of these exports, approximately 60% of the total sultana crop being exported. Dried fruit production has decreased since that time as fruit has been diverted into wine production. Over the 1994 marketing year the dried vine fruit export figure dropped to 17,500 tonne.

Table grape exports have fluctuated between 10,000 and 15,000 per year throughout the 1990s.

Countries where exported

The major markets where Australian wine is exported are the United Kingdom (44% of total value), USA (19%), New Zealand (7%), Canada (5%), Japan (2%) and various European countries.

Approximately 80% of Australian dried fruit exports are sold to Germany, the United Kingdom, Canada, Japan and New Zealand. The remaining 20% is exported to other European and Asian countries.

Important table grape export markets in the recent past have been Singapore, Malaysia, Indonesia, Hong Kong, the United Kingdom and New Zealand.

International MRLs

The table below details Australian and proposed overseas tolerances for azoxystrobin in significant Australian export commodities.

Country	Food Commodity MRL (mg/kg)					
	Grapes	Wine	Dried grapes	Meat	Offal	Milk
Australia	2.0	-	5.0	*0.01	0.01	0.005
EU	2.0	-	-	*0.01	*0.01	*0.01
USA	1.0	-	-	*0.01	*0.01	*0.01
New Zealand	1.0	0.5	-	-	-	-
Canada	2.0	0.5	-	-	-	-
Japan	10.0 (vine)	-	-	-	-	-

Overseas registrations and use patterns

Wettable granule and suspension concentrate formulations of azoxystrobin are registered in 25 countries under a variety of tradenames. The first registration occurred in Germany in 1996 for use in cereal crops. The active is now registered for use in the USA and many parts of Europe and Latin America.

The predominant crops it is registered for use on are cereals, bananas, tomatoes, cucumbers and grapes. It is currently registered in 19 countries and Europe for use on grapes (USA, South Africa, Europe, Austria, Bulgaria, Croatia, Czech Republic, France, Hungary, Italy, Romania, Serbia, Slovakia, Slovenia, Spain, Switzerland, Turkey, Japan, Taiwan and Thailand), and is currently being considered for registration in grapes in a further four countries (Canada, Australia, New Zealand and Germany).

Use-patterns for azoxystrobin in grapes are similar worldwide as registration has been centrally coordinated. All countries exhibit similar claims for use, and an application rate of 25 g a.i./100 L (or 250 g a.i./ha). The maximum number of applications per season ranges from 3 to 8 and the withholding periods from 14 to 21 days.

CODEX Alimentarius Commission MRL

No CODEX MRL has been established for azoxystrobin in grapes.

Australian MRLs

The MRLs recommended for inclusion in the Australian *MRL Standard* are as follows:

Grapes	2.0
Dried grapes	5.0
Edible Offal (mammalian)	0.01
Meat (mammalian)	*0.01
Milks	0.005

Potential risk to trade

The recommended MRL for table grapes of 2.0 mg/kg azoxystrobin is in line with the tolerances which have been established/proposed in all countries except the USA and NZ. The USA does not represent a significant market for export of table grapes, and so no potential risk to trade is anticipated for this commodity.

No other countries have yet proposed the establishment of a MRL for azoxystrobin in dried grapes. European and Australian data has been provided in support of a MRL of 5.0 mg/kg for azoxystrobin in dried grapes in Australia. It may be therefore be anticipated that should Europe establish an MRL for azoxystrobin in dried grapes that this tolerance would be very similar to the MRL recommended in Australia. Europe represents a significant portion of the Australian export market for dried fruit. In the absence of tolerances for dried grapes in the importing countries, or CODEX MRLs for azoxystrobin in dried grapes, trade concerns may arise.

