Public Release Summary
on

Evaluation of the new active

AMINOETHOXYVINYLGLYCINE (AVG)

in the product

RETAIN PLANT GROWTH REGULATOR

National Registration Authority
for Agricultural and Veterinary Chemicals

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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 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.

CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ANZFA	Australia New Zealand Food Authority
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	Bodyweight
d	Day
DM	Dry Matter
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EUP	End Use Product
FAO	Food and Agriculture Organisation of the United Nations
F_o	original parent generation
g	Gram
GAP	Good Agricultural Practice
GC- MSD	Gas Chromatography with Mass Selective Detector
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	Hour
ha	Hectare
Hct	Haematocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HPLC-UV	High Performance Liquid Chromatography with Ultra-Violet detector
id	Intradermal
im	Intramuscular
ip	Intraperitoneal
IPM	Integrated Pest Management
iv	Intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	Kilogram
K_{oc}	Organic carbon partitioning coefficient

L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	Milligram
mL	Millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
ng	Nanogram
NHMRC	National Health and Medical Research Council
NOEC	No Observable Effect Concentration
NOEL	No Observable Effect Level
OC	Organic Carbon
OM	Organic Matter
PHI	Pre-Harvest Interval
po	Oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RAC	Raw Agricultural Commodity
RBC	Red Blood Cell Count
s	Second
sc	Subcutaneous
SC	Suspension Concentrate
SPE	Solid Phase Extraction
STMR	Supervised Trials Median Residue
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
TRR	Total Radioactive Residues
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
m**g**	Microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHO	World Health Organisation
WHP	Withholding Period

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of *RETAIN® PLANT GROWTH REGULATOR (RETAIN®)*, which contains the new active ingredient aminoethoxyvinylglycine (AVG).

Responses to this Public Release Summary (PRS) will be taken into account by the National Registration Authority (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 AVG, covering toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the NRA upon request (see order form on last page). They can also viewed at the NRA Library, located at the NRA's offices, Ground Floor, 22 Brisbane Avenue, Barton, ACT.

Written comments should be submitted by Monday **17 September 2001**, and addressed to:

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Applicant

Valent BioSciences (a division of Sumitomo Chemical Australia Pty Limited)

Product Details

It is proposed to register *RETAIN®*, containing 150g/kg AVG, as a water soluble powder. The product will be imported fully formulated and packaged in 415 g water soluble bags, from the USA.

The product is for use in apples, peaches and nectarines, to improve harvest management, fruit quality and storage potential. The rationale behind the product, is that AVG is a fermentation metabolite that inhibits endogenous production of ethylene in plant tissues. Ethylene affects plant processes such as fruit maturation, ripening and abcisssion.

The rate of product use is 830 g/ha. *RETAIN®* is proposed for registration in all states.

Products containing AVG are registered for use on apples in Mexico, Canada (temporary), USA, South Africa, New Zealand, Chile and South Korea. An application for registration, for use in apples, has also been submitted in Taiwan.

As yet, there are no overseas registrations for AVG in stone fruit. Registration applications for use in peaches and/or nectarines have been submitted in South Africa, New Zealand, South Korea and Taiwan.

CHEMISTRY AND MANUFACTURE

ACTIVE CONSTITUENT

Manufacturers

The active constituent in *RETAIN*® is aminoethoxyvinylglycine (AVG). AVG is an approved TGAC for use in Australia (approval number 51106, held by Valent BioSciences – A division of Sumitomo Chemical Australia). The TGAC is manufactured by Abbott Laboratories, 1401 Sheridan Road, North Chicago, USA.

Common name: Aminoethoxyvinylglycine (AVG) hydrochloride
IUPAC name: (S)-trans-2-amino-4-[2-aminoethoxy]-3-butenoic acid hydrochloride
CAS name: L-alpha-(2-aminoethoxyvinyl)glycine hydrochloride
CAS Number: 55720-26-8
Manufacturer's code: ABG-3097

Physical and Chemical Properties

Physical state:	Fine powder
Colour:	Beige to off-white
Physical state	Crystalline solid
Odour	Amine like
Melting point	178 - 183°C (with decomposition)
Specific gravity (density)	0.42±0.06 g/cm^3 at room temperature (RT)
Water solubility	421.8 g/mL
Solubility in other solvents	0.2 g/mL in methanol 0.00046 – 0.017 g/mL in hexane (at RT)
Dissociation constants (pKa)	1) 2.84 2) 8.81 3) 9.95 (at 20°C)
Octanol/water partition coefficient	Log P_{OW} = -3.98
pH	6.9 ± 0.4 (1% solution at RT)
UV /visible absorbance	No peaks between 200 and 600 nm
Storage stability:	Product is stable and is not corrosive

Summary of the NRA's Evaluation of AVG Technical Grade Active Constituent (TGAC)

The Chemistry and Residues Evaluation Section of the NRA has evaluated the chemistry aspects of AVG TGAC (manufacturing process, quality control procedures, batch analysis results and analytical methods), and found them to be acceptable.

On the basis of the data provided, it is proposed that the following Minimum Compositional Standard be established for AVG TGAC:

Active constituent	**Minimum content**
Aminoethoxyvinylglycine	Not less than 800 g/kg

Other compounds of toxicological significance are not expected to occur in AVG TGAC as a result of the raw materials and the synthetic route used.

The Chemicals and Non-Prescription Medicines Branch of the Therapeutic Goods Administration has considered the toxicological aspects of AVG TGAC, and advised that there are no toxicological objections to the approval of this chemical.

The NRA accepts the findings and recommendations of its advisers on these criteria.

The NRA is satisfied that the proposed importation and use of AVG TGAC would not be an undue toxicological hazard to the safety of people exposed to it during its handling and use.

PRODUCT

Distinguishing name:	*RETAIN PLANT GROWTH REGULATOR*®
Formulation type:	Water soluble powder (in water soluble bag)
Active constituent concentration:	Aminoethoxyvinylglycine (AVG) 150 g/kg

Physical and Chemical Properties of the Product

Physical state:	Fine powder
Colour:	Off-white – pale yellow
Odour	Odourless
Specific gravity	0.78 ± 0.15 g/cm^3
pH	5.5 ± 0.2 (10% aqueous solution)
Corrosive hazard	Non-corrosive
Biological hazard	None
Dangerous goods classification	Not a dangerous good
Storage stability:	Stability data provided by the applicant demonstrate the stability of the product, when stored for 24 months at 25°C and 14 days at 54°C.

Recommendation

Based on a review of the chemistry and manufacturing details provided by the applicant, registration of *RETAIN*® **is supported**.

TOXICOLOGICAL ASSESSMENT

Evaluation of Toxicology

The toxicological database for aminoethoxyvinylglycine (AVG), which consists primarily of toxicity tests conducted using animals, although lacking a chronic toxicity study, is quite extensive. In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available.

