Public Release Summary
on

Evaluation of the new active

UNICONAZOLE-P

in the product

SUNNY PLANT GROWTH REGULATOR

National Registration Authority
for Agricultural and Veterinary Chemicals

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Australia

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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 Aged Care (Chemicals and Non-prescription Medicines Branch), Environment Australia (Risk Assessment and Policy Section), the National Occupational Health and Safety Commission (NOHSC) 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.

The information and technical data required by the NRA to assess the safety of new chemical products and the methods of assessment must be in accordance with 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 it 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
bw	body weight
d	Day
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	estimated environmental concentration
Fo	original parent generation
h	Hour
Hct	Haematocrit
Hg	Haemoglobin
HPLC	high pressure liquid chromatography *or* 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
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	Level at which residues can be detected
LOQ	Level at which residues can be quantified
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
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
NOEC/NOEL	no observable effect concentration/level
OC	Organic carbon
OECD	Organisation for Economic Cooperation and Development
OM	Organic matter
po	Oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
RBC	Red Blood Cell count
s	Second
sc	Subcutaneous
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
µg	microgram
US EPA	United States Environmental Protection Agency
WHP	withholding period

SUMMARY

This publication outlines the regulatory considerations and provides a summary of the data evaluated for the proposed registration of **SUNNY PLANT GROWTH REGULATOR** (*Sunny*). *Sunny* is a suspension concentrate formulation containing **50 g/L uniconazole-p**. It is proposed that the product will be used for the improvement of fruit shape and reduction in vegetative growth in avocados.

The NRA has assessed the data submitted by the applicant in support of the proposed use of uniconazole-p. The following information is provided for public comment before the NRA determines whether to register the product in Australia. Comments should be submitted by **1 September 2000** to the NRA at the address indicated on page 1.

Public Health Aspects

Toxicology

Uniconazole-p, the active ingredient in *Sunny*, is rapidly absorbed after oral ingestion and extensively metabolised by the liver. There is no accumulation in the tissues and the metabolites are rapidly excreted in the faeces and urine. It has moderate acute oral toxicity and low acute dermal and inhalation toxicity. It is a slight eye irritant, but not a skin irritant or skin sensitiser. The formulated product, *Sunny*, containing 50 g/L uniconazole-p, has a similar acute toxicological profile except that has very low acute oral toxicity.

In repeat dose studies in mice, rats and dogs, the main adverse effect caused by oral ingestion of high doses of uniconazole-p was an increase in the size and weight of the liver. Fat accumulation in the liver was also consistently observed at high doses. Although observed less consistently, increases in the activity of some enzymes indicated altered liver function as a response to uniconazole-p exposure. In long term studies, there was no evidence of an increase in cancer. This result is further supported by several studies which show that uniconazole-p does not damage genetic material.

Uniconazole-p had no effects on reproductive behaviour or performance of rats and no effect on foetal development in rabbits. At doses that were not toxic to the mother, there were no effects on the rat foetus.

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

Residues in Food

In plants, uniconazole-p was shown to be extensively metabolised. The major component of the residue was unchanged parent compound. The rat metabolism experiments conducted at exaggerated dose rates indicated that uniconazole-p was extensively metabolised and rapidly excreted. The major component of the residue in liver was unchanged parent compound.

As regards the residue definition, uniconazole-p was the major component of the residue in both plants (apple, tomato) and animals (rat). It is appropriate to establish the residue definition as the sum of uniconazole-p and its Z-isomer as the analytical method does not differentiate between the two compounds. Validated analytical methods were capable of quantifying uniconazole-p residues in avocados to 0.01-0.02 mg/kg.

The residue data from South Africa and Australia support the applicant's proposed MRL of *0.02 mg/kg for avocado. The proposed use-pattern as a spray at flowering precludes the need for the establishment of harvest withholding periods.

Given the lack of detectable residues in avocados it is not necessary to set animal MRLs for uniconazole-p.

Consideration of the maximum residues of uniconazole-p expected in avocados leads to the conclusion that the use of uniconazole-p in this crop does not pose a threat to human health or trade.

The following amendments to the *MRL Standard* are recommended:

Table 1

Compound	Food	MRL (mg/kg)
Uniconazole-p		
DELETE:		
	FT 0326 Avocado	T*0.02
ADD:		
	FT 0326 Avocado	*0.02

Table 3

Compound	Residue
ADD:	
Uniconazole-p	Sum of uniconazole-p and its Z-isomer expressed as uniconazole-p

The following WHPs are recommended in relation to the above MRL for *Sunny*:

Harvest:
Avocado Not required when used as directed

Occupational Health and Safety Aspects

NOHSC has conducted a risk assessment on *Sunny* containing uniconazole-p at 50 g/L as a suspension concentrate formulation for use on avocados. Workers can safely use *Sunny* when handled in accordance with the control measures indicated in this assessment.

Uniconazole-p is classified as hazardous based on evidence that it is of moderate acute oral toxicity in rats. However, *Sunny* is not classified as hazardous as the level of uniconazole-p that it contains is below the cut-off of 25%.

Sunny possesses low acute oral and dermal toxicity in rats. The product was a slight eye irritant but not a skin irritant in rabbits and does not induce skin sensitisation in guinea pigs.

Sunny is proposed for the enhancement and improvement of fruit shape and reduction in vegetative growth in avocados. It will be applied as a high volume (dilute) spray, using orchard spraying equipment. The proposed rate is 24 L/ha of uniconazole-p in a minimum of 1200L water/ha.

Worker exposure data were not available for uniconazole-p or *Sunny*. The occupational health and safety risk assessment was based on estimates obtained from an exposure model.

Based on the risk assessment, cotton overalls buttoned to the neck and wrist and a washable hat and elbow length PVC gloves are recommended for users of *Sunny*. A re-entry statement is not recommended for this product.