The use of Amistar may impact upon wine trade. The wine export market constitutes up to 50% of sales for some large producers and therefore this is a significant area of concern for potential users of the product. The results from trials provided, demonstrated that the maximum residue for grapes treated at the label rate should be below the MRL which has been set at 2.0 mg/kg. However, some countries have separate wine MRLs proposed for azoxystrobin of 0.5 mg/kg (Canada and New Zealand). Residue data in wine from Australian trials has shown that use of azoxystrobin at less than the maximum label rate can result in wine residues of 0.5 mg/kg. It may therefore be expected that use at the maximum label rate may result in wine residues that comply with the Australian MRL in grapes, but which exceed overseas wine tolerances.

In general, data showed that wine-making reduced azoxystrobin residues from the levels observed in grapes, but this trend was not observed with the consistency required to guarantee that grapes containing up to 2 mg/kg of azoxystrobin would provide wine containing 0.5 mg/kg or less. Advice has been sought from the Australian Wine Research Institute which indicates that in the situation where finite residues are observed in wine as a result of adherence to the label use-pattern, use of the product is generally not recommended after 80% capfall for grapes to be used in production of export wine. This advice should permit wine production with nil detectable residues, and satisfaction of residue tolerances in all potential export markets.

Animal transfer data was presented to establish animal MRLs, all of which are at the limit of quantitation, apart from offal which has a finite MRL of 0.01 mg/kg recommended. Azoxystrobin residues should not present a risk to meat exports as it presents a nil residues situation.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Azoxystrobin is not currently listed in the NOHSC List of Designated Hazardous Substances. NOHSC has determined azoxystrobin to be a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances. This classification is based at least on its acute inhalational toxicity.

The following risk phrase is assigned:

R23 Toxic by inhalation

Substances containing azoxystrobin at or greater than 3% are classified as hazardous.

Azoxystrobin is a pale brown powdery solid. It is of low acute toxicity by the oral and dermal routes, and is of moderate toxicity by the inhalational route. It is a slight skin and eye irritant in rabbits, but is not a skin sensitiser in guinea pigs.

Amistar WG Fungicide is classified by Crop Care Australasia Pty. Ltd. as a hazardous substance based on the acute eye irritation effects, in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances.

Amistar WG Fungicide is a water dispersible granule formulation with wetting agents. It is of low acute toxicity by all routes. It is a slight skin irritant and moderate eye irritant in rabbits, but has no skin sensitising properties in guinea pigs.

The product will be imported fully formulated in bulk containers and re-packed in Australia in 1 and 2 kg poly bottles (High Density Polyethylene with a neck opening of 63-72 mm), 3 kg plastic bottle with measuring cap and 2, 5 and 10 kg packs which consist of a cardboard box with a plastic liner.

Transport, storage and retailing

A maximum of four operators would be involved in the re-packing process. The process of emptying the bulk containers and re-packing the product is automated. Therefore, direct handling of the product is likely to be minimal. Transport, storage and retail workers will handle the packaged product, and could only become contaminated in the event of a packaging breach.

Advice on safe handling of the product during routine use is provided in the material safety data sheet (MSDS) for Amistar WG Fungicide.

End use

Amistar WG Fungicide is to be used for the control of powdery mildew, downy mildew and Botrytis bunch rot in grapes. It is to be applied as a foliar fungicide as part of a season long spray program from early flowering to pre-harvest in rotation with products from different chemical groups. The recommended application rate is 37.5 or 50 g product/100 L (0.025% azoxystrobin) with a maximum of 3 applications per season and no more than 3 consecutive sprays at 10-16 day intervals. Application

will be by either boom spray equipment fitted with hydraulic nozzles or trailer mounted air blast sprayers in spray volumes of 500-1500 L/ha. The withholding period for harvesting is 14 days.

Exposure of end users will be predominantly through the dermal route during mixing/loading, application and clean-up procedures. Inhalation exposure to spray mist or dust may occur. Given the product is non-volatile and not expected to be dusty, and is of low inhalational toxicity, exposure to product mist or dust is not expected to be significant. The product is a slight skin and moderate eye irritant. Considering the dilution of the product in the working strength solution (0.05 % w/v), the prepared spray is not expected to be irritating to the eyes.