Where possible, considerations of the species-specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are used to develop acceptable limits for dietary or other intakes at which no adverse health effects in humans would be expected.

Toxicokinetics and Metabolism

Following a single oral dose of 2.25 or 50 mg/kg bw of ^{14}C-AVG to **rats**, absorption was rapid and extensive, although not complete (over 80% of the administered dose), and excretion was prolonged over many days. The primary route of excretion was via the urine (approximately 57 to 74%) with faecal excretion a minor route (11.4 to 13.6%). Elimination in expired air was substantial at a dose of 2.25 mg/kg bw (18 to 22%) but much less significant at 50 mg/kg bw (4.8%). Unchanged AVG accounted for only a small proportion of recovered radiolabel with the bulk of that recovered accounted for by; alpha-N-acetyl- AVG, a series of peaks described only as “polars” and an unidentified metabolite. A minor metabolite identified, at 1.6 and 4.3% of the low dose, was terminal-N-acetyl-AVG, the major metabolite in apples.

Acute Studies

AVG was of low oral toxicity in **rats** (LD_{50} = 6480 mg/kg bw), low dermal toxicity in **rabbits** (LD_{50} >2000 mg/kg bw, no deaths) and moderate inhalation toxicity in **rats** (LC_{50} = 1130 mg/m^3). It was a slight skin irritant and a moderate eye irritant in **rabbits**, but was not a skin sensitiser in **guinea pigs**.

The product *RETAIN*® has low oral and inhalational toxicity in the **rat** (LD_{50} >7000 mg/kg bw, LC_{50} >1450 mg/m^3), low dermal toxicity in the **rabbit** (LD_{50} >5000 mg/kg bw), is not a skin irritant but is a slight eye irritant in the **rabbit**. Based on a consideration of the skin sensitising properties of the individual ingredients, the product is not considered likely to be a skin sensitiser.

Short-Term Studies

Repeat dose studies with AVG have been conducted in **rats** over periods of 28 days (administered in the diet at levels equivalent to doses of 0, 0.5, 2.5, 5 or 15 mg/kg bw/day), 21 days (applied dermally at 0, 100, 500 or 1000 mg/kg bw/day), and for 90 days in two separate studies (administered in the diet at levels equivalent to doses of 0.5, 2.0 and 10 mg/kg/day and 0, 0.2, 0.4 and 4.0 mg/kg bw/day).

In all these studies the most sensitive indicator of AVG effects was a reduction in the activity in the blood of liver derived enzymes (AST and ALT), and this was the only effect seen in the dermal study at the highest dose of 1000 mg/kg bw/day. This reduction in enzyme activity is not an adverse effect in itself, but is a marker for the pharmacological activity of AVG (AVG is an inhibitor of pyridoxal phosphate dependent enzymes, of which class AST and ALT are members). At oral doses of 5 mg/kg bw/day and above animals tended to eat less and at 4 mg/kg bw/day and above tended to gain less weight. The weights of the liver and kidneys tended to increase in animals treated at 2 to 4 mg/kg bw/day and above Microscopic changes were also seen in the cellular structure of these organs (hepatocellular vacuolation, vacuolation and fatty changes of renal proximal convoluted tubule epithelium, kidney inflammation) from 0.5 mg/kg bw/day for the liver and from 2 mg/kg bw/day for the kidney. After 90 days at 10 mg/kg bw/day inflammation of the muscular wall of the heart was more common in males and white blood cell counts (lymphocytes) were reduced in both sexes. The overall NOEL across all these studies was 0.2 mg/kg bw/day based on a reduction in blood AST activity at higher doses.

Long-Term Studies

No long term studies have been conducted with AVG.

Reproduction and Developmental Studies

Rats were treated in the diet with AVG in the diet at 0, 0.4, 2.2, 4.0 and 8.0 mg/kg bw/day, from before mating through until females had weaned their pups. Clinical signs were minimal and confined to mild constipation. During the first few weeks of the study animals treated at 4 and 8 mg/kg bw/day gained less weight and ate less. The fertility of females at 8 mg/kg bw/day was reduced, as was the proportion of males which sired a litter. At 8 mg/kg bw/day the length of pregnancy was prolonged, the number of pups born alive, the number of implantation sites and pup survival were reduced, and at 4 and 8 mg/kg bw/day pup weights were lower. Prostate weights were lower in adult males at 8 mg/kg bw/day There were no effects at 2.2 mg/kg bw/day.

Rats were treated with AVG in the diet at 0, 0.8, 2.5, 4.0 and 8.0 mg/kg bw/day through 2 successive generations. At 4 and 8 mg/kg bw/day parental animals ate less and gained less weight, pregnancy rates were reduced, total litter loss was increased, some males had smaller testes and epididymides, abscesses and/or enlarged and/or firm mammary glands were seen in some females, and liver weights were increased in both sexes. Kidney weights were increased and microscopic changes in the liver (periportal hepatocellular vacuolation) was more common at all doses primarily in males. At 8 mg/kg bw/day, the sperm had decreased movement and more commonly had an abnormal shape. Microscopic structural alterations were seen in the testes and epididymides (cellular debris in the epididymides, vacuolation of the seminiferous epithelium, degeneration of the seminiferous tubule and multinucleate giant cells in the testis) at 8 mg/kg bw/day.

Reduced thymus weight and size were observed in parental animals, occasionally at 2.5 mg/kg bw/day and more generally at 4 and 8 mg/kg bw/day. This correlated with depletion of tissues related to immune function (lymphoid tissue) in males at 4 and 8 mg/kg bw/day and females at 8 mg/kg bw/day, and cysts were noted at 8 mg/kg bw/day in some animals. The live litter size and the post natal survival rate were reduced at 4 and 8 mg/kg bw/day. Pup weights were lower at 2.5 mg/kg bw/day and above. Behaviour abnormalities were noted in a few first generation pups at 8 mg/kg bw/day (rocking, swaying or lurching, impaired use of the hindlimbs and reduced activity) and clinical signs were more common in second generation pups. These consisted of being cool to the touch, pale in colour, having an unkempt appearance, and laboured respiration at 4 and/or 8 mg/kg bw/day. Exfoliation of appendages was noted in some pups at 8 mg/kg bw/day as was hair loss of the hindlimbs and blackening and swelling of the tail tip. Early developmental landmarks (balanopreputial separation and vaginal patency) were delayed in the first generation of pups at 8 mg/kg bw/day. Pup spleen weights were decreased at 8 mg/kg bw/day in both generations. There were no neonatal effects at 0.8 mg/kg bw/day, parental toxicity was seen at all doses but there were no effects on reproduction at 2.5 mg/kg bw/day.