Environmental Aspects

Uniconazole-p is stable to hydrolysis and the principal degradation pathway appears to be by photolysis in solution. Microbial breakdown in aerobic soils in the dark is slow. Laboratory studies showed that uniconazole-p is not likely to leach from sandy-loam soils. However, when applied to sandy soils with low organic matter uniconazole-p is easily eluted with water. A field dissipation study showed some evidence for an initial rapid dissipation in one of the two soils, however, a significant amount of remained after the initial dissipation and dissipated with a half-life >100 days.

Uniconazole-p is non-toxic to birds, bees and earthworms, slightly to moderately toxic fish and aquatic invertebrates. The toxicity to algae is unclear. Rates up to 12× the proposed rate did not inhibit soil respiration.

The hazard to birds, fish, aquatic invertebrates, bees, earthworms and soil microbes, even using worst case assumptions was determined to be low. With the limited use pattern and low aquatic exposure, the lack of algae and aquatic plant studies is not considered critical for the proposed use.

Efficacy and Crop Safety Aspects

Data from long term use of the product in Israel and more particularly South Africa, with its similar growing conditions, has been coupled with data from confirmatory trials over the last two years in Australia to demonstrate that the product will provide improved fruit shape and vegetative growth control in avocados.

No direct phytotoxicity of the product at label rates was shown or is known to occur. There are however carryover effects and rates for use of the product on the same trees the following season will need to be adjusted on an individual orchard block basis with advice from the distributor.

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of ***SUNNY PLANT GROWTH REGULATOR (Sunny),*** which contains the new active ingredient, **uniconazole-p**.

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.

Copies of full technical evaluation reports on uniconazole-p, covering toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the NRA on request (see order form on last page). They can also be viewed at the NRA library located at the NRA offices, Ground Floor, 22 Brisbane Avenue, Barton ACT 2604.

Written comments should be submitted by **1 September 2000** and addressed to:

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AgVet Chemicals Evaluation Section
National Registration Authority
PO Box E240 Phone (02) 62723152
Kingston ACT 2604 Fax (02) 62723218

Applicant
Aquamarine B V.

Product Details
It is proposed to register *Sunny* containing uniconazole-p at 50g/L as a suspension concentrate formulation. *Sunny* will be imported fully formulated and packaged in 1 and 5 litre containers.

Uniconazole-p inhibits the endogenous biosynthesis of gibberellin. This reduction in the level of endogenous gibberellin results in the inhibition of vegetative growth. By inhibiting this growth at the time of fruit set in avocados, changes to fruit characteristics (reduced "neck", size) can be induced.

The proposed use of Sunny will be for application at flowering to Fuerte, Hass and Pinkerton varieties of avocados. As with all plant growth regulators factors such as tree vigour, uniformity of flush, stress, day length, water regime, temperature etc will effect response and hence the rate will need to be adjusted with advice from the supplier.

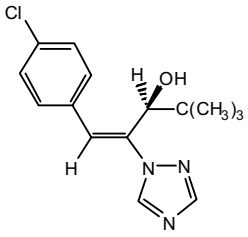
Formulations comparable to *Sunny* are registered in Israel and South Africa for the same purpose as that proposed for Australia and in the USA for use in ornamentals.

CHEMISTRY AND MANUFACTURE

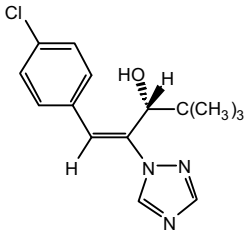
Active Constituent

The active constituent, uniconazole-p, is manufactured in Japan by Sumitomo Chemical Company Limited.

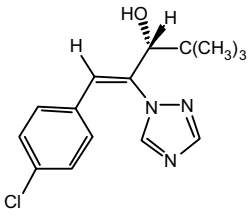
Chemical Characteristics of the Active Constituent
Common name (SA or ISO common name): uniconazole-p
Synonyms and code number: S-3307D
Chemical name
(IUPAC): (E)-(RS)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl)-pent-1-en-3-ol
(CAS RN): 83657-22-1
Molecular formula: $C_{15}H_{18}N_3OCl$
Molecular weight: 291.5 g/mol
Chemical structure: uniconazole-p contains a double bond and one chiral centre. Four isomers are possible (2 geometrical isomers, E and Z, each with two optical isomers, R and S because of the chiral centre). The major isomer is the ES isomer.



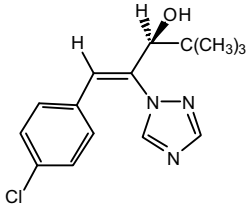
ES isomer



ER isomer



ZR isomer



ZS isomer

Physical and Chemical Properties of Pure Active Ingredient
Physical state: crystalline solid
Colour: white-light brown
Odour: none
MP: 152.1-155.0°C
Density: 1.28 g/mL at 25°C
Solubility in water: 8.41 mg/L at 25°C
Solubility in organic solvents: 0.9 % w/w in xylene; 11.3 % w/w in methanol; 10.9 in chloroform.
Vapour pressure: 5.82 (mm Hg) at 200°C; 19.0 at 230°C, 38.3 at 250°C, 95.8 at 280°C. Estimate at 20°C is 4.0 x 10^{-5} mm Hg.
Octanol/water partition coefficient: log P_{OW} = 3.77 at 25°C
pH: 5.7 (1% aqueous suspension); 5.9 (10% aqueous suspension)
Storage stability: uniconazole-p is stable for up to 6 months at 60°C.
Pesticide group: Plant growth regulator:
Chemical family: Triazole derivative:

Product

Distinguishing name or trade name: *Sunny Plant Growth Regulator*
Formulation type: Suspension Concentrate
Active constituent concentration: 50 g/L (of ES isomer)
Mode of action: Gibberellin biosynthesis inhibitor, which is a plant growth regulator that is absorbed by the roots and stems, with translocation in the xylem to growing points.