No worker exposure data were available for azoxystrobin or Amistar WG Fungicide. The risk assessment was based on exposure estimates from the UK Predictive Operator Exposure Model. The risk assessment showed that the risk was acceptable for mixer/loaders wearing gloves, applicators, and workers performing combined tasks wearing gloves during mixing/loading.

The risk assessment indicated that elbow length PVC gloves and face shield or goggles are recommended when opening the container and preparing the spray.

Entry into treated areas or handling treated crops

Workers re-entering treated crops may come into contact with product residues. Workers are expected to re-enter treated crops immediately after spray application. Residue studies showed that the levels of transferrable residues on grape leaves following 6 applications of azoxystrobin declined steadily. Given the low acute systemic toxicity and topical hazards of the product, and the dilution in the final spray (0.05%), no re-entry statement is recommended.

Recommendations for safe use

Workers involved in transport, storage, and retailing should be protected by safe work practices and training. End users should follow the instructions and Safety Directions on the product labels. Safety Directions include the use of elbow-length PVC gloves and face shield or goggles when opening the container and preparing the spray.

The personal protective equipment recommended should meet the relevant Standards Australia standards specified below:

AS 2161-1978 Industrial Safety Gloves and Mittens (Excluding Electrical and Medical Gloves)

AS 1337-1992 Eye Protection for Industrial Applications.

Manufacturers and importers should produce a MSDS for hazardous products containing azoxystrobin. These should contain information relevant to Australian workers, as outlined in the NOHSC National Code of Practice for the Preparation of

Material Safety Data Sheets. Employers should obtain the MSDS from the supplier and ensure that their employees have ready access to it.

Conclusions

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

ENVIRONMENTAL ASSESSMENT

Environmental exposure

Azoxystrobin is likely to have widespread use in Australian grape growing areas. Following application, any azoxystrobin not captured by the crop is expected to mainly become associated with the soil compartment, either directly beneath the crop or in smaller concentrations at off-target locations receiving spray drift deposits. Further movement may occur in the sorbed state if soil particles are transported in erosive runoff events. Degradation in the field primarily involves photodegradation at the soil surface, with microbial metabolism a significant secondary route for breakdown. Environmental fate data are summarised below.

Hydrolysis

Three studies were submitted. Standard hydrolysis studies at ambient temperatures found no significant hydrolysis of azoxystrobin between pH 5 and pH 9. Accelerated studies at alkaline pH and elevated temperature confirmed that abiotic hydrolysis will not be a significant degradation pathway for azoxystrobin in the environment.

Photolysis

Laboratory studies showed that azoxystrobin is moderately susceptible to photolysis in solution, with a half-life in the order of 2-4 weeks determined under sterile conditions and light intensity characteristic of summer sunlight. Degradation was more rapid (half-life of a few days) in natural river water, probably reflecting photosensitisation as dark controls were stable. Degradation formed a complex mixture of photoproducts, none of which persisted, after an initial photoisomerisation.

Studies in the sorbed state indicated that surface photolysis may provide a significant degradation pathway for azoxystrobin in the field. Laboratory studies suggested a likely half-life of 1-2 weeks on soil surfaces under summer sunlight. Again, photodegradation pathways were complex. There was substantial mineralisation to carbon dioxide. The most prominent degradates under laboratory conditions, apart from carbon dioxide, were a pyrimidinol (retaining the cyanophenyl ring) and a benzoic acid (from transformation of the phenylacrylate moiety).

Metabolism

Studies in soils and aquatic systems found azoxystrobin to be moderately persistent, particularly in sediment where it rapidly partitions. First half-lives in six aerobic soils ranged from 55 to 135 days, and in two anaerobic soils from 50-55 days. The first half-life in two aquatic systems was 150 days. The initial degradation product, azoxystrobin acid, was stable under anaerobic conditions such as found in sediment. Further degradation occurred under aerobic conditions, with the formation of carbon dioxide. Intermediate metabolites, including the two possible hydroxypyrimidines derived from ether cleavage, were detected in small amounts.