AVG was not a teratogen when administered to pregnant **rats** during the period of foetal organ formation at oral doses of 0, 0.5, 2.2 or 10 mg/kg bw/day. Maternal toxicity at 10 mg/kg bw/day, was minimal, consisting of red material around the nose, decreased defecation, reduced food consumption, lower body weight gains, and lower pregnant uterine weights. Effects on the foetuses were confined to lower body weights and delays in bone calcification. The NOEL for maternal and embryofoetal toxicity was 2.2 mg/kg bw/day.

Genotoxicity
AVG did not induce mutation in ***Salmonella typhimurium*** at up to 5000 µg/plate (+S9/-S9) or cultured L5178Y mouse lymphoma cells at up to 5000 µg/ml (+S9/-S9). An *in vivo* bone marrow micronucleus test in rats at oral doses of up to 5000 mg/kg bw was also negative.

Special Studies
In an immunotoxicity study (SRBC), female **rats** were administered doses of 0, 1.25, 2.5, 5 or 15 mg/kg bw/day AVG in the diet for 4 weeks with a recovery period, without treatment, of a further 4 weeks. At 15 mg/kg bw/day, decreased activity, rough fur, coldness to the touch and emaciated appearance were seen in 2 rats, animals ate less and gained considerably less weight, and thymus weights were reduced at the end of the treatment period, but had returned to control levels after 4 weeks without treatment. Marked immunosuppression was observed at 15 mg/kg bw/day only, which largely, but not completely, resolved after 4 weeks without treatment.

PUBLIC HEALTH STANDARDS

Poisons Scheduling

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

On the basis of its toxicity, the NDPSC included AVG in Schedule 6 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) with preparations containing 15% or less of AVG exempt from scheduling. Consequently the product *RETAIN*® is not scheduled.

There are provisions for appropriate warning statements and first-aid instructions on the product label.

NOEL/ADI
Based on the NOEL of 0.2 mg/kg bw/day in the 90-day **rat** dietary study and a safety factor of 1000 to reflect the lack of a chronic toxicity study, the Acceptable Daily Intake (ADI) for AVG is 0.0002 mg/kg bw/day.

Summary

The product *RETAIN*® is a soluble powder formulation containing the active ingredient AVG at 150 g/kg which is new to the Australian market.

AVG is rapidly and extensively absorbed following oral administration and excreted primarily in the urine over 2 to 3 days. The acute oral and dermal toxicity of AVG is low. The inhalational toxicity is moderate and the compound is a slight skin and moderate eye irritant but not a skin sensitiser. The product, *RETAIN*®, has a similar acute toxicity profile except that the inhalational toxicity is low, it does not irritate the skin and the eye irritancy is only slight.

In repeat-dose studies in **rats**, the primary effect of AVG were alterations in the microscopic structure of the liver and kidneys and a reduction in the activity of marker enzymes in the blood (AST and ALT). The reduction in AST and ALT activity is not an adverse effect in itself but is a useful measure of AVG exposure. As the duration of dosing was increased the dose at which effects were seen substantially decreased. Some evidence of a suppressed immunity was also seen but only at the high doses. Although there were no long-term dosing studies several specialised studies have shown that AVG does not damage genetic material. In reproduction studies, high doses of AVG caused a reduction in fertility, pup survival and development. However, a clear no effect level for all reproductive and developmental effects was established.

In **mammals** the proposed mode of action of AVG involves inactivation of an enzyme involved in the formation of the essential amino acid, L-cysteine. Since this amino acid is necessary for the normal synthesis of protein in the liver, there will be a reversible reduction in protein synthesis activity with increasing duration of exposure to AVG. Many of the effects observed at higher doses, reduced weight gain and changes in the liver and kidneys for example, are therefore likely to be a reflection of this mechanism.

Conclusion

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

RESIDUES ASSESSMENT

The Chemistry and Residues section of the NRA has undertaken a residues assessment of a formulated product based on the new active constituent aminoethoxyvinylglycine (AVG).

Data concerning residues in apple, peach, nectarine, metabolism in plants and animals and chemistry were considered as part of the residue evaluation of the application.

Metabolism

In **rats** the major route of elimination of radiolabelled AVG was urine. Urinary elimination accounted for up to 60.4% and 74.0% of the dose following a single oral administration at 2.25 mg/kg and 50 mg/kg respectively. Feacal elimination accounted for up to 14.5% and 12.7% of the dose following the low and high dosage respectively. The amounts of radioactivity in the tissues and carcasses 168 hours after the low and high dose were up to 4.7% and 8.4% of the dose respectively. The main urinary metabolites were the terminal- and N-acetylated derivatives of AVG. The terminal-acetylated derivative, which was observed as the major metabolite in apples, accounted for 10.2% of the dose in high dose male rats.

In apples translocation of AVG from leaves to fruit was negligible. In fruit treated directly with AVG approximately 50-100% of the total radioactive residues were removed by rinsing in water. Parent compound was always the major residue in the surface rinse solutions. A number of metabolites or degradants were observed in the rinse solution, peel and pulp, although they generally accounted for less than 10% of the Total Radioactive Residues (TRR) individually.

The only metabolite found to be present at greater than 10% of the TRR was subsequently identified as terminal-N-acetyl AVG. This metabolite was observed in the rat and was tentatively identified as being present in the goat.

Analytical methods

AVG is extracted from homogenised apple or stone fruit samples with a phosphate buffer. The extract is filtered and cleaned up by solid phase extraction (SPE) on a strong cation exchange cartridge. Residues are determined by high performance liquid chromatography (HPLC) with fluorescence detection and pre-column derivitisation. The derivitisation is performed by reaction of AVG with o-phthaldialdehyde. Limits of Quantitation (LOQ) were in the range 10-50 µg/kg. Suitable validation data were provided.

Storage stability

Samples of apple, nectarine and peach were stored frozen for less than 6 months prior to determination of residues. Storage stability data for apple, apple juice, wet apple pomace and peach were provided and indicate that residues do not degrade significantly when stored frozen for 6-12 months. The results obtained in the residue trials are considered an accurate reflection of the residues present at sampling.

Residue definition

The parent compound is adequate for the purpose of monitoring Good Agricultural Practice (GAP). The residue definition should be aminoethoxyvinylglycine *per se*. Note that the common name refers to the hydrochloride salt.

Residue trials

Apple (125 g ai/ha, single application, 7 day WHP)
Residue field trials conducted in Australia, New Zealand and the US were provided for evaluation. All trials included treatments that were consistent with proposed Australian GAP.

Residues in apples harvested 7 days after a single application at 125 g ai/ha were (median underlined) <20, <20, <20, <30, <30, <30, <30, <u>≤30</u>, <30, <30, 29, 39, 41, 51, 52 µg/kg (n=15). A Maximum Residue Limit (MRL) of 0.1 mg/kg (equivalent to 100 µg/kg) is appropriate.