Physical and Chemical Properties of the Product
Physical state: Suspension Concentrate
Density: 1.04 g/mL
Acidity, alkalinity or pH: 6.5-8.5
Viscosity: 1100-2500 cps
Storage stability: Stable for 14 days at 54°C

MSDSs for the inactive constituents were provided and are acceptable.

Conclusion

Based on a review of the details provided by the applicant the registration of *Sunny,* in relation to its Chemistry and Manufacture, is supported.

TOXICOLOGICAL ASSESSMENT

The toxicological database for uniconazole-p, which consists primarily of toxicity tests conducted using animals, is quite 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 the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are used to develop acceptable limits for dietary or other intakes at which no adverse health effects in humans would be expected.

Toxicokinetics and Metabolism

After oral administration to rats, uniconazole-p was rapidly absorbed. The amount excreted within 24 hours of administration depended upon the dose. However, 98-100% of any administered dose was excreted within 7 days. Uniconazole-p was extensively metabolised in rats with approximately 80-90% of the administered dose excreted as biotransformation products. Faecal excretion accounted for approximately 30-60% and urinary excretion accounted for the remainder of total excretion. Males tended to excrete slightly more in the faeces than females. Negligible (0.1% of the administered dose) excretion occurred via exhaled air and tissue accumulation did not occur.

Acute Studies

Uniconazole-p is of moderate acute oral toxicity in rats (LD_{50} =430 mg/kg bw in females and 460 mg/kg bw in males), low acute dermal toxicity in rats (LD_{50} >2000 mg/kg bw) and low acute inhalation toxicity in rats (LC_{50} >2750 mg/m^3). It is a slight eye irritant but not a skin irritant in rabbits. It is not a skin sensitiser in guinea pigs.

Sunny is of very low acute oral toxicity in rats (LD_{50} >2000 mg/kg bw) and low acute dermal toxicity in rats (LD_{50}>2000 mg/kg bw). It is a slight eye irritant but not a skin irritant in rabbits. It is not a skin sensitiser in guinea pigs.

Short-Term Studies

In a 90-day study rats were fed uniconazole-p at dietary concentrations of 0, 30, 100, 1000 or 3000 ppm. Body weights were decreased at 1000 ppm and 3000 ppm. Changes in serum chemistry (increased cholesterol, triglycerides, phospholipids, alanine amino transferase and

aspartate aminotransferase) observed in the two highest dose groups indicate altered fat metabolism and altered liver function. Enlarged livers and increased liver weights in males and females at 1000 and 3000 ppm and increased thyroid weights in males at 3000 ppm were accompanied by histopathological changes in these tissues. Histopathological changes in the thyroid were observed in males and females at 100, 1000 and 3000 ppm. The NOEL in this study was 30 ppm equal to 2.25 mg/kg bw/day in males and 2.42 mg/kg bw/day in females.

In a 90-day study, dogs were given uniconazole-p in gelatin capsules at doses of 0, 5, 20, 80 or 320 mg/kg bw/day. One male at 320 mg/kg died. Increased liver weights and size, changes in serum chemistry (increased alkaline phosphatase) and liver function tests in dogs at 20, 80 and 320 mg/kg/day suggest that the liver was the target organ for the toxic effects of uniconazole-p. Histopathological changes in livers at high doses were also observed. The male that died showed histopathological changes consistent with those observed in other treated animals. The NOEL was 5 mg/kg bw/day.

Long-Term Studies

In an oncogenicity study mice were fed uniconazole-p at dietary concentrations of 0, 10, 40, 200 or 1500 ppm for 78 weeks. Survival in males in the control group was low compared with treated groups. Increased liver weights accompanied by histopathological changes in the liver were observed at 1500 ppm. A slight increase in the incidence of malignant neoplasms was observed in females at 1500 ppm and a slight increase in the incidence of benign neoplasms was observed in males at 1500 ppm. The incidence of hepatic adenomas and carcinomas was slightly increased in males at 1500 ppm but not females. Age related histopathological changes in a variety of tissues were also observed with increased incidence in males at 1500 ppm. The NOEL was 200 ppm, equal to 28.5 mg/kg bw/day in males and 37.5 mg/kg bw/day in females.

In a combined chronic/oncogenicity study, rats were fed uniconazole-p at dietary concentrations of 0, 10, 40, 200, or 1000 ppm for 106 weeks. Reduced body weights and increased liver weights were observed at 1000 ppm. Histopathological changes in livers were observed at 200 and 1000 ppm. No increase in the incidence of tumours was observed. The NOEL was 40 ppm equal to approximately 1.86 mg/kg bw/day in males and 2.36 mg/kg bw/day in females.

In a chronic study, dogs were administered uniconazole-p in gelatin capsules at doses of 0, 2, 20 or 200 mg/kg bw/day for 52 weeks. Serum alkaline phosphatase activity was markedly increased in males and females at 20 and 200 mg/kg bw/day. Liver weights were increased in males at 20 and 200 mg/kg bw/day and in females at 200 mg/kg bw/day. Histopathological changes were observed in livers of males and females at 200 mg/kg bw/day. The NOEL was 2 mg/kg bw/day.

Reproduction and Developmental Studies

In a two generation reproduction study, rats were fed uniconazole-p at dietary concentrations of 0, 15, 150, or 1500 ppm. Two females in the F_0 generation died during difficult labours. The litters of these rats died prior to the death of the parent. In each generation, body weights and food consumption of rats at 1500 ppm were reduced during growth, gestation and lactation.

Histopathological changes in livers from rats treated at 1500 ppm were observed in the F_0 and F_1 generations. There was no effect on reproductive behaviour or performance.