Mobility

Standard batch adsorption studies in eight different soils placed azoxystrobin in the low to medium mobility class, with soil organic carbon partition coefficients ranging from 210 to 1070. Similar studies were also conducted on metabolites. Azoxystrobin acid and the benzoic acid derivative had medium to very high mobility, and the pyrimidinol fragment medium to high mobility. Mobility of these weakly acidic metabolites was highest in alkaline soils.

No leaching studies were submitted, but leaching potential can be predicted as low using the GUS nomogram, based on consideration of mobility data and field half-lives.

Field dissipation

Field studies have been conducted at numerous locations in Europe and North America, involving either single applications to bare soil or multiple treatments at fortnightly intervals. Azoxystrobin dissipated rapidly after application, with half-lives of 2-39 days. Azoxystrobin acid, the main metabolite detected in laboratory studies, and the photoisomer which predominated in the laboratory photolysis studies, were not seen in the field unless radiolabelled azoxystrobin was used to improve sensitivity. The two main field degradates were the pyrimidinol (retaining the cyanophenyl ring) and a benzoic acid (from transformation of the phenylacrylate moiety) as seen in the laboratory soil photolysis study. Field dissipation appears to predominantly involve photolysis at the soil surface, with microbial activity a supporting pathway that appears more efficient in the field than in the laboratory. In multiple treatment studies, the two degradates could each be found at levels up to about 30-40% of the theoretical residues from a single application. Following a single application, peak metabolite levels did not exceed 20%. The metabolites did not persist, and had declined below the limit of detection (roughly equivalent to 5% of a single application) by 1-6 months after treatment. Residues were mainly confined to the surface fractions (0-5 or 0-15 cm) of soils.

Environmental effects

Birds

Testing with the standard test organisms bobwhite quail and mallard duck found azoxystrobin to be practically nontoxic under conditions of acute oral or subacute dietary exposure. No significant adverse effects were noted in reproductive testing with the same species.

Aquatic organisms

Testing found azoxystrobin to be moderately to highly toxic to four species of fish, with acute LC50s in the order of 1 mg/L and no distinction between technical active and formulated product. The dose-response curve was very steep. Chronic NOECs in two species were some 5-10 times lower. Azoxystrobin acid was practically nontoxic to rainbow trout.

Toxicity to a variety of aquatic arthropods ranged generally from moderate to very high. Crustacea were particularly sensitive, with acute EC50s of a few hundred ppb typical (for example, 160-270 µg/L in three tests with *Daphnia magna*). The most sensitive organism tested was mysid shrimp with a 48 hour EC50 of 68 µg/L. Chronic sensitivity was similar to acute, with a 21 day EC50 of 150 µg/L and NOEC (number of young) of 44 µg/L in *Daphnia magna*. More sensitive acute endpoints were obtained with filter-feeding cladocerans exposed to a WG formulation, but these were considered an artefact of the increased filtration rates in cladocerans maintained under clean laboratory conditions. No significant effects on filter feeding cladocerans were seen in mesocosms receiving applications of 10 or 30 g/ha azoxystrobin (nominally 1 or 3 µg/L) as a WG formulation. Molluscs, rotifers, water boatmen, chaoborids, damselflies and mayflies were less sensitive than crustacea, with typical EC50s of a few ppm indicative of moderate toxicity.

Azoxystrobin was very highly toxic to a green alga, marine diatom and a marine alga in laboratory testing. Slight toxicity was seen in testing with a blue green alga, and moderate toxicity with duckweed.

Terrestrial invertebrates

Azoxystrobin was at worst very slightly toxic to bees and slightly toxic to earthworms in standard laboratory testing. Field and laboratory testing with a range of beneficial organisms (mites, carabid beetles, hoverflies and parasitic wasps) found azoxystrobin to be either harmless or slightly harmful. Elevated rates of azoxystrobin had no effect on soil microbial function as determined by respiration and nitrogen mineralisation.

