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Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active afidopyropen in the product Versys Insecticide

APVMA Product Number 82738

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

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PREFACE

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

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health, Department of Environment and Energy, and State Departments of Primary Industries.

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

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

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

About this document

This is a Public Release Summary.

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

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

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

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of Versys Insecticide should be granted. Submissions should relate only to matters that are required by the APVMA to be taken into consideration in determining whether the safety, efficacy or trade criteria have been met. Submissions should state the grounds on which they are based.

Submissions must be received by the APVMA by close of business on Tuesday, 10 April 2018 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

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

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

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

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

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

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

Further information

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

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

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

1 INTRODUCTION

1.1 Purpose of application

BASF Australia Ltd has applied to the APVMA for registration of the new product Versys Insecticide containing the new active constituent afidopyropen as a dispersible concentrate (DC) formulation. Versys Insecticide contains 100 g/L afidopyropen.

The active constituent afidopyropen and the product Versys Insecticide will be manufactured and formulated overseas, then imported to Australia in 1, 5 and 10 Litre, high density polyethylene (HDPE) containers with tamper-evident caps.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Versys Insecticide, and approval of the new active constituent, afidopyropen.

1.2 Product claims and use pattern

Versys Insecticide is intended for the control of green peach aphid (*Myzus persicae*), cabbage aphid (*Brevicoryne brassicae*), currant lettuce aphid (*Nasonovia ribis-nigri*) and cotton/melon aphid (*Aphis gossypii*); and for the suppression of silverleaf whitefly in brassica vegetables, celery, cucurbits, fruiting and leafy vegetables (including brassica leafy vegetables), parsley, potato, sweet potato, ginger and cotton. The product is also intended for the control of aphids in ornamentals.

The proposed use of Versys Insecticide for control of aphids is limited to 2 applications (with a 14 day interval) at a rate of 100 mL/ha (10 g afidopyropen/ha) before rotating to an alternative insecticide, with a maximum of 4 applications per crop.

When used for suppression of silverleaf whitefly, a single application is made at 350 mL/ha (35 g afidopyropen/ha) before rotating to an alternative insecticide. For this use pattern, the product is limited to a maximum of 2 applications in any one crop and, if using for whitefly suppression in conjunction with aphid control, no more than 2 additional applications at the 100 mL/ha rate for aphid control may be made.

Versys Insecticide is to be applied by ground equipment in a minimum of 200 L water/ha and is to be mixed with Hasten Spray Adjuvant at 0.2% v/v when applying for suppression of silverleaf whitefly.

1.3 Mode of action

Afidopyropen disrupts the gating of vanilloid-type transient receptor (TRPV) channel complexes in chordotonal stretch receptor organs of insects, which are critical for the senses of hearing, gravity, balance, acceleration, proprioception, and kinaesthesia. This disrupts feeding and other behaviours in target insects leading to death by starvation.

For resistance management purposes, Versys Insecticide is a group 9D insecticide.

1.4 Interim scheduling decision

At the time of this publication, the final scheduling decision for afidopyropen has not been made. The Scheduling Delegate's interim decision was published on the 5 February 2018. Afidopyropen is proposed for inclusion in *Appendix B: Substances Considered Not to Require Control by Scheduling* of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). The proposed implementation date is 1 June 2018 with the Scheduling Delegate's Final decision expected to be published on 10 April 2018.

1.5 Overseas registrations

There are currently no overseas registrations for afidopyropen. This submission has been assessed under a workshare arrangement where registrations for the same formulation and uses have been submitted concurrently in USA, Canada and Mexico.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

As purified active ingredient, afidopyropen is a white powder, while the technical material is yellow coloured. Both the purified active ingredient and the technical grade active ingredient, are odourless at room temperature. Afidopyropen has a very low vapour pressure of < 9.9 x10-6 Pa at 25 °C. The water solubility is low, at 25 mg/L at 20 °C. The active ingredient has a good solubility in dichloromethane, acetone, methanol and ethyl acetate (> 500 g/L) and a lower solubility in toluene (5.5 g/L), while the solubility in n-hexane is low (7.7 mg/L). Afidopyropen does not dissociate in water. The octanol/ water partition coefficient (log10Pow) of 3.45 indicates that afidopyropen is lipophilic. The technical grade active ingredient is not surface-active. Afidopyropen is not highly flammable, explosive, or oxidizing.