Pregnant rabbits were given uniconazole-p by gavage at doses of 0, 1, 3, 10 or 20 mg/kg bw/day on days 7 to 19 of gestation. Reduced food consumption and weight gain were observed in maternal rabbits at the highest dose. However, no effect of uniconazole-p on foetal development was observed. The NOEL was 10 mg/kg bw/day.

Rats were given uniconazole-p orally at doses of 0, 1, 5, 25 or 50 mg/kg bw/day during the period of organogenesis. Maternal body weight gain was reduced at the beginning of treatment in groups given 25 or 50 mg/kg bw/day on days 9 and 12 of gestation. Other than variations in bone development (supernumerary ribs) at 25 and 50 mg/kg bw/day no effect was observed on foetal development. The NOEL for this study was 5 mg/kg bw/day.

Genotoxicity

Uniconazole-p did not increase the incidence of gene mutation in *Salmonella typhimurium* (Ames test) or *Escherichia coli* WP2uvrA. It did not induce formation of micronuclei in mouse bone marrow cells nor did it induce sister chromatid exchange in CHO-K1 cells.

PUBLIC HEALTH STANDARDS

Acceptable Daily Intake

The NOEL, based on a 106-week rat study, is 1.86 mg/kg/day. In order to calculate the acceptable daily intake (ADI) for humans, a safety factor is applied to the NOEL. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animals data to humans, variation within the human population, the quality of experimental data, and the nature of potential hazards. Using a safety factor of 100, an ADI of 0.02 mg/kg/day was chosen for uniconazole-p.

Poisons Schedule

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

The NDPSC recommended that uniconazole-p be listed in Schedule 6 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). Scheduling in the SUSDP is not required for preparations containing 50 g/L uniconazole-p or less. There are provisions for appropriate warning statements and first-aid directions on the product label.

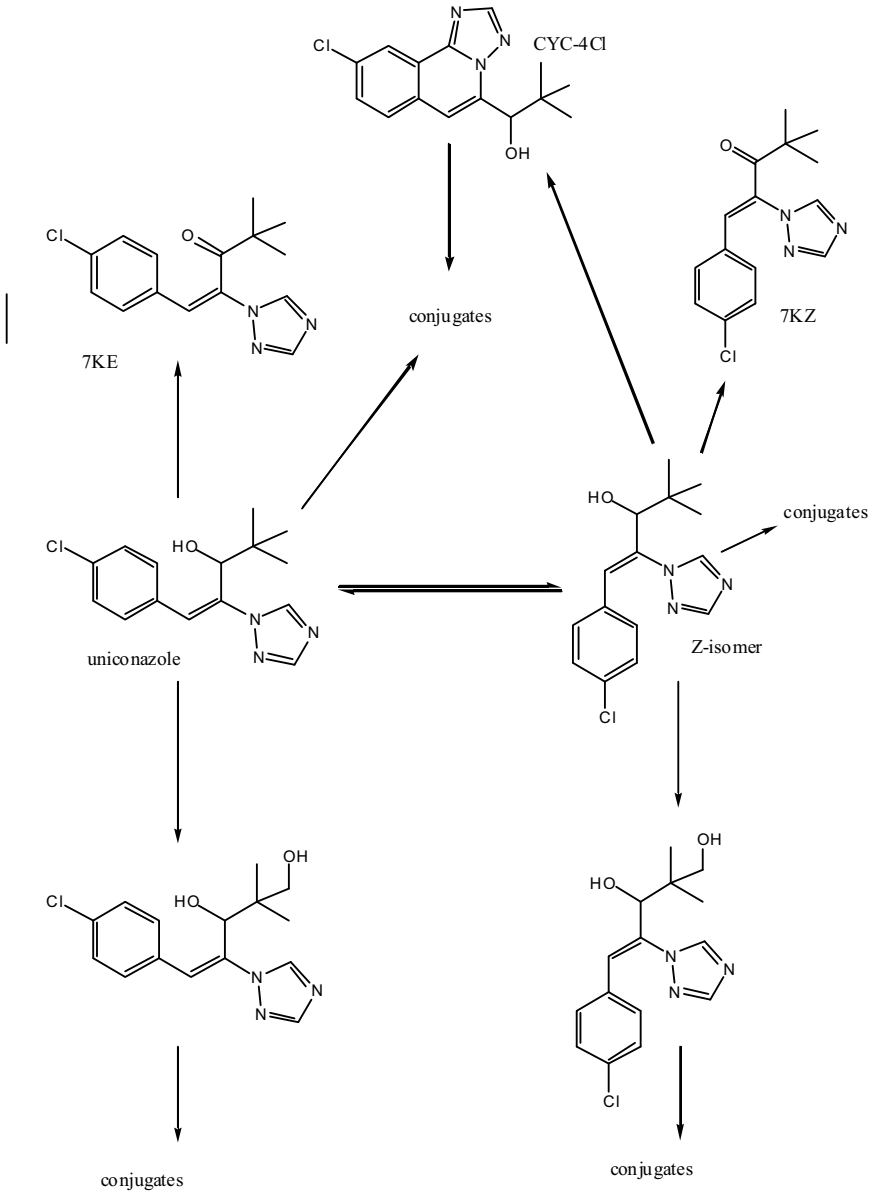
RESIDUES ASSESSMENT

Residues In Food Commodities

The applicant has provided plant and animal metabolism studies and crop residue studies in support of the registration of *Sunny*.

Metabolism

The metabolism and distribution of uniconazole-p was studied in apples and tomatoes using ^{14}C-



uniconazole-p. Apple trees were injected with 25 mg ^{14}C-uniconazole-p and stems and apples harvested 86 days after the injection. Tomatoes were treated with 2 foliar sprays of ^{14}C-uniconazole at 14 day intervals and at a rate of 0.14 kg ai/ha with a PHI of 49 days. Plants were separated into branches/stems, leaves and edible fruit and the radioactive residues characterised by 2-D TLC and HPLC co-chromatography. The major component of the total radioactive residue was parent

compound with minor amounts of the geometric Z-isomer as well as CYC-4Cl and the corresponding conjugates. The major metabolic pathways were E/Z isomerisation followed by cyclisation, hydroxylation at the terminal carbon and conjugation and is shown in the scheme above. In the case of tomatoes oxidation of the hydroxyl group to a ketone also occurred. In summary, in plants the major component of the residue in fruit is unchanged parent compound.