Peach and nectarine (125 g ai/ha, single application, 7 day WHP)
Residue field trials conducted in Australia and the US were provided for evaluation. All trials included treatments that were consistent with proposed Australian GAP.

AVG residues in peaches harvested 7 days after treatment at 125 g ai/ha were (median underlined) <20, <24, <24, <24, <30, <u>≤50</u>, <u>≤50</u>, 30, 49, 66, 75 and 102 µg/kg (n=12). An MRL of 0.2 mg/kg (ie. 200 µg/kg) is considered appropriate for peaches.

A single trial on nectarines was provided (AVG <10 µg/kg at 7 day PHI). Extrapolation of residue data from peaches to nectarines is acceptable. An MRL of 0.2 mg/kg (ie. 200 µg/kg) is also appropriate for nectarines.

Processing studies
Processing studies were undertaken in conjunction with two of the US residue trials on apples. AVG concentrated slightly in pomace (processing factors 1.30 & 2.13) but were depleted in juice (0.59 & 0.51) and wet pomace (0.76 & 0.50). The metabolism study in apples indicated that approximately 50-90% of the total radioactive residue was removed by rinsing the fruit in water.

Animal feed commodity MRLs
Based on a review of 15 residue trials, the supervised trials median residue (STMR) for apple Raw Agricultural Commodity (RAC) was less than the LOQ of the analytical method. AVG concentrates only slightly in pomace (dry) and this is likely to be due to reduction in water content rather than preferential partitioning into the pomace fraction. Quantifiable residues are unlikely to occur in apple pomace and consequently an MRL will not be recommended at this time.

Animal commodity MRLs
Given that quantifiable residues are not expected to occur in animal feed commodities it is concluded that the risk of AVG residues occurring in animal tissues is small. Consequently, no animal commodity MRLs will be recommended at this time.

Estimated dietary intakes
The chronic dietary risk is estimated by the National Estimated Daily Intake (NEDI) calculation, encompassing all registered/temporary uses of the chemical and dietary intake data from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with accepted guidelines. [Φ]

[Φ] Guidelines for predicting dietary intake of pesticide residues (revised), World Health Organisation, 1997.

The NEDI for AVG is equivalent to 30% of the ADI. It is concluded that the chronic dietary exposure is small and the risk is acceptable.

Bioaccumulation potential
AVG has a calculated log P value of –3.98 indicating that it is unlikely to preferentially concentrate in fat. The **goat** metabolism study (although incomplete) did not indicate that AVG concentrates in the fat. Total residues in fat were approximately 10-30% of total AVG residues in muscle.

Recommendations

Registration of the product:
Registration of *RETAIN*® for use on apples and peaches is **supported** on the basis of evaluation of the residue data.

Recommended amendments to the MRL Standard:

Table 1

Compound	Food		**MRL (mg/kg)**
Aminoethoxyvinylglycine			
Delete	FP 0226	Apple	T 0.1
	FS 0012	Stone fruit	T 0.2
Add	FP 0226	Apple	0.1
	FS0247	Peach	0.2
	FS 0245	Nectarine	0.2
	FS 0012	Stone fruit [except peach, nectarine]	T 0.2

The temporary MRL is to be retained to cover product evaluation trials under an existing permit.

The MRL recommendations indicated above will be conveyed to the Australia and New Zealand Food Authority (ANZFA), for consideration for incorporation into Standard A14 of the Food Standards Code and consequent adoption into the State/Territory food legislation.

Withholding periods:
DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION.

Protection statement:
DO NOT DO NOT GRAZE TREATED VEGETATION , OR CUT FOR STOCK FOOD.

SUMMARY

Residues of AVG were found predominantly on the surface of apples and were largely removed by rinsing with water. One significant metabolite was present and was identified as terminal-N-acetyl AVG. The major apple metabolite was also observed in the rat and tentatively identified in the goat.
The residue definition should be aminoethoxyvinylglycine *per se*.
Residue field trial data were presented for apples, peaches and nectarines and allowed the recommendation of suitable MRLs.
Registration of *RETAIN*® is unlikely to pose an undue risk to human health or trade.
Amendments to the *MRL Standard* are recommended.
The following withholding period statement is recommended in conjunction with the above MRLs:
DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION.

The following protection statement is recommended:
DO NOT GRAZE TREATED VEGETATION, OR CUT FOR STOCK FOOD.

Commodities exported and main destinations

Australian exports of **apples** (1997/98, Australian Horticultural Statistics Handbook, 1999-2000)

Destination	Volume, tonnes (Value, $'000)	
Malaysia	12,976	(11,199)
Singapore	8,839	(8,665)
United Kingdom	2,906	(7,300)
Sri Lanka	2,729	(2,238)
Indonesia	1,748	(1,688)
Philippines	1,328	(813)
Hong Kong	1,326	(1,505)
Taiwan	1,228	(1,754)
Fiji	1,015	(736)
Papua New Guinea	924	(1,043)
Other	1,022	(1,363)
Total of all destinations	**36,041**	**(38,304)**

Australian exports of **peaches** (1997/98, Australian Horticultural Statistics Handbook, 1999-2000)

Destination	Volume, tonnes (Value, $'000)	
Singapore	261	(624)
United Arab Emirates	145	(396)
Saudi Arabia	77	(262)
Malaysia	40	(110)
Taiwan	33	(112)
France	23	(79)
United Kingdom	16	(60)
Hong Kong	12	(44)
Italy	5	(12)
Bahrain	3.2	(14)
Indonesia	1	(5)
Other	4.1	(11.6)
Total of all destinations	**620**	**(1,730)**

Australian exports of **nectarines** (1997/98, Australian Horticultural Statistics Handbook, 1999-2000)

Destination	Volume, tonnes (Value, $'000)	
Taiwan	1088	(2,231)
Hong Kong	797	(1,823)
United Arab Emirates	65	(160)
Singapore	23	(76)
Malaysia	19	(50)
Saudi Arabia	10	(42)
Syria	8	(32)
Vietnam	2.4	(5.8)
Thailand	2.3	(3)
France	2.2	(9.2)

United Kingdom	1.8	(9.3)
Bahrain	1	(4.9)
Other	1	(8)
Total of all destinations	**2,021**	**(4,454)**

Percentage of total production exported from Australia

Commodity	Total production, tonnes, 1997	Total exported, tonnes, 1997/98	% Exported
apples	353,069	36,041	10.2
peaches	72,098	620	0.86
nectarines	21,888	2,021	9.2

Overseas registration status

The applicant stated that AVG is registered for use on **apples** in Mexico, Canada (temporary), USA, South Africa, New Zealand, Chile and South Korea. An application for registration, in apples, has also been submitted in Taiwan.