Table 1: Key identification information for afidopyropen

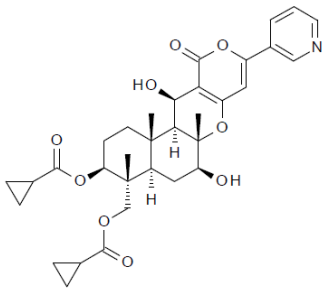
COMMON NAME (ISO):	afidopyropen
CHEMICAL NAME:	[(3*S*,4*R*,4a*R*,6*S*,6a*S*,12*R*,12a*S*,12b*S*)-3-[(cyclopropanecarbonyl)oxy]-6,12-dihydroxy-4,6a,12b-trimethyl-11-oxo-9-(pyridin-3-yl)-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*,11*H*-benzo[*f*]pyrano[4,3-*b*]chromen-4-yl]methyl cyclopropanecarboxylate
PRODUCT NAME:	Versys Insecticide
MANUFACTURERS CODE:	BAS 440 I and ME 5343
CAS REGISTRY NUMBER:	915972-17-7
EMPIRICAL FORMULA:	$C_{33}H_{39}NO_9$
MOLECULAR WEIGHT:	593.66 g/mol
STRUCTURAL FORMULA:	

Table 2: Key physicochemical properties of the active constituent afidopyropen

COMMON NAME (ISO):	afidopyropen
PHYSICAL FORM:	Solid (Powder)
COLOUR:	Yellow (technical grade)
ODOUR:	Odourless
MELTING RANGE:	147.3 - 160 °C
DENSITY:	1.300 g/cm^3 (20 ºC)
OCTANOL/WATER PARTITION COEFFICIENT (KOW):	$Log_{10}P_{ow}$ = 3.45 at 25 ±1 °C.
VAPOUR PRESSURE AT 25OC:	<9.9 ×10^{-6} Pa at 25 °C and <1.5 ×10^{-5} Pa at 50 °C.
PH:	Reported pH 5.3 and pH 5.8 at a 1% dilution in pure water and CIPAC water D respectively at 23 ºC
HENRY'S LAW CONSTANT:	H < 2.34 x 10-^{4} Pa m^3/mol
SOLUBILITY IN ORGANIC SOLVENTS (AT 20 OC):	Acetone >500 g/L Methanol >500 g/L Dichloromethane >500 g/L Toluene 5.54 g/L Hexane 7.66 mg/L Ethyl acetate >500 g/L
SOLUBILITY IN WATER:	25.1 mg/L at 20 ºC
FLAMMABILITY:	Not considered highly flammable
OXIDISING PROPERTIES:	Not oxidizing
HYDROLYSIS IN WATER:	Hydrolytically stable at pH 4 and 7, with half-lives estimated to be greater than 1 year at 25 ºC
DEGRADATION RESULTING FROM HYDROXYL RADICAL (OH) ATTACK:	Afidopyropen atmospheric half-life is: $t_{1/2}$ = ln2/[(193.5015×10^{-12} cm^3 molecule^{-1} sec^{-1}) × (1.5×10^6 molecules cm^{-3})] = 0.663 hours = 0.055 days (12 hour day)
DEGRADATION RESULTING FROM OZONE (O3) ATTACK:	Afidopyropen atmospheric half-life is:$t_{1/2}$ = ln2/[(315.900024×10^{-17} cm^3 molecule^{-1} sec^{-1}) × (7× 1011 molecules cm^{-3})] = 5.224 minutes = 0.004 days
UV/VIS ABSORPTION (MAX.):	Neutral pH (methanol) = λ_{max}231 nm, Neutral pH (Aqueous) 7.44 = λ_{max}231 nm (Acidic) pH 1.03 = λ_{max}231 nm, (Basic) pH 13.36 = λ_{max}231 nm

2.2 Formulated product

The product Versys Insecticide will be manufactured overseas and will be available in 1 L, 5 L and 10 L HDPE containers. Versys Insecticide is a dispersible concentrate formulation containing 100 g/L afidopyropen as the only active constituent.