Plants

Phytotoxicity was evaluated by examining germination and growth in a range of crops and weeds. No significant adverse effects were observed.

Environmental hazard

Terrestrial fauna

For the maximum rate proposed, 375 g/ha in viticulture, initial residues of 80 ppm may be expected on short range grass, 37 ppm on long grass, 45 ppm on broad leaved plants and 5 ppm on fruits. Quail and mallards remained in good health when maintained on a diet containing 5200 ppm in dietary toxicity testing. No impairment of reproductive parameters occurred in quail fed 3000 ppm or mallards fed 1200 ppm azoxystrobin in the diet. The proposed uses of azoxystrobin are therefore not expected to present a hazard to birds. A similar conclusion may be reached for mammals.

The maximum rate of 375 g/ha would leave residues of around 500 µg/kg in 5 cm soil, well below levels that exerted toxic effects on earthworms in laboratory testing. Hazard to earthworms is low.

The maximum rate proposed equates to 3.75 µg/cm², which in turn approximates the exposure that a bee foraging during application may be expected to experience. This

exposure would not be expected to elicit any toxic effects, based on laboratory testing. Hazard to bees is low.

Testing of predators and parasites found some adverse effects, but much less than with toxic standards. From a population perspective, azoxystrobin is not expected to be harmful to predatory or parasitic organisms.

Aquatic fauna

A screening level assessment that considers the effects of spray drift (or runoff), conservatively estimated to provide 10% of the concentration that would arise from overspray, predicts a residue of 25 µg/L in 15 cm water from application at the maximum rate of 375 g/ha. For fish, this is less than 10% of the lowest acute LC50, indicative of minimal hazard.

For invertebrates exposed to spray drift or runoff from treatment of grapes at 375 g/ha, the exposure concentration reduces to about 40% of the acute LC50 for mysid shrimp, the most sensitive indicator organism. For the next most sensitive organism, the copepod *Macrocyclops fuscus*, predicted exposure is about 20% of toxicity. The threshold of 10% is not breached for any other aquatic invertebrate, based on test results using technical azoxystrobin. Use of the US EPA's GENEEC model to simulate multiple applications confirms these conclusions.

These considerations indicate that most aquatic fauna should remain unaffected by azoxystrobin, even using the conservative assumptions that drift of 10% from the maximum rate of 375 g/ha distributes through and persists in a shallow water body. Environmental fate studies indicate that azoxystrobin will not persist in the water column but will largely partition to sediment. Even if some organisms are affected by a drift or runoff event, impacts on populations would not be expected as invertebrates have rapid regeneration times, and repopulation would occur from unexposed or less exposed areas that have not received such high levels of drift or have deeper water. Label warnings of aquatic toxicity are warranted, however, in order to minimise the risk of isolated invertebrate impacts.

As application rates to potatoes, tomatoes and cucurbits are lower than for grapes, use of azoxystrobin in these crops is not expected to present a significant environmental hazard to aquatic fauna.

Terrestrial and aquatic flora

Phytotoxicity studies in a range of terrestrial plants exposed to elevated rates of azoxystrobin indicate that the likelihood of off-target damage to non-target plants is low.

Algae are sensitive to azoxystrobin. The EC₅₀ for the freshwater diatom *Navicula pelliculosa* is similar to the LC₅₀ for mysid shrimp, and the general ecotoxicological profiles are similar in invertebrates and algae. By analogy with the hazard assessment for aquatic invertebrates, some limited impacts may occur in shallow water where high levels of drift occur from high rate applications. In most situations, no impacts

would be expected. Because of their exponential growth habits, algae are able to rapidly recolonise areas where algal damage has occurred. No long term or widespread damage to algal colonies is expected from the proposed uses of azoxystrobin.