The animal metabolism of uniconazole was studied in rats. On single dosing of male and female rats orally with ^{14}C-uniconazole at 1 or 200 mg/kg bw, nearly 100% of the dose was excreted in faeces (34-59%) and urine (40-67%) within 7 days. Peak tissue concentrations were attained 1 to 8 hours post-dose. The adrenal gland and liver had the highest peak concentrations of radioactivity for any tissue, 4.57 and 2.59 mg equiv./g for adrenal and liver respectively. The major component of the residue in liver was unchanged parent compound. Recoveries of radioactivity with methanol from blood, kidney and liver were 76-99.1%. The half-lives for radioactivity in liver, kidney and adrenal gland were 5.5, 8.5 and 9.5 hours respectively.

Differences were observed in the relative concentrations of metabolites of uniconazole-p in the various tissues of female and male rats. The sex related differences were attributed to the different abilities of male and female rats to biotransform xenobiotics. The major metabolites for both sexes were CH_2OH-7E and COOH-7E for liver and COOH-7E for kidney. Triazole was a major metabolite in blood of males, but minor in that of females. Pre-treatment of rats with uniconazole-p for 14 days did not significantly alter the observed ^{14}C-excretion and ^{14}C-tissue residues. Uniconazole-p was the major component of the radioactive residue in rat liver.

Residue Definition

As regards the residue definition and analytical method. Uniconazole-p comprised the major component of the radioactive residue in both plant and animal tissues. As the analytical method measures both uniconazole and its geometric Z-isomer it is appropriate to include the Z-isomer in the residue definition. The residue definition for uniconazole-p should be established as:
Uniconazole-p the sum of uniconazole-p and its Z-isomer expressed as uniconazole-p

Avocados

Uniconazole-p was applied to avocado orchards with trees at various stages of maturity (8-20 years old) and at a number of different locations in South Africa and Australia. Either a single application (late inflorescence at full bloom) or two applications (early and late inflorescence at full bloom) were made as a foliar spray at various rates. Samples were collected *ca.* one month before harvest, which is typically 5-6 months post-application, and at normal harvest.

No residues of uniconazole-p were detected in any samples of mature fruit that developed from sprayed flowers. The application rates used encompassed those proposed for the Australian registration (50-100 g ai/100 L). The analytical method LOD was 0.02 mg/kg in the South African trials while the LOQ was 0.01 mg/kg in the Australian trial. As the majority of trials were conducted with in South Africa it is appropriate to set the MRL for uniconazole-p in avocados at *0.02 mg/kg.

As uniconazole-p is sprayed at flowering and harvest occurs some 6 months or more later, it is not necessary to set a harvest WHP.

Animal feed commodities

Avocados are not considered an animal feed commodity and it is not necessary to set animal feed MRLs for avocados.

Animal MRLs

No detectable residues are expected in avocados. Additionally, avocados are not normally considered an animal feed. Given the non-detectable residues and the low likelihood of feeding, it is not necessary to set animal commodity MRLs for uniconazole-p.

Storage Stability

All samples were analysed within 1 month of sampling and were stored at <–20°C prior to analysis. It is considered that the short interval between sampling and analysis is sufficient to ensure the results provide a true indication of residues present.

Processing

No processing studies were provided. This is acceptable as no detectable residues are expected and avocados are not usually processed.

Maximum Daily Intake Calculations

The risk to human health from the use of uniconazole-p is considered to be small. The chronic dietary risk is estimated by the national estimated daily intake (NEDI) calculation. The NEDI calculation shows that the intake is equivalent to 0.004% of the ADI for uniconazole-p. As it is widely recognised this calculation is a gross overestimate of actual dietary intake, we conclude that the chronic dietary exposure is small and the risk is acceptable. The estimate of the daily intake is further reduced if the STMR values for avocado are used. In this case the NEDI accounts for 0.002% of the ADI.

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

The company has stated that uniconazole-p is registered for use in on avocados in Israel and South Africa. MRLs have not been set for uniconazole-p in either South Africa or Israel. In addition, uniconazole-p is registered in the USA as a plant growth regulator for ornamentals.

No CODEX MRLs exist for uniconazole-p in avocados and so the use of uniconazole-p may present a risk to Australian trade. Australian avocado production was estimated to be 21,500 tonnes in 1997 (Australian Horticultural Statistics Handbook, 1997/98 edition). The major export markets for Australian avocados are Singapore, Hong Kong and Thailand. In the 1996/97 season a total of 122 tonnes of avocado were exported (value $A395,000). Clearly avocado is a minor export commodity and any economic penalty arising from violations of the standards of importing countries would be small. In addition, residue trials did not detect any residues of uniconazole-p at harvest. The risk to Australian trade in avocados from the use of uniconazole-p is negligible.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Uniconazole-p is not on the NOHSC *List of Designated Hazardous Substances*. Based on the NOHSC *Approved Criteria for Classifying Hazardous Substances,* uniconazole-p is classified as hazardous. This classification is based on evidence that uniconazole-p is of moderate acute oral toxicity. The following risk phrase is allocated to uniconazole-p:

R22 Harmful if swallowed

Uniconazole-p is in the form of white crystalline solid with a faint characteristic odour. Uniconazole-p is of moderate acute oral toxicity, low acute dermal toxicity and low acute inhalation toxicity. It is a slight eye irritant but not a skin irritant in rabbits and does not induce skin sensitisation in guinea pigs.