There are no overseas registrations for AVG in **stone fruit** yet. Applications for registration, in stone fruit, have been made in South Africa, New Zealand, South Korea and Taiwan.

CODEX Alimentarius Commission MRL

AVG has not been considered by CODEX. No CODEX MRLs have been established.

Potential risk to Australian export trade

Apples

Although a finite MRL has been recommended for AVG in apples, the likelihood of apples containing finite AVG residues entering export markets is considered to be small. The STMR for AVG in apples was less than the LOQ of the analytical method based on a PHI of 7 days. Finite residues were observed in 5 out of 15 samples treated according to GAP.

Under actual conditions of use, the typical PHI would be 21 days, allowing further decline in residues. An additional mitigating factor, is that radiotracer studies showed that a minimum of 50% of the total AVG residue is removed by rinsing fruit in water. Apples are routinely washed prior to packing and this would further reduce the likelihood of finite residues occurring.

The risk to trade is considered to be small, however, industry groups should be made aware of the situation.

Peaches and Nectarines

Residues in peaches were slightly higher than apples, although the STMR was also less than the LOQ of the analytical method. Finite residues were observed in 5 out of 12 samples treated according to GAP. Based on 1997/98 figures only a very small proportion of peach production (0.86%) enters export markets. In the one nectarine trial provided residues of AVG were less than the Limit of Detection of the analytical method.

Compared to peaches, a higher percentage of nectarine production enters export markets, although the absolute exports of nectarines are significantly less than peaches.

It is considered that the overall risk to trade is small, however, Australian Fresh Stone Fruit Growers Association should be made aware of the situation and adopt industry-based mitigation strategies if considered necessary.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

The National Occupational, Health and Safety Commission (NOHSC) has conducted a risk assessment on *RETAIN*® containing 150 g/kg aminoethoxyvinylglycine (AVG), as a new technical grade active constituent.

AVG is classified as hazardous according to NOHSC *Approved Criteria for Classifying Hazardous Substances* based on its inhalation toxicity and reproductive and developmental effects observed in **rats**.

AVG will be manufactured overseas as a beige to off-white powder. AVG has low acute oral toxicity in **rats**, low acute dermal toxicity in **rabbits**, moderate inhalational toxicity in **rats**, is a slight skin and moderate eye irritant in **rabbits** and is not a skin sensitiser in **guinea pigs**.

RETAIN® has low oral toxicity, low dermal toxicity and low inhalational toxicity and only slight eye irritancy with no skin irritancy.

Formulation, repackaging, transport, storage and retailing

RETAIN® will be packed in 415 g water-soluble bags sealed inside a metallised polyester laminate pouch, with a polyethylene lining and heat sealed closure. It will be imported into Australia fully packaged and ready for sale. Transport workers, store persons and retailers will handle the packaged product, and could only become contaminated if the packaging were breached.

Advice on safe handling of the product during routine application is provided in the Material Safety Data Sheet (MSDS) for *RETAIN*®.

Use and exposure

The product is to be applied three to four weeks prior to the anticipated beginning of the normal harvest period. *RETAIN*® will be applied by air blast spray at a rate of 830 g/ha in approximately 800 – 1200 L/ha [max. 0.104% *RETAIN*® (w/v), 0.016% AVG (w/v)]. The product is proposed for use at a maximum of 1 application per year.

The draft label states that a non-ionic organo-silicone surfactant (Nufarm's Spraymate Freeway Penetrant), at 50-100 mL/100L water, must be added to this product.

Assessment of end use exposure during use

For end users, the main route of contamination will be dermal and ocular. Exposure is possible when applying spray and cleaning equipment.

The product is packed in a water-soluble bag. Worker exposure during loading is expected to be minimal. No protective equipment is required when loading. Mixing in open tank will require personal protective equipment (PPE; see below).

Inhalation exposure to product mist is possible. However, *RETAIN*® is of low inhalation toxicity, and will be applied outdoors. Overall, inhalation risk is not likely to be substantial for users of this product.

The active constituent is considered to be a moderate eye irritant and accidental exposure when mixing should be avoided. Concentration of the active constituent in the final spray is very low (0.016%). Therefore *RETAIN*® is unlikely to pose undue risk to the eye while spraying. Consequently NOHSC does not recommend any safety equipment to protect eyes.

There are no worker exposure studies submitted on AVG or *RETAIN*®. NOHSC used the UK Predictive Operator Exposure Model (POEM) and the US Pesticide Handlers Exposure Database (PHED) to estimate applicator exposure to *RETAIN*®. Based on the predicted exposure levels from both modelling tools, NOHSC recommends the use of gloves and chemical resistant clothing whilst mixing and applying the product. Applicators using a closed cab may not require chemical resistant clothing.

Personal Protective Equipment (PPE)

In order to protect workers from repeated exposure to *RETAIN*® during mixing and application, the use of the following PPE is recommended: chemical resistant clothing buttoned to the neck and wrist and a washable hat and elbow length PVC gloves.

Entry into treated areas

Re-entry to treated areas is possible when fruits or for performing other tasks. Considering that systemic and reproductive effects were seen at low doses of AVG, and in the absence of relevant worker exposure studies, re-entry to treated area should be restricted as long as possible (i.e.: until harvesting is required). The Withholding Period for *RETAIN*® is 7 days, NOHSC therefore proposes a default re-entry period of 7 days.

Recommendations for safe use

Users should follow the instructions and Safety Directions on the Product label. Safety Directions include the use of chemical resistant clothing buttoned to the neck and wrist and washable hat, and elbow length PVC gloves, when mixing and using the spray.

The PPE recommended should meet the relevant *Standards-Australia*.

Re-entry statement

"Do not allow entry into treated areas for 7 days after treatment. When prior entry is necessary, wear chemical resistant clothing buttoned to the neck and wrist and a washable hat and chemical resistant gloves. Clothing must be laundered after each day's use".

Information provision

Material Safety Data Sheet

Manufacturers and importers should produce a MSDS for AVG and *RETAIN*®.

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.

Conclusion

NOHSC **supports** the registration of AVG in *RETAIN*® at 150 g/kg as a water-soluble powder, for use as plant regulator to improve harvest management, fruit quality, and storage potential of apples, peaches, and nectarines.

RETAIN® can be used safely if handled in accordance with the instructions on the product label and any other measures described above. Additional information is available on the MSDS for *RETAIN*®.

ENVIRONMENTAL ASSESSMENT

Introduction

Valent BioSciences, a division of Sumitomo Chemical Australia Pty Ltd has applied for the registration of the new end use product *RETAIN*®, containing the technical grade active constituent (TGAC) aminoethoxvyinylglycine (AVG) at 150 g a.i./kg. This product will be used as a plant growth regulator for apples, peaches and nectarines. It is a natural product, prepared biosynthetically by a *Streptomyces* isolate that occurs naturally in soil.