Conclusions

Adequate data have been presented to enable prediction of the likely fate of azoxystrobin in the environment, and the likelihood of adverse impact to non-target organisms. Bioaccumulation data were not provided, but bioaccumulation potential in fish would be expected to be low, based on the relatively low partition coefficient.

Assessment indicates that there may be a slight hazard to sensitive aquatic invertebrates inhabiting shallow water if high rates of drift occur from applications at the upper end of the proposed range. Note that this assessment includes a number of conservative assumptions. It is not expected that any small and isolated invertebrate impacts from use of azoxystrobin would be ecologically significant. However, the standard warning under the heading PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT should be strengthened as follows:

**HIGHLY TOXIC TO AQUATIC LIFE. DO NOT CONTAMINATE DAMS,
WATERWAYS OR DRAINS WITH THE CHEMICAL OR USED CONTAINERS.**

**DO NOT APPLY UNDER METEOROLOGICAL CONDITIONS OR FROM
SPRAYING EQUIPMENT WHICH COULD BE EXPECTED TO CAUSE SPRAY
TO DRIFT ONTO ADJACENT AREAS, PARTICULARLY WETLANDS,
WATERBODIES OR WATERCOURSES.**

EFFICACY AND SAFETY ASSESSMENT

Efficacy

Fifteen trials on 9 different grape varieties were conducted in the major grape growing regions of Australia. Efficacy data was obtained on downy mildew, powdery mildew and Botrytis bunch rot.

The data was evaluated by experts in the various State Agriculture Departments. They considered that sufficient numbers of experiments were conducted to cover infection pressures that ranged from low to heavy for most diseases in a wide range of weather conditions and grape growing areas of Australia.

The number of applications, range of doses and methods of application were adequate to interpret the data in relation to commercial conditions.

The results presented show that 6 to 7 applications of Amistar at 37.5 or 50 g/100L controls powdery mildew, downy mildew and Botrytis bunch rot to levels that are as good as or better than the standard fungicide programme.

For fungicide resistance management, azoxystrobin has been placed in a new activity group, K, called strobilurins.

In order to reduce development of resistance, the Avcare Fungicide Resistance Action Committee strategies recommend avoidance of application of fungicides from only one activity group for long periods. It is therefore now proposed that a maximum of 3 applications of Amistar occur in any one season, with an alternative chemical from another activity group to be used if required. This program is considered likely to be effective in managing the diseases whilst reducing the onset of fungicide resistance.

Crop safety

Amistar was applied at application rates twice and four times the label rate for a full season on 9 different grape varieties. Crop safety was assessed by visual observations and yield measurements in some trials in the absence of disease.

In two experiments, slight interveinal chlorosis developed on leaves sprayed with high rates of Amistar. The phytotoxicity was not permanent, only developed early in the season and did not appear to adversely affect yield. Nevertheless, some caution as to the possibility of mild phytotoxicity should be mentioned on the label as concentrate sprays may be used in commercial situations.

No affect on grape juice fermentation of white or red grape varieties was observed following use of the product in a full season protective spray program.

LABELLING REQUIREMENTS

The following is the draft label for the product:

CAUTION

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

AMISTARTM WG

Fungicide

ACTIVE CONSTITUENT : 500g/kg AZOXYSTROBIN

GROUP	K	FUNGICIDE
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**For control of downy mildew and powdery mildew and suppression of
botrytis bunch rot on grapes.**