Substances are hazardous when they contain concentrations of ≥25% uniconazole-p. Sunny cannot be classified as hazardous according to NOSHC criteria as it contains only 5% uniconazole-p.

Sunny is a suspension concentrate formulation. It possesses low acute oral and inhalation toxicity in rats and low acute dermal toxicity in rabbits. The product is a slight eye irritant but not a skin irritant. The product will be supplied in 1 and 5 litre high-density polyethylene (HDPE) bottles.

Formulation, Transport, Storage And Retailing

Sunny will be formulated overseas and imported into Australia in sale packs. Transport workers, storepersons and retailers will handle the packaged product and could only become contaminated if the packaging were breached.

Use

Sunny is proposed for the enhancement and improvement of fruit shape and reduction in vegetative growth in avocados. It will be applied as a high volume (dilute) spray, using orchard spraying equipment fitted with mechanical or hydraulic agitation. The proposed rate is 24L/ha in a minimum 1200L water/ha.

The main route of exposure to the product is dermal. Workers may be exposed to spray mist from the product spray. Functions that can lead to exposure to the product include opening containers, mixing/loading, application, cleaning up spills, and cleaning/maintaining equipment.

Entry Into Treated Areas Or Handling Treated Crops

There are no re-entry studies available for *Sunny*. Based on the toxicity of the product and its use pattern, a re-entry statement is not recommended at this stage.

Recommendations For Safe Use

Workers involved in transport, storage and retailing should be protected by safe work practices and training. Users should follow the instructions on the product label. Based on the toxicity of the active ingredient and the product, cotton overalls buttoned to the neck and wrist and a washable hat and elbow-length PVC gloves are recommended for mixers/loaders and applicators of *Sunny*.

The personal protective equipment recommended should meet the relevant Standard Australian standards specified below:

AS 3765-1990	Clothing for protection against hazardous chemicals
AS 2161-1978	Industrial Safety Gloves and Mittens (Excluding Electrical and Medical Gloves)

Material Safety Data Sheet

Aquamarine BV has produced Material Safety Data Sheets (MSDSs) for uniconazole-p and *Sunny*. 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, when appropriate.

Conclusions

Sunny can be used safely if handled in accordance with the instructions on the product label.

ENVIRONMENTAL ASSESSMENT

Introduction

Aquamarine BV has applied for the registration of the new product, *Sunny* containing the active constituent uniconazole-p at 50 g/L. This product will be used as a plant growth regulator for avocados.

Registration is sought in Queensland, New South Wales and Western Australia. Products containing uniconazole-p have not been previously registered in Australia.

Environmental Fate

Hydrolysis
In a study conducted according to US EPA Guidelines, there was no hydrolysis at pH 4, 7, and 9 after 30 days at 25°C. Hydrolysis is not expected under normal environmental conditions.

Photolysis
In two studies conducted to meet US EPA Guidelines using either phenyl or triazole ring labelled material, the photolytic half-life at pH 7 was determined as 43.5 and 36.5 hours respectively of natural sunlight equivalent. There were a number of degradates noted, seven of which were identified and a degradation scheme proposed. Both studies using the differently radiolabelled material showed the same principal metabolites. The initial product is the Z-isomer (~20%) which undergoes an internal cyclisation to form a tricyclic product (~45%). This product undergoes a number of elimination, oxidation and ring opening reactions to form 4-chloro-2- (1H-1,2,4-triazol-5-yl)-benzaldehyde (~50% at the end of the study). The data from both studies was used in modelling studies that confirmed the proposed scheme.

In soil photolysis studies using either the triazolyl or phenyl ring labelled uniconazole-p, conducted to meet US EPA requirements, the photo-degradation was much slower. Equilibrium was established between the parent compound and its Z-isomer. At the end of both studies, >70% of the originally applied radiolabel was recovered as unchanged parent and around 10% as the Z-isomer. Half-lives of 140.4 days and 78.5 days were derived by extrapolation of the data.

Photolysis in water under Australian conditions could be a significant route of degradation, especial for material directly exposed to light. Degradation is expected to be significantly slower for material not directly exposed. Photolysis on soil is not expected to be a significant route of degradation.

Metabolism
A single aerobic soil degradation study, generally conducted to meet US EPA and European Guidelines, used a single soil, with an incubation period of 1 year. At the completion of the study >80% of the originally applied radiolabel was recovered as unchanged parent, and a half-life of 1450 d was determined by extrapolation. There were three metabolites found, two were present in level <1% and were not identified, the third was identified and was present at levels below 3%. Uniconazole-p is rated as very slightly degradable in laboratory studies in the dark from this single soil. However, no data are available to clarify whether persistence may be expected in the field.

Mobility
In batch adsorption/desorption studies performed to meet US EPA requirements using 11 different soils from the Japan, the K_{oc} ranged from 240 for a sandy loam to 1,100 for a loam. Uniconazole-p was rated as having low to medium mobility in the soils tested.

Four of the soils (a sand, three sandy loams) used in the adsorption/desorption studies were used in the column leaching studies of fresh and 28 day aged samples, conducted to US EPA. Leaching was observed in the sandy soil but not in three sandy loam soils.

Field Dissipation
A soil dissipation study conducted on two soils showed some evidence for an initial rapid dissipation on one of the soils. However, a significant amount of remained after the initial dissipation and dissipated with a half-life >100 days.

Environmental Toxicity

Uniconazole-p was slightly toxic to bobwhite quail in both acute oral and 5-day dietary studies. Similarly, the 5-day dietary study in mallard ducks showed that uniconazole-p was slightly toxic to mallard ducks.