Table 3: Key characteristics and physicochemical properties of Versys Insecticide

DISTINGUISHING NAME:	Versys Insecticide
FORMULATION TYPE:	Dispersible Concentrate (DC)
ACTIVE CONSTITUENTS CONCENTRATION:	100 g/L afidopyropen
PHYSICAL FORM:	Clear liquid with golden yellow colour
ODOUR:	Odourless
PH VALUE:	pH = 7.61 (Pure Water), pH = 7.3 (CIPAC water D)
RELATIVE DENSITY:	1.0267 g/cm3 @ 20 ºC
VISCOSITY:	Non-Newtonian fluid: viscosity decreasing with increasing shear rate.
SURFACE TENSION:	Average surface tension is 33.17 mN/m at 0.17 % concentration in pure water at 20 oC.
FLASH POINT:	Has a flashpoint of 95.5 oC
AUTO-IGNITION TEMPERATURE:	385 °C
THERMAL STABILITY:	Exothermic effect in the range 350–440 °C with a decomposition energy of -270 J/g in a closed glass crucible Small exothermic effect in the range 105–145 °C with a decomposition energy of -10 J/g in a closed gold plated crucible
OXIDISING/ REDUCING ACTION	Reacts moderately with strong oxidizing agents (e.g. potassium permanganate) but does not react with reducing agents (e.g. iron) or with water
EXPLOSIVE PROPERTIES:	No explosive properties
CORROSIVE HAZARD:	Not corrosive to HDPE containers

2.3 Recommendations

The APVMA has evaluated the chemistry aspects of afidopyropen and Versys Insecticide (physico-chemical properties, identification, manufacturing process, quality control procedures, stability, batch analysis results and analytical methods) and found them to be acceptable.

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

APVMA active constituent standard for afidopyropen

Table 4: APVMA active constituent standard proposed for the active constituent afidopyropen

CONSTITUENT	SPECIFICATION	LEVEL
Afidopyropen	afidopyropen content	925 g/kg minimum

From a chemistry and manufacture perspective, approval of afidopyropen and registration of Versys Insecticide is supported.

3 TOXICOLOGICAL ASSESSMENT

3.1 Introduction

The toxicological assessment considered the proposed use of Versys Insecticide for control of aphids and suppression of silverleaf whitefly in cotton and a range of horticultural crops. To support the application, toxicological data were provided for afidopyropen and several of its metabolites. For more information about metabolic pathways of afidopyropen in plants and animals refer to 4.1 Metabolism.

3.2 Summary of the evaluation of toxicological studies

The toxicological database for afidopyropen, which consists primarily of toxicity studies conducted in rats, mice, rabbits and dogs, is considered sufficient to determine the toxicology profile of afidopyropen and characterise the risk to humans. In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species does 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 takes into account the likely human exposure levels compared with those, 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-Adverse-Effect-Level (NOAEL) are used to develop acceptable limits for dietary or other intakes at which no adverse health effects in humans would be expected.

3.3 Chemical class

Afidopyropen belongs to a new chemical class of insecticides which binds to, overstimulates and inactivates vanilloid-type transient pressure receptor channels in insects. The consequence of this activity is to inhibit plant-sucking insects' ability to feed, resulting in starvation and death.