**NET CONTENTS : 1, 2, 3, 5
&10kg**

Crop Care Australasia Pty Ltd, 77 Tingira St, Pinkenba Qld 4008

DIRECTIONS FOR USE : All States

CROP	DISEASE	RATE g/100	CRITICAL COMMENTS
Grapes (Table, Wine & Dried)	<p>Powdery mildew (<i>Uncinular necator</i>)</p> <p>Downy mildew (<i>Plasmopara viticola</i>)</p> <p>Botrytis bunch rot* (<i>Botrytis cinerea</i>)</p>	37.5 or 50	<p><u>Application Method and Rate</u> Apply in a sufficient volume of water to achieve thorough coverage of all foliage and fruit. The volume of water required to achieve this will depend on the stage of vine growth and vigour. An application volume of 500L/ha is suggested at the start of the season, increasing to 1500L/ha in a vigorous crop at full canopy. Adjust spray nozzles to direct spray droplets to the canopy present. Apply the higher rate of application in the following circumstances</p> <ol style="list-style-type: none"> 1. Where humid conditions favour powdery mildew infection, particularly on susceptible varieties. 2. At the start of the season when there has been a heavy carry over of powdery mildew infection (flag shoots are present). <p><u>Spray Timing and Interval</u> Apply two or three consecutive applications at 10-16 day intervals at any time between early shoot growth and 14 days before harvest. Use the shorter interval during periods when climatic conditions are favourable for disease infection.</p> <p><u>*Botrytis Bunch Rot</u> Amistar WG must not be used alone for Botrytis control at critical times such as 80-100% capfall and preharvest. It must be tank mixed with or substituted for with a specific Botryticide at these critical times. When Amistar WG is used in a seasonal spray programme it will provide control of Botrytis additional to that of specific Botryticides such as Sumisclex® and Bravo®.</p> <p><u>Resistance Management</u> Disease control may be reduced if strains of pathogens less sensitive to Amistar WG develop. DO NOT use Amistar WG curatively. As a precaution, do not apply more than a total of 3 applications of Amistar WG per crop in one season. If consecutive applications of Amistar WG are used they must be followed by at least the same number of applications of fungicide(s) from a different group(s) before Amistar WG is used again in that crop in the current or following season. DO NOT use Amistar WG for disease control in grapevine nurseries.</p>

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

WITHHOLDING PERIOD

GRAPES: DO NOT HARVEST FOR 14 DAYS AFTER APPLICATION

WARNING

Amistar WG is extremely phytotoxic to certain apple varieties.

AVOID SPRAY DRIFT. Extreme care must be used to prevent injury to apple trees.

DO NOT spray Amistar WG where spray drift may reach apple trees.

DO NOT spray when conditions favour drift beyond the area intended for application.

Conditions which may contribute to drift include thermal inversions, excessive wind speed, certain sprayer nozzle/pressure combinations, small spray droplet size etc.

DO NOT use spray equipment which has been previously used to apply Amistar WG to spray apple trees. Even trace amounts can cause unacceptable phytotoxicity.

GENERAL INSTRUCTIONS

Application

Do not use concentrate exceeding 100g/100L when applying through low volume application equipment. In these cases adequate coverage of all plant surfaces is still required to achieve control of diseases.

Export of Treated Produce

Growers should note that while MRLs have been set in major wine export destinations, currently there is no MRL set in Canada. To achieve no detectable residues, application should not be made after 80% capfall.

Mixing

Fill tank 50-75% full then start agitation. Slowly pour granules into tank and maintain agitation throughout spraying. **DO NOT** pre-mix 'Amistar WG' granules.

Compatibility/Tank Mixing

'Amistar WG' may be mixed in the spray vat with any one of the following products : 'Bravo[®]' 720, 'Sumisclex[®]' 500, 'Captan[®]' WG, 'Talstar[®]' 80SC.

A mixture of 'Amistar' WG with more than one of these products or with any other product may be ineffective or may cause serious damage. The use of such a mixture is not recommended and would therefore be entirely at the user's risk.

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

Fungicide Resistance Warning

GROUP	FUNGICIDE
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Amistar WG Fungicide is a member of the Strobilurin and related products group of fungicides. For fungicide resistance management the product is a Group K fungicide.