Aquatic toxicity studies for uniconazole-p indicate that it is moderately toxic to carp and slightly toxic to Rainbow trout. Results from the *Daphnia* study are inconclusive, it is possible that with a longer period of observation immobilisation of all or some of the effected *Daphnids* at the 10 mg a.i./L may result and hence uniconazole-p may be classified as moderately toxic to *Daphnids*.

Uniconazole-p is relatively non-toxic to honey bees based on a single acute contact toxicity study. Uniconazole-p is very slightly toxic to earthworms. Treatment of soils with levels up to 12× the maximum proposed application rate had no effect on the respiration of soil organisms.

There are no data for algae/aquatic plants.

Prediction of Environmental Hazard

Hazard Arising From Use
It is proposed that *Sunny* be applied to avocados once per year. It is to be applied with ground based spray rigs in such a manner as to cover the top two thirds of the canopy without run-off.

Exposure of non-target organisms may occur through direct contact of treated trees, spray drift or from run-off. Volatilisation is unlikely to occur.
Birds
As a worst case, assuming that a mallard duck (most sensitive species tested) consumed short range grass treated with the maximum application rate of uniconazole-p as 100% of its diet. Based on estimated residue levels the calculated Q value (EEC/LC50) for mallard duck is < 0.1, indicating an acceptable dietary hazard for birds from uniconazole-p. In addition, avocados do not carry ripe fruit

likely to attract birds. Hence, the use of uniconazole-p as proposed is not expected to result in a hazard to birds.

Aquatic organisms
Based on the maximum application rate and either direct overspray or 10% spray drift into a 15 cm deep 1 ha pond the concentrations will be 0.8 and 0.08 mg/L, respectively. These are below toxic levels and the calculated Q value indicate that the use of uniconazole-p at the maximum rate would not be expected to have adverse effect on fish or aquatic invertebrates except for rainbow trout in the event of direct overspray of a water body. Direct overspray of a water body is not expected as it is anticipated that the product will only be applied with ground rigs.

However, no indication of the toxicity of uniconazole-p to algae or aquatic plants has been provided. Hence, the potential hazard to algae and aquatic plants has not been evaluated.

Non-Target Invertebrates
The maximum application rate of uniconazole-p of 1.2 kg/ha corresponds to 12 µg/cm^2. Assuming that a bee in a spray cloud has a target area of 1 cm^2 an exposure level of approximately 12 µg/bee may be expected if uniconazole-p is sprayed at the maximum rate. At the minimum recommended rate (0.6 kg/ha) an exposure rate of 6 µg/bee would be expected. The contact LD50 for bees was >20 µg/bee, with no mortalities observed at test concentrations up to 20 µg/bee. Thus, it is anticipated that bees in the trees at the time of spraying, timed to coincide with flowering, would not receive a lethal dose of uniconazole-p.

As a worst case, the maximum application rate applied directly to the soil would give an EEC of 9.2 mg/kg soil in the top 1 cm of soil. Assuming an LC50 for earthworms of 1,000 mg/kg soil this would give a Q value <0.01. Hence, it is not expected that the proposed use of uniconazole-p on avocados will present a hazard to earthworms.

The results of the soil respiration study indicate that the proposed use of uniconazole should not present a hazard to soil respiration.

Desirable vegetation
When used according to label directions, the exposure, and therefore the hazard, to native and non-target vegetation should be negligible.

Conclusion

Considering the restricted use pattern, when used according to label directions and good agricultural practice, the hazard is limited but every care should be taken not to contaminate natural waterways with this product. The draft labels contain warning statements to this effect that are satisfactory.

EFFICACY AND CROP SAFETY ASSESSMENT

This summarizes the trials conducted in Australia and overseas with *Sunny* (containing the active constituent uniconazole-p), providing information in relation to improvement of fruit shape, reduction in vegetative growth and crop safety in avocados.

Efficacy

This product should prove to be a valuable tool for those avocado growers seeking to improve their commercial viability by producing more marketable fruit. *Sunny* should be used as part of an integrated management strategy on well maintained orchards. Data from trials and commercial use of the product in Israel and South Africa over the last ten years clearly demonstrate that claims of improved fruit shape and reduced vegetative growth are justified when the product is used on healthy, unstressed trees. Data from local trials conducted over the last two seasons have confirmed these claims under Australian conditions.

Crop Safety

In all trials, both Australian and overseas, no phytotoxic damage was observed on leaves or flowers following the foliar applications of *Sunny* and there was no affect on tree health as further supported by the yield data. The same results were obtained when the Australian trials were conducted with the same treatments on the same trees for two consecutive seasons.

There has been some concern expressed on the long term use of *Sunny* and other triazole products on the sustainable health of avocado trees. The use of *Sunny* on avocado trees to promote increased fruit size and greater yield does impose some stress levels on the tree as a greater proportion of available resources are diverted to fruit and less are available for growth in other parts of the tree. It is essential therefore that trees are maintained in optimum condition and careful attention needs to be paid to overall orchard management, control of Phytophthora root rot, management of alternate bearing and timely harvesting ("hanging" fruit will continue to use the tree's resources). The product should not be used without the advice of the distributors, Sumitomo Chemical Australia.

Conclusion

Sufficient data from suitably designed, scientifically conducted and statistically analysed trials has been presented to substantiate the claims for use as shown on the draft label. As long as the product is used according to label instructions and Good Agricultural Practice it should be suitable for the proposed purpose.