3.4 Toxicokinetics and metabolism

Following administration to rats, about 70% of an oral dose of afidopyropen was absorbed rapidly from the gastro-intestinal tract and distributed mainly to the liver, bile, kidney, urine, red blood cells, adrenal and thyroid glands, heart muscle, lung, prostate, pancreas and adipose tissue. Rats metabolised afidopyropen to CPCA-carnitine and numerous other metabolites by hydrolysis, N-oxidation and hydroxylation reactions, and conjugation with glucuronic acid. CPCA-carnitine was identified as toxicologically significant, because its formation leads to impairment of long-chain fatty acid transport across mitochondrial membranes and deficiency in energy generation within cells. Repeated doses of afidopyropen increased the expression of metabolic enzymes in the liver. Even so, increases in dose caused saturation of the metabolic pathway and disproportionately high increases in the blood level of the chemical and its metabolites, especially in female rats.

Afidopyropen and its metabolites were eliminated slowly, having half-lives of up to 19 hours in plasma, 44 hours in red blood cells and 97 hours in the blood. Male rats excreted up to 15% of the administered dose via the urine, entirely as metabolites. A further 40% was excreted in the bile (possibly after recycling metabolites between the intestine and liver), which was eliminated via the faeces together with the unabsorbed 30% of the dose. By contrast, females voided up to 22% of the administered dose in the urine, with a corresponding decrease in the balance excreted via the faeces.

3.5 Acute studies

In rats, afidopyropen was of low acute oral and dermal toxicity (LD_{50}s were >2000 mg/kg bw via both routes) and also of low inhalational toxicity (LC_{50} >5480 mg/m^3). When ground into a powder, afidopyropen was a slight eye irritant but did not irritate the skin in rabbits. Afidopyropen did not cause skin sensitisation in a maximisation test in Guinea pigs.

Versys Insecticide was of low acute oral and dermal toxicity in rats (LD_{50}s were >2000 and >5000 mg/kg bw via the respective routes) but of moderate inhalation toxicity, with an LC_{50} between 600 and 1130 mg/m^3. The product was a slight eye and moderate skin irritant in rabbits, but did not cause skin sensitisation in a Buehler test in Guinea pigs.

3.6 Systemic effects

Repeat dose studies by oral administration to mice, rats and dogs showed adverse effects predominantly involving the blood cell-generating system, liver, central nervous system and cardiac and skeletal muscle. Based on impaired survival, depressed bodyweight, decreased blood cell synthesis in the bone marrow, haematological abnormalities, cardiac fibrosis and vacuolation in multiple organs including the liver, kidney, urinary bladder, brain, spinal nerve tissue and heart after dietary administration at 445 / 333 mg/kg bw/d in males and females respectively, the NOAEL in mice over 78 weeks was 76 mg/kg bw/d. Rats showed increased prothrombin time, reduced blood cholesterol levels and hepatocellular vacuolation at dietary feeding levels $\geq$14.6 mg/kg bw/d; over 52 weeks of treatment the NOAEL in rats was 7.3 mg/kg bw/d. In dogs, vacuolation in brain tissue, biochemical and histological evidence of liver injury, and histopathological changes in the intestine and gall bladder were observed at $\geq$20 mg/kg bw/d; the NOAEL over 52 weeks of treatment was 8.0 mg/kg bw/d.

In a 28-day rat study via the dermal route, the Lowest-Observable-Adverse-Effect-Level (LOAEL) was 1000 mg/kg bw/d (the highest dose administered), based on single-cell fatty change and necrosis observed in the livers of some animals. However, it was not possible to assign a NOAEL because there was no histological examination of liver tissue from rats treated at the low and mid doses (100 and 300 mg/kg bw/d, respectively).

Carcinogenicity and genotoxicity

Afidopyropen was not mutagenic or genotoxic with or without metabolic activation in vitro, and was not genotoxic in vivo or carcinogenic in mice treated for 78 weeks at dietary doses of up to 445/333 mg/kg bw/d in males and females, respectively. In two 24-month carcinogenicity studies with rats there were positive findings at dietary feeding levels of 1000 and 3000 ppm: formation of lung carcinomas occurred in small numbers of females and males, and the incidence of pre-cancerous lesions and adenocarcinoma of the uterus became increased in females. The uterine tumours were formed by a non-genotoxic mechanism arising from agonistic activity [binding] by afidopyropen and some of its metabolites at dopamine D2 receptors, leading to interference with hormonal regulation, disruption of the female reproductive cycle and excessive growth of the endometrium (the uterine lining). Due to physiological differences between rats and humans, however, this mode of cancer formation does not occur in women. No carcinogenic activity was observed in rats at or below a dose of 12.9 mg/kg bw/d.