Environmental Fate: Degradation and Metabolism

Hydrolysis

The hydrolysis of AVG has been investigated under hot acidic conditions. AVG completely degraded and the products were identified as the ethanolamine cyclic acetal-lactone of aspartate semialdehyde, the cyclic hemiacetal-lactone of aspartate semialdehyde and ethanolamine hydrochloride. However, the relevance of this reaction pathway under environmental conditions is questionable. The company also stated that the AVG is not hydrolysed rapidly at room temperature at pH values near neutrality but no supporting data was provided.

Photolysis

The company has provided a non-GLP study where a series of samples of AVG in aqueous solution were irradiated with a xenon lamp. The results of an unspecified assay of the samples showed that the concentration of AVG did not decline with increased irradiation. This is consistent with AVG containing no functional groups that would absorb visible or ultraviolet radiation.

Metabolism

The degradation was investigated using radio-labelled AVG (0.167 mg/kg) in four soil types according to EU and USEPA Guidelines. Degradation in the sandy loam and loam soils was very quick. The rates of degradation in the sandy soils were slightly slower. In all cases only two major metabolites (Met A and Met B) were detected. These metabolites also degraded rapidly and were not identified. The maximum peak concentration of these metabolites (~20% for both Met A and Met B) was reached in the sandy soils. A third metabolite (Met C) was detected at low levels (<5%) in all soils.

The DT50 for AVG in the soils was ranged between 1.6-4.3 days for all soils. The major metabolites also showed short dissipation times, the DT50 for Met A ranged from 2.2-8.9 d and 0.5-6.9 d for Met B. Based on the Mensink classification, the DT50 values for the soils indicate that AVG and its major metabolites are readily degradable.

In two further studies, AVG-producing *Streptomyces* strain in sterile Amberex mediums were fed with AVG labelled in the 3 and 4 (vinylic) positions. The incubations were conducted for 72 h in a laboratory shaker at 28 °C. The studies differed in the amount of glucose supplement added. In the first study AVG was the major food source (0.5% w/v glucose with 100 µCi of [^{3}H]-AVG) for the bacteria. After 72 h, the 37% of the applied radiolabel remained as [^{3}H]-AVG. No attempt was made to identify the other sources of radioactivity. Evaporation to dryness of the test sample resulted in the loss of a substantial percentage of the radioactivity as volatile tritium species.

In study 2, the presence of a greater proportion of glucose (0.5% w/v glucose with 100 µCi of [^{3}H]-AVG) resulted in a greater residual amount of [^{3}H]-AVG (66% of applied), indicating that in the presence of other substrate the degradation of AVG is slower. The relevance of this test, using the strain which produces the active, is unclear.

Mobility Studies

Mobility
A study of adsorption/desorption of AVG onto four soils, was conducted in accordance with OECD and US EPA Guidelines. Calculated K_{OC} values ranged from 561-7495 classifying AVG as having low mobility to immobile depending on soil type ($600 < K_{OC} < 7500$). Adsorption of AVG generally increased with increasing clay content.

HPLC analysis of the supernatant from the highest test concentrations indicated that degradation of AVG occurred during the study. The greatest degradation was observed in soil samples containing the highest clay content.

Environmental Toxicity
AVG was moderately toxic to bobwhite quail in acute oral and highly toxic in 5-day dietary studies.

The results of the aquatic toxicity studies for AVG indicate that it is practically non-toxic to Rainbow trout and *Daphnia.* AVG in the *RETAIN*® formulation was shown to be moderately toxic to *Daphnia*. AVG is highly toxic to both algae and duckweed.

The results of the terrestrial toxicity studies for AVG indicate that it is very slightly toxic to honeybees and earthworms, and that it is not expected to have an adverse effect on non-target vegetation at the label rate.

Prediction of Environmental Hazard: Summary of Environmental Effects Studies

Hazards Arising from Use

It is proposed that AVG be applied to apples, peach and pear trees once per year. The EUP is to be applied with ground based spray rigs with coarse to very coarse droplets to cover 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 bobwhite quail consumed short-range grass, treated with the maximum application rate of AVG as 100% of its diet, the dietary EEC would be 27 mg a.i./kg food. The calculated Q value (EEC/LC50) for bobwhite quail is then 0.12, indicating a marginal dietary hazard for birds from AVG.

However, this quotient represents the worst case in that the quail consumes only treated food. If less than 85% of the food consumed is treated the calculated Q drops below 0.1 which indicates no environmental risk. Hence, the use of AVG as proposed is not expected to result in an unacceptable hazard to birds.

Aquatic organisms
The calculated hazard quotients, based on the maximum application rate and either direct overspray or 10% spray drift into a 15 cm deep 1 ha pond, indicate that the use of AVG would not be expected to have adverse effects on fish or aquatic invertebrates.

However, the quotients for algae and duckweed indicate that a potential hazard if direct overspray of the water body occurs. As it is not intended that the product be directly applied to water this is not likely to occur. This potential hazard is diminished if spray drift is considered. At 10% spray drift the hazard quotient for duckweed reduces below the level of concern. For algae the quotient falls into the range where the hazard may be mitigated by restricted use.

The hazard resulting from spraydrift was refined using the variation of spray drift with distance, taken from the work of Ganzelmeier and Rautmann. The refined Q values indicate that the hazard to algae and duckweed is sufficiently mitigated, if the distance between the orchard and the waterbody is greater than 15 or 5 m, respectively. The use of the coarse to very coarse droplet sizes indicated by the company will reduce the spray drift and, hence, the potential hazard. It should also be noted that in the effect on algae was reversible. Given that the product is applied once per season and degrades readily, exposed algae will have a chance to recover, and the use of *RETAIN®* is not expected to result in adverse effects on these organisms.

Non-Target Invertebrates
The maximum application rate of AVG of 125 g/ha corresponds to 1.25 µg/cm^2. The hazard to honey bees may be estimated on the assumption that a bee in a spray cloud has a target area of 1 cm^2. Hence, an exposure level of approximately 1.25 µg/bee may be expected if AVG is sprayed, at the maximum rate, while bees are actively foraging. The contact and oral LD50s for bees were >100 µg/bee. Thus, it is anticipated that there would not be an adverse affect on any bees that are in the trees at the time of spraying.

If the maximum application rate of 125 g/ha were sprayed directly onto soil a maximum concentration 83 µg/kg would result in the top 10 cm of soil. Hence, the use of AVG at the maximum rate is not expected to adversely affect earthworms as the LC50 is >1000 mg/kg.