Some naturally occurring individual fungi resistant to the product and other Group K fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungal population if these fungicides are used repeatedly. These resistant fungi will not be controlled by this product or other Group K 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, Crop Care Australasia Pty Ltd accepts no liability for any losses that may result from the failure of this product to control resistant fungi.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
HIGHLY TOXIC TO AQUATIC LIFE. DO NOT CONTAMINATE DAMS,
WATERWAYS OR DRAINS WITH THE CHEMICAL OR USED CONTAINERS.

DO NOT APPLY UNDER METEOROLOGICAL CONDITIONS OR FROM SPRAYING EQUIPMENT WHICH COULD BE EXPECTED TO CAUSE SPRAY DRIFT ON ADJACENT AREAS, PARTICULARLY WETLANDS, WATERBODIES OR WATERCOURSES.

STORAGE AND DISPOSAL (1, 2 and 3kg)

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. Empty containers and product should not be burnt.

STORAGE AND DISPOSAL (5 and 10kg)

Store in the closed, original container in a dry, cool, well-ventilated area out of direct sunlight. Shake empty into spray tank. Do not dispose of undiluted chemicals on site. Puncture or shred 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. Empty containers and product should not be burnt.

SAFETY DIRECTIONS

Will irritate the eyes. Avoid contact with eyes and skin. When opening the container and preparing spray wear elbow-length PVC gloves and face shield or goggles.

If clothing becomes contaminated with product or wet with spray, remove clothing immediately. If product or spray on skin, immediately wash area with soap and water. If in eyes, wash it out immediately with water. Wash hands after use.

After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each day's use, wash gloves, face shield or goggles and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131 226. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

Additional information is listed in the Material Safety Data Sheet No.: 1997

Conditions of sale

Crop Care Australasia Pty Ltd will not accept responsibility whatsoever and howsoever arising and whether for consequential loss or otherwise in connection with the supply or use of these goods other than responsibility for the merchantable quality of the goods and such responsibilities mandatorily imposed by Statutes applicable to the sale or supply of these goods. To the extent allowed by such Statues the liability of Crop Care Australasia Pty Ltd is limited to the replacement of the goods or (at the option of Crop Care Australasia Pty Ltd) the refund of the price paid and is conditional upon a claim being made in writing and where possible sufficient part of the goods to enable proper examination being returned to Crop Care Australasia Pty Ltd within thirty days of delivery.

UN No. 3077	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (CONTAINS BETA-METHOXYACRYLATE FUNGICIDE) MARINE POLLUTANT
In a Transport Emergency Dial 000 Police or Fire Brigade P.G.III	SPECIALIST ADVICE IN EMERGENCY ONLY 1800 033 111 ALL HOURS - AUSTRALIA-WIDE HAZCHEM 3 <Z>

Crop Care Australasia Pty Ltd is the licensed user of 'Amistar' which is a Trade Mark of Zeneca Limited.

'Sumislex' is a Registered Trade Mark of Sumitomo Chemical Company Limited.

'Bravo' is a Registered Trade Mark of Zeneca Pty Ltd.

'Talstar' is a Registered Trade Mark of FMC Corporation, Philadelphia, USA.

BN

DOM

Bar code
and
Label identification no.

Crop Care



NRA Approval No. : 50519/

Crop Care Australasia Pty Ltd
A.C.N. 061 362 347
77 Tingira Street, PINKENBA Qld 4008.

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 P_{ow}	Log to base 10 of octanol 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

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- National Registration Authority for Agricultural and Veterinary Chemicals 1996, *Ag Manual: The Requirements Manual for Agricultural Chemicals*, NRA, Canberra.
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NRA PUBLICATIONS ORDER FORM

To receive a copy of the full technical report for the evaluation of azoxystrobin in the product Amistar WG Fungicide, please fill in this form and send it, along with payment of \$30 to:

David Hutchison
Agricultural and Veterinary Chemicals Evaluation Section
National Registration Authority for Agricultural and Veterinary Chemicals
PO Box E240
Kingston ACT 2604

Alternatively, fax this form, along with your credit card details, to the contact officer above at (06) 6272 3218

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