Reproductive and developmental toxicity

A single-generation dose range-finding study was performed with afidopyropen in rats. Parental females displayed deficits in food consumption and bodyweight gain at and above a dietary feeding level of 1500 ppm, depressed ovary and uterus weights at 3000 ppm and prolonged reproductive cycle length at 6000 ppm. Reduced numbers of live-born pups and decreased post-natal survival were observed from 1500 ppm upwards, together with decreases in implantations at 3000 and 6000 ppm.

Based on these results, two two-generation reproduction studies were conducted at afidopyropen dietary levels of up to 2000 ppm during which parental prostate, ovary and uterus weights became depressed and there were shortfalls in implantations at the F1 mating and in the numbers of F2 pups per litter. Decreased maternal food consumption was correlated with depressed bodyweight gain in adults and pups from 500 ppm upwards, delayed puberty in pups at and above 1000 ppm, and deficits in nursing behaviour among lactating females at 2000 ppm.

A cross-fostering study at a maternal dietary concentration of 1500 ppm found that rat pups were more sensitive to toxicity from exposure via milk from treated females, than to afidopyropen/metabolites when exposed in utero during the gestation period. Across the two multi-generation studies, the NOAELs for toxicity to the parental generations and offspring were both 300 ppm (27 and 22 mg/kg bw/d in parental rats and offspring, respectively), while the NOAEL for reproductive toxicity was 500 ppm (32.5 mg/kg bw/d).

In a developmental toxicity study with rabbits, afidopyropen had no observable effects on maternal health or foetal survival, growth or development at maternal oral doses of up to 32 mg/kg bw/d. However, dose-related toxicity occurred during a range-finding study, seen as decreased maternal food consumption and bodyweight, abortion and premature delivery at 100 mg/kg bw/d, and maternal deaths, abortion and embryolethality at 300 mg/kg bw/d. The overall NOAEL in rabbits was 32 mg/kg bw/d.

In rats, one range-finding and two definitive developmental studies were performed which demonstrated foetal toxicity in the presence of maternal toxicity at oral doses of 100 mg afidopyropen/kg bw/d. The most sensitive effects were depression in maternal food consumption and bodyweight gain, together with delayed foetal development (seen as increases in skeletal variations including supernumerary or lumbar rib and fusion of the zygomatic bone). However, there were no treatment-related foetal malformations. Treatment at 500 and 1000 mg/kg bw/d caused severe maternal illness or death and was lethal to embryos. The overall NOAEL in rats was 50 mg/kg bw/d.

Neurotoxicity

Although causing slight tremors, hypothermia and decreased motor activity in rats following a single oral dose of 2000 mg/kg bw, afidopyropen was not neurotoxic in a 90-day study at up to the highest administered dietary dose of 396 mg/kg bw/d.

Immunotoxicity

Afidopyropen was not immunotoxic in a 28-day rat study at dietary doses of up to 278–374 mg/kg bw/d.

Toxicological studies on metabolites

M440I007, a plant metabolite of afidopyropen, caused no observable toxicity after oral administration to female rats at the acute limit dose of 2000 mg/kg bw. The only effect occurring during a 90-day dietary study in rats, was slight depression in bodyweight gain and bodyweight in females. The NOAEL was set at 708 mg/kg bw/d. No evidence of mutagenic or clastogenic activity was obtained with M440I007 with or without metabolic activation in vitro, or in an in vivo assay.