Desirable vegetation
No adverse effects were observed on ten plant species exposed to 124 g/ha (approximately the label rate) representing a diversity of plant genera. Hence, the potential hazard of AVG to non-target vegetation is low.

Conclusion
It is proposed that AVG be applied to apples, peaches and nectarines once per year. The EUP is to be applied with ground based spray rigs in such a manner as to cover the canopy without run-off.

Considering the relatively limited use pattern, the application contains adequate environmental fate and toxicity data to demonstrate that the use of *RETAIN®* (according to label and GAP), is unlikely to result in acute poisoning of wildlife, fish etc.

EFFICACY AND CROP-SAFETY ASSESSMENT

This summarises the field trials conducted in Australia with *RETAIN*®. Information is provided in relation to efficacy and crop safety of the product.

The application is for the improvement of harvest management, fruit quality and storage potential of apples, peaches and nectarines.

Justification for Use

RETAIN® is a naturally occurring plant growth regulator which inhibits endogenous production of ethylene in plant tissues. Ethylene affects plant processes such as fruit maturation, ripening and abcission. Inhibiting ethylene production within the plant can provide a delay in harvest (i.e. improved harvest management) depending on fruit variety, reduction in pre-harvest fruit drop, delayed fruit maturation that allows for a natural enhancement in size, maintenance of fruit firmness, improved fruit quality (e.g. reduced incidence of and/or severity of some fruit disorders) and enhanced storage potential.

As limited storage potential exists for stonefruit, any treatment that can prolong storage life, whilst maintaining fruit quality, is desirable.

Also, in both apples and stonefruit, a common problem is to harvest fruit at optimum maturity **and** colour development. Environmental conditions can delay colour development, whilst advancing fruit maturity (e.g. warm weather effect on red varieties), so a treatment that can delay maturity until colour develops more is advantageous. As pre-harvest fruit drop can increase because fruit is left on the tree to develop colour, then a treatment that prevents this whilst colour develops is also an advantage.

Lastly, there is a growing need to expand the "harvest window" in large blocks of a single variety, whilst maintaining optimum maturity. This allows for efficiencies in equipment availability and labour management during harvesting, handling, grading, packing and/or processing an increasingly large volume of fruit. Clearly it can also allow some marketing management, to avoid market "gluts", with their devastating effect on grower incomes. A less obvious effect of non-optimum fruit maturity/quality on market prices, is that it can have a carry-over effect, lowering demand and therefore prices of subsequent high quality fruit. Hence spreading the "harvest window" whilst maintaining fruit quality is highly desirable for stable market returns.

Effficacy

- **Trial design in relation to provision of controls, treatment group size, number of replicates, age and type of animal, plant varieties and stage of growth etc:**
  The trial designs are adequate and acceptable, with appropriate replicates, treatment group-sizes, treatments, analysis of results and interpretation of results.

- **Experimental conditions in relation to relevant variables, such as pest/disease pressure, weather conditions, soil type etc:**
  There was an adequate spread and number of trials over a range of locales, varieties and climatic conditions.

Whilst the apple trial-locales relied heavily on New Zealand sites and cool areas of Australia, the results were deemed to be acceptable for Australia nationally, though further work in warmer Australian apple regions is recommended. Similarly, it is recommended that a wider range of Australian apple varieties be tested, and future work on the effect of different root-stocks (i.e. tree size/vigour) would also be useful.

None-the-less, there is sufficient variety of experimental conditions in the current trials to be meaningful for a registration on **apples**.

For peaches/nectarines, locales were Australian, though with a tendency to ones with warm, dry summers. Hence it is recommended that trials in cooler climate and/or low-chill stone-fruit areas be done in the future. Similarly low chill and fresh peach varieties should be tested in the future.

None-the-less, there is sufficient variety of experimental conditions in the current trials to be meaningful for a registration on **peaches** and **nectarines**.

- **Analysis of trial data and its interpretation, including efficacy relative to dose/application rate and application/administration:**
  Adequate statistical analysis has been conducted on the trial data, using standardised analyses.

  A number of trials had inconsistent sampling techniques for fruit, and some of the fruit colour assessments did not always differentiate whether background colour was being measured, or red blush "over cover".

  However, this did not detract from the acceptability of the overall data package.

- **Trial validation with respect to the person responsible for the trial, location of the trial, date of trial:**
  Protocols were well established and implemented in the main.

- **General applicability of the trial data to the use of the candidate preparation under commercial conditions:**
  Data sets have been well presented in the main, and are generally easy to follow, though there was considerable variation in the presentation of some experimental work.

  In general, trial protocols were established to gather data relevant to the registration process: i.e. relevant to the commercial use of the product.

- **Presentation of Data**
  Presentation of data overall was acceptable, though there was considerable variation in the presentation of some experimental work

- **Efficacy data supporting the label claims:**
  Data have covered those claims which appear on the latest draft label. As stated above, further work is recommended to more specifically define the effect of tree root-stock, Australian varieties and varying Australian growing areas.

- **Directions for Use; including adequacy of supporting data for application rate/dosage and method of application/administration:**
  Supporting data for yield response, phyto-toxicity, application and equipment, compatibility and wetting agents is adequate.

Crop Safety

- *RETAIN*® was applied in trials over a number of seasons, at the highest proposed recommended rate. *RETAIN*® showed no adverse effect on crop yield or tree health.

Conclusions

Sufficient data from suitably designed, scientifically conducted and statistically analysed trials has been presented to substantiate the claims for use as shown on the proposed label. Some additional trial work is recommended to confirm safety/efficacy on varieties used in Australia, and under Australian cultural and climatic conditions.

When the product is used according to label instructions and Good Agricultural Practice, it should be suitable for the intended purpose.

LABELLING REQUIREMENTS
(DRAFT LABEL)

(Measure-pack Label: Label suite page 1 of 5)

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

ReTain â

PLANT GROWTH REGULATOR

Active Constituent:
150 g/kg aminoethoxyvinylglycine (AVG)

A naturally occurring plant growth regulator for apples, peaches and nectarines which can improve harvest management, fruit quality and storage potential

IMPORTANT: BEFORE USE, READ ALL DIRECTIONS IN LEAFLET.

WATER-SOLUBLE PACK. KEEP DRY.

415 g NET

Valent BioSciences
(A division of Sumitomo Chemical Australia Pty Ltd) A.B.N. 21 081 096 255
501 Victoria Ave, Chatswood, NSW 2067 ph: (02) 9904 6499

STORAGE AND DISPOSAL:
Store in original packaging in a safe, well ventilated area as cool as possible. Do not expose to extremes of temperature. ReTain® is supplied in a water soluble bag packaged inside a metallised polyester pouch. Once the pouch is opened, the entire contents of the bag must be used. Dispose of outer foil pack in garbage.