Proposed Draft Label

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

SUNNY
Plant Growth Regulator

ACTIVE CONSTITUENT: 50 g/L **UNICONAZOLE-P**

A plant growth regulating material for enhancement and improvement of fruit shape and reduction in vegetative growth

Contents: 1 L, 5 L

Distributed By: Sumitomo Chemical Australia Pty Ltd
501 Victoria Avenue
CHATSWOOD NSW 2967

EMERGENCY TELEPHONE: 1800 024 973

Facsimile: (02) 9904 7499
ACN 081 096 255

DIRECTIONS FOR USE:
For technical advice on the use of this product, consult Sumitomo Chemicals Australia Pty Ltd on (02) 9904 6499

RESTRAINTS:
DO NOT use on avocado trees which are under stress – see Orchard Management in General Instructions
DO NOT allow spray mixture to stand for prolonged periods
DO NOT mix with very hard water (> 1000 mg/kg solutes)
DO NOT mix with water which has a pH outside the range 4.5 - 5.5

Situation	Purpose	State	Rate	Critical Comments
Avocados (Fuerte, Hass, Pinkerton)	Enhancement and improvement of fruit shape Reduction in vegetative growth	NSW, QLD, WA only	1 - 2 L plus 2 L UP 50/100 L water or anionic wetting agent at 0.05%	Spray at flowering. Do not apply to trees on which fruit are present. In most fully grown orchards use 1200 L spray mixture/ha. Reduce proportionally for smaller trees Growing conditions can affect plant response to this product, i.e. day length, temperature, water regime, seasonal factors etc. Dose rate will depend on factors such as uniformity of flush, tree vigour etc and growers should consult Sumitomo Chemical Australia before deciding on the dose rate applicable to their orchard. See Orchard Management in General Instructions

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

WITHHOLDING PERIOD: NOT REQUIRED WHEN USED AS DIRECTED.

GENERAL INSTRUCTIONS:
Sunny is a plant growth regulator, which acts by influencing gibberellin production. The major effect of Sunny on avocados is the enhancement and improvement of fruit shape. An improved fruit size distribution and yield improvement are often associated with the use of Sunny. Sunny should only be used on healthy trees in well-managed orchards.

Orchard Management:
1. Do not apply Sunny® to trees that have shed more than 15% of their leaves when flowering as it is likely that these trees have a significant level of Phytophthora infection;
2. Harvest Sunny®-treated trees as soon as the fruit reaches maturity as "hanging" fruit will continue to accumulate oil to the detriment of flowering and cropping the following season.
3. Maintain optimum growing conditions and practise close orchard management to minimise stress and alternate bearing.

MIXING INSTRUCTIONS:
Shake container well before use. Half fill the spray tank with clean water and whilst constantly agitating add the required amount of Sunny. Thereafter, add 2% of UP 50 foliar feed or a registered anionic wetting agent at 0.05%. Fill the spray tank to the required level with water while agitating. Ensure vigorous agitation of the mixture in the tank during mixing and spraying.

SAFETY DIRECTIONS:
Will irritate the eyes. Avoid contact with eyes. Wash hands after use. When opening the container, preparing the spray and using the prepared spray, wear cotton overalls buttoned to the neck and wrist, a washable hat and elbow-length PVC gloves. After each day's use, wash gloves and contaminated clothing.

FIRST AID:
If poisoning occurs contact a doctor or Poisons Information Centre (Telephone: 13 1126)

PROTECTION OF LIVESTOCK, WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

Do not contaminate streams, rivers, waterways or dams with the chemical or used containers. Do not allow the chemical to contact other crops, pastures or desirable vegetation.

STORAGE:

Keep out of reach of children. Store in the closed original container in a well ventilated area, as cool as possible. Do not store for prolonged periods in direct sunlight.

DISPOSAL:

Triple, or preferably pressure, rinse containers before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemical 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. Empty containers and product should not be burnt.

MSDS: An MSDS is available for this product by telephoning the number shown

Batch No Date of Manufacture

CONDITIONS OF SALE:

The use of SUNNY being beyond the control of the manufacturer, no warranty expressed or implied is given by Sumitomo Chemical Australia Pty Ltd regarding its suitability, fitness or efficiency for any purpose for which it is used by the buyer, whether in accordance with the directions for use or not and Sumitomo Chemical Australia Pty Ltd accepts no responsibility for any consequences whatsoever resulting from the use of this product.

NRA Approval Number:

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 octonol water partitioning co-efficient.
Metabolism	The conversion of food into energy
Photodegradation	Breakdown of chemicals due to the action of light.
Photolysis	Breakdown of chemicals due to the action of light.
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body.
Toxicology	The study of the nature and effects of poisons.

Bibliography/Further Reading

Biologische Bundesanstalt für Land- und Forstwirtschaft Verzeichnis zugelassener Pflanzenschutzmittel (BBA) (Federal Biological Research Centre for Agriculture and Forestry), Berlin http://www.bba.de/english/bbaeng.htm

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

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

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

National Registration Authority for Agricultural and Veterinary Chemicals 1997, *Ag Requirements Series: Guidelines for Registering Agricultural Chemicals*, NRA, Canberra.

National Registration Authority for Agricultural and Veterinary Chemicals 1996, *MRL Standard: Maximum Residue Limits in Food and Animal Feedstuffs*, NRA, Canberra.

National Registration Authority for Agricultural and Veterinary Chemicals 1997, *Ag Labelling Code—Code of Practice for Labelling Agricultural Chemical Products*, NRA, Canberra.

Organisation for Economic Co-operation and Development, Paris FRANCE http://www.oecd.org/ehs/pest_tg.htm

United States Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances (OPPTS), Office of Pesticide Programs (OPP). http://www.epa.gov/OPPTS_Harmonized/

NRA PUBLICATIONS ORDER FORM

To receive a copy of the full technical report for the evaluation of uniconazole-p in the product ***Sunny Plant Growth Regulator***, 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 (02) 62723218.

Name (Mr, Mrs, Ms, Dr)_____

Position _____

Company/organisation _____

Address _____

Contact phone number (___) _____

I enclose payment by cheque, money order or credit card for $_____

Make cheques payable to 'National Registration Authority'.

___ Bankcard ___ Visa ___ MasterCard ___ Amex

Card number _____/_____/_____/_____ Expiry date ...../...../.....

Signature_____ Date _____