3.7 Poisons scheduling

The delegate to the Secretary of the Department of Health and Ageing sought advice from the Advisory Committee on Chemical Scheduling (ACCS) on the scheduling of afidopyropen, which was discussed at the November 2017 meeting of the ACCS. The Scheduling Delegate's interim decision was published on 5 February 2018. Afidopyropen is proposed for inclusion in *Appendix B: Substances Considered Not to Require Control by Scheduling* of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). The proposed implementation date is 1 June 2018 with the Scheduling Delegate's Final decision expected to be published on 10 April 2018.

3.8 NOAEL/ADI/ARfD

Acceptable Daily Intake (ADI)

In repeat-dose toxicity studies with afidopyropen, the most sensitive species was the rat, within which the lowest observable adverse effect level (LOAEL) was 14.6 mg/kg bw/day, a dose causing toxicity to the haematopoietic (blood cell-generating) system and liver during a 12-month study by dietary administration. The APVMA considers it appropriate to use the NOAEL of 7.3 mg/kg bw/d in this study to establish an ADI.

Given that the toxicological database for afidopyropen is extensive (including several long-term oral toxicity studies in mice, rats and dogs, and carcinogenicity studies in mice and rats), a 100-fold uncertainty factor (allowing for differences in toxicokinetics, toxicodynamics and sensitivity between and within species) is considered appropriate. Since no especially sensitive population groups were identified during this evaluation, no additional safety factor is required.

Applying an uncertainty factor of 100 to the NOAEL of 7.3 mg/kg bw/d, based on increased prothrombin time and decreased blood cholesterol level in male rats and hepatocellular vacuolation in female rats at the next higher dose in a 12-month toxicity study by dietary administration, an ADI of 0.07 mg/kg bw/d (rounded) can be established for afidopyropen.

Acute Reference Dose (ARfD)

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

Following administration of an oral dose of afidopyropen, the most sensitive species was the rabbit. Shortly after the commencement of treatment at 100 mg/kg bw/d in a developmental toxicity range-finding study, pregnant female rabbits displayed inappetence (decreased food consumption) followed by bodyweight loss and abortion or premature delivery. The NOAEL for maternal and foetal effects in the subsequent main (fully guideline-compliant) study was 32 mg/kg bw/d, which the APVMA considers appropriate to use for setting an ARfD. An uncertainty factor of 100 is considered appropriate for application to this NOAEL to allow for differences in toxicokinetics, toxicodynamics and sensitivity between and within species. Hence an ARfD of 0.3 mg/kg bw for afidopyropen can be established and this ARfD is considered to be applicable for the general population.