SAFETY DIRECTIONS
Will irritate the eyes. Avoid contact with eyes. Wash hands after use. When mixing and using the prepared spray wear chemical resistant clothing buttoned to the neck and wrist and 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 the Poisons Information Centre. Phone 13 11 26

MATERIAL SAFETY DATA SHEET
Additional information is listed in the Material Safety Data Sheet

NRA Approval No.: 52453/ . . . .
Batch No.:
Date Of Manufacture:

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

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NRA Approval Number: 52453/ . . . .

ReTain â

PLANT GROWTH REGULATOR

DIRECTIONS FOR USE:

RESTRAINTS
Do not apply if rain is expected within 8 hours of ReTain® application.
Do not apply products containing either 1-naphthylacetic acid (NAA) or ethephon, after treatment of blocks with ReTain® .
Do not use ReTain® with management tools that affect apple maturity such as foil mulch, girdling, etc.
Do not apply ReTain® when trees may be nutrient, water, insect or disease stressed.

CROPS	RATE	CRITICAL COMMENTS
		Use an organosilicone surfactant such as Maxx Organosilicone Surfactant or Nufarm's Spraymate™ Freeway Penetrant 50-100 ml/100 L water (see mixing instructions for further details). This is essential to ensure good coverage of fruit maximising the efficacy of ReTain
Apples	830 g/ha	Apply 21-28 days prior to the anticipated beginning of the normal start of harvest for the current season (i.e. the first pick for each apple variety and block to be treated). 800-1200 L/ha of water is recommended to achieve total coverage, but avoiding run-off. Use of higher water volumes will reduce efficacy.
Peaches Nectarines		Apply 7-14 days prior to the anticipated beginning of the normal start of harvest for the current season (i.e. the first pick for each variety and block to be treated). 1000 - 1500 L/ha of water is recommended to achieve total coverage, but avoiding run-off. Use of higher water volumes will reduce efficacy.

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

WITHHOLDING PERIOD:
DO NOT HARVEST 7 DAYS AFTER APPLICATION
DO NOT GRAZE TREATED VEGETATION, OR CUT FOR STOCK FOOD.

GENERAL INSTRUCTIONS

ReTain® Plant Growth Regulator contains 15% of AVG. AVG is a fermentation metabolite that inhibits the endogenous production of ethylene in plant tissues. Ethylene affects plant processes such as fruit maturation, ripening, and abscission. Inhibiting ethylene production with ReTain® can provide several benefits for apple, peach and nectarine growers, including one or more of the following: Improved harvest management (delay in harvest depending on variety), reduction of preharvest fruit drop, delayed fruit maturation that allows for natural enhancement in size, maintenance of fruit firmness, improved fruit quality (e.g., reduced incidence and/or severity of fruit disorders) and enhanced storage potential.

Responses vary between different varieties. Some varieties naturally produce low levels of ethylene and the effect of ReTain® is likely to be less than in varieties which produce high levels of ethylene. For apple varieties which produce high ethylene levels during harvest (e.g. Red Delicious, Gala, Royal Gala), the maturation delay may be 7-14 days, while for low ethylene producing varieties (e.g. Fuji, Granny Smith), the delay may only be 2-5 days. The maturity delay with peaches and nectarines is less apparent than in apples, however, depending on variety the delay is likely to be 0-5 days. Many varieties of ReTain® treated peaches and nectarines have significantly enhanced firmness over the harvest and storage periods. For more information on specific varieties please consult your local Sumitomo Chemical representative.

MIXING:

Prepare spray material by cutting open the foil pack and removing the single inner water soluble bag containing 415 g of ReTain® . Add the water soluble bag to a clean spray tank containing 400-600 L (apples) or 500-750 L (peaches and nectarines) of clean water (pH 6-8). This is sufficient water volume to treat 1/2 ha of fruit trees. To treat a greater area, add ReTain® bags and water volumes in equivalent ratios to that above. Total spray volume should be calculated to achieve total coverage, but not run-off (for apples - 800 to 1200 L/ha; for peaches and nectarines - 1000 - 1500 L/Ha, depending on tree size and spacing).

Use of Adjuvants: ReTain® ***must*** be used with a non-ionic organosilicone surfactant (Maxx Organosilicone Surfactant or Nufarm's Spraymate™ Freeway Penetrant are recommended) in order to obtain the optimum response.
For Gala and Royal Gala varieties use a final concentration of 50 ml/100 litres in the spray tank.
For other varieties use a final concentration of 50-100 ml/100 litres in the spray tank.
Do not use a surfactant concentration more than 100 ml/100 litres. To minimise foaming, add the surfactant last and minimise agitation. ReTain® is very soluble and agitation is not usually required during application. Discard any unused spray material at the end of each day.

APPLICATION:

Apply ReTain® at the recommended timing prior to the anticipated beginning of the normal harvest period (i.e. the first pick) for each variety and block to be treated. The normal harvest period for a particular orchard block refers to the time when trees not treated with ReTain® would be harvested. The optimum response in achieved when ReTain® is applied to apples 21-28 days prior to the anticipated beginning of the normal harvest, and to peaches and nectarines 7-14 days prior to the anticipated beginning of the normal harvest. Applications made either too early or too late may reduce the efficacy of the ReTain®.

SPECIAL CONSIDERATIONS:

Apply when drying conditions are slower, such as in the early to mid-morning period, in order to ensure adequate absorption. Do not apply ReTain® in the late afternoon or early evening if the fruit is still warm.
Allow a 24 hour interval between application of ReTain® and application of any other sprayed agricultural product, or overhead irrigation.
Keep water pH between 6 and 8 for best results.

COMPATIBILITY:

Do not tank-mix ReTain® with agricultural products other than DiPel® DF or an organosilicone surfactant. Compatibility data for ReTain® with other agricultural products are limited.

PRECAUTIONS

RE-ENTRY PERIOD: Do not allow entry into treated areas for 7 days after treatment. When prior entry is necessary, wear chemical resistant clothing buttoned to the neck and wrist and a washable hat and chemical resistant clothes. Clothing must be laundered after each day's use.

PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS:

Do NOT contaminate ponds, waterways or drains with the product or used packets.

STORAGE AND DISPOSAL:

Store in original packaging in a safe, well ventilated area as cool as possible. Do not expose to extremes of temperature. ReTain® is supplied in a water soluble bag packaged inside a metallised polyester pouch. Once the pouch is opened, the entire contents of the bag must be used. Dispose of outer foil pack in garbage.

SAFETY DIRECTIONS:

Will irritate the eyes. Avoid contact with eyes. Wash hands after use. When mixing and using the prepared spray wear chemical resistant clothing buttoned to the neck and wrist and 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 the Poisons Information Centre. Phone 13 11 26.
MSDS: Additional information is listed in the Material Safety Data Sheet.

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 partioning 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.

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