4 RESIDUES ASSESSMENT

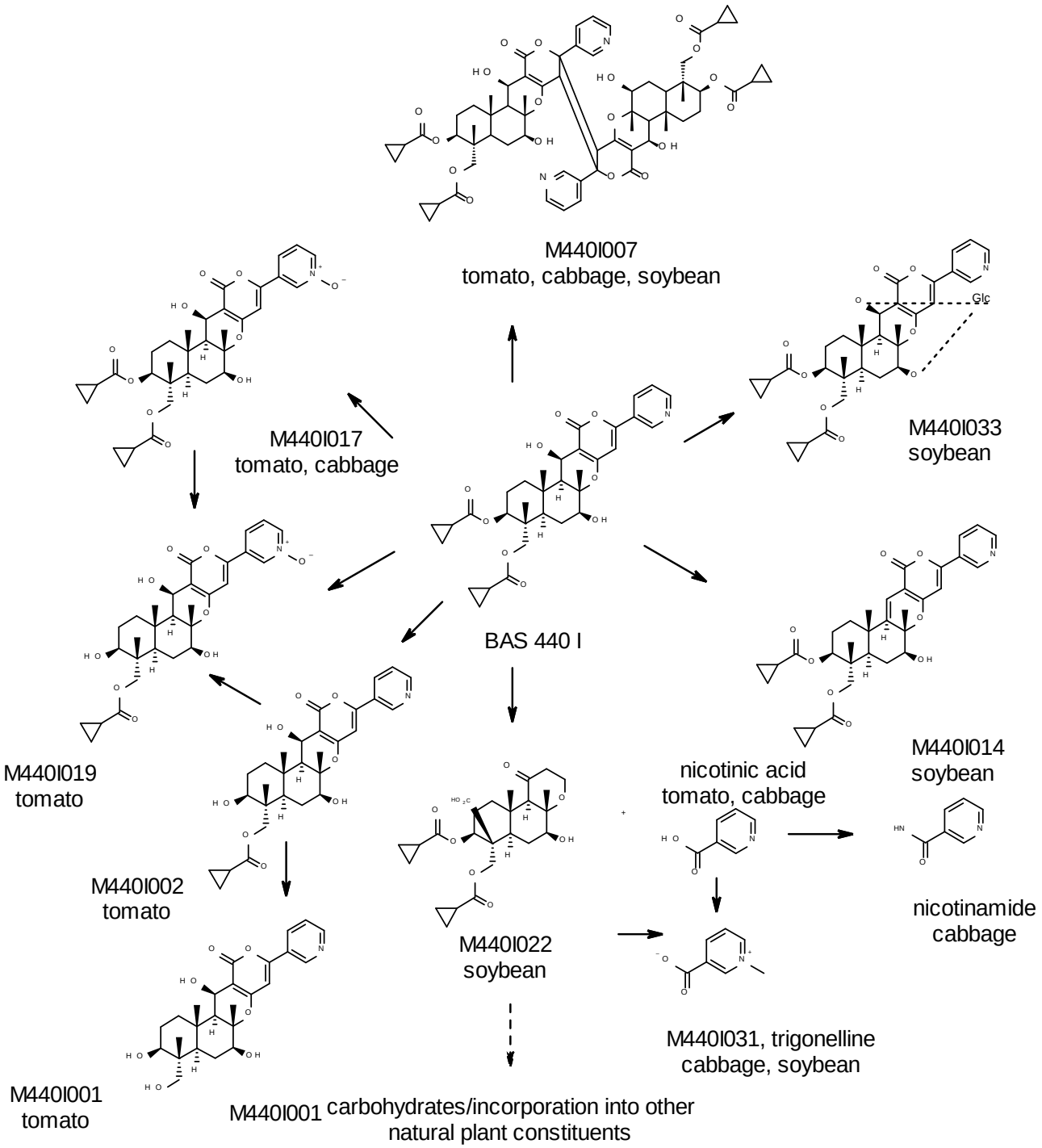
4.1 Metabolism

Plants

The metabolism of afidopyropen was investigated in commodities from three different crop groups: tomato (fruits), cabbage (leafy crops) and soybeans (pulses and oilseeds). Four different radiolabel positions were used. Tomato and cabbage studies were conducted with 14C-label on the nicotinic acid 9-C (nicotinic acid label) or on the pyranone-4-C (pyranone label). Studies with soybean were conducted with the pyranone label, with a nicotinic acid label (multiply labelled on pyranone-6C, pyridine-2,6-C) or with the label on the carbonyl of both cyclopropane carboxylic acid groups.

Afidopyropen (BAS 440 I) was present in significant levels (6.9 – 61.3% TRR (Total Radio Active Residues), 0.033–3.80 mg/kg) in all crop samples except soybean seed. The main metabolic transformation in all crop categories was the formation of a dimer of BAS 440 I (metabolite M440I007) (n.d. – 49.9% TRR, up to 3.53 mg/kg), which was formed by cycloaddition at the double bond in the pyranone (pyrone) ring. The studies with the nicotinic acid label indicated that the nicotinic acid ring of BAS 440 I is cleaved and low levels of nicotinic acid and/or nicotinamide were observed in tomato, cabbage and soybean. In soybean and cabbage, the nicotinic acid was further metabolised to trigonelline, a product of niacin metabolism that occurs naturally in a wide range of plants particularly in legumes. Trigonelline was the predominant component identified (0.179 mg/kg, 47.3% TRR) in soybean seed in the study with the nicotinic acid label. Studies with the pyranone label indicated that degradation of the molecule also occurs in the pyranone ring. Polar molecules were identified as sugars (carbohydrates) particularly in the soybean seed which indicated the formation of two-carbon fragments and incorporation of the 14C-label into plant sugars and other plant matrices. In the study with the pyranone label in tomato, low amounts (≤ 0.08 mg/kg, 3.6% TRR) of metabolites with cleavage of ester groups (M440I001, M440I002) were detected on tomato leaves. Components due to hydrolysis of the ester groups were not identified in tomato fruit, cabbage or soybean. The only metabolites to exceed 10% TRR in plant matrices are the dimer M440I007 and trigonelline (soybean seed and pods only).

The proposed metabolic pathway for afidopyropen in primary crops is summarised below:

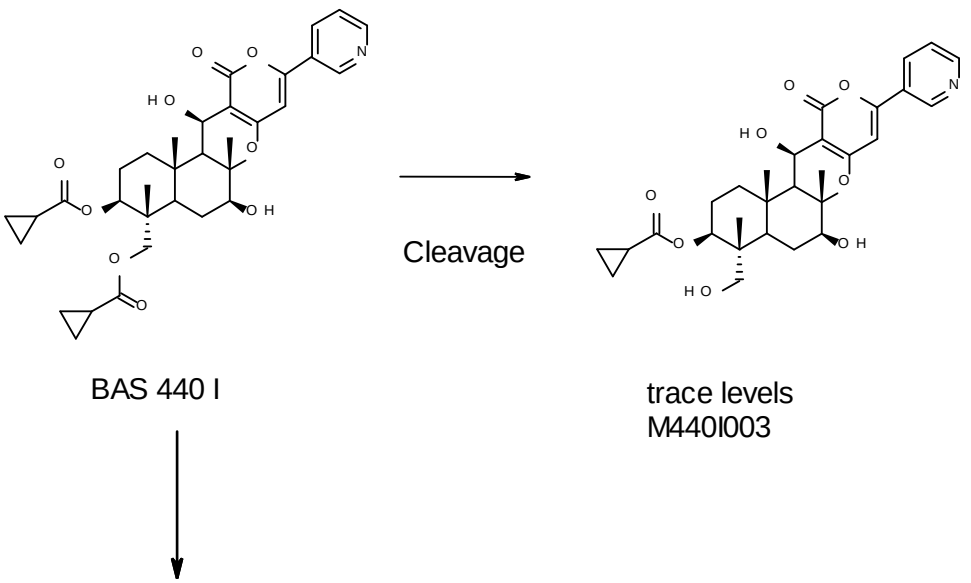


Summary of metabolism of afidopyropen (BAS 440 I) in plants

Confined rotational crops

The applicant has provided details of 3 rotational crop studies conducted on confined rotational crops including a root vegetable, a leafy vegetable and a cereal, using a variety of label positions. Radiolabelled afidopyropen was applied to bare soil and crops planted following at 30, 60, 90, 120 or 365 day Plant Back Interval (PBI).

BAS 440 I was not detected in any sample of confined rotational crops. One metabolite of BAS 440 I, M440I003, was detected in trace amounts (0.9% TRR, 0.001 mg/kg) in spring wheat straw planted 31 days after treatment at 125 g ai/ha (Nicotinic acid label). M440I003, an aerobic soil metabolite, results from ester hydrolysis at the 4-hydroxyl methyl position and could occur through uptake from the soil rather than cleavage of BAS 440 I within the plant. Uptake was generally low, and BAS 440 I was metabolised to a number of low level polar and nonpolar metabolites all occurring at ≤0.008 mg/kg. A significant amount of radiolabel was not extractable using methanol or water. Enzyme treatment released a range of polar components each comprising ≤0.008 mg/kg, indicating incorporation or inclusion of the radiolabel into plant biomolecules.



Proposed metabolic pathway for afidopyropen (BAS 440 I) in confined rotational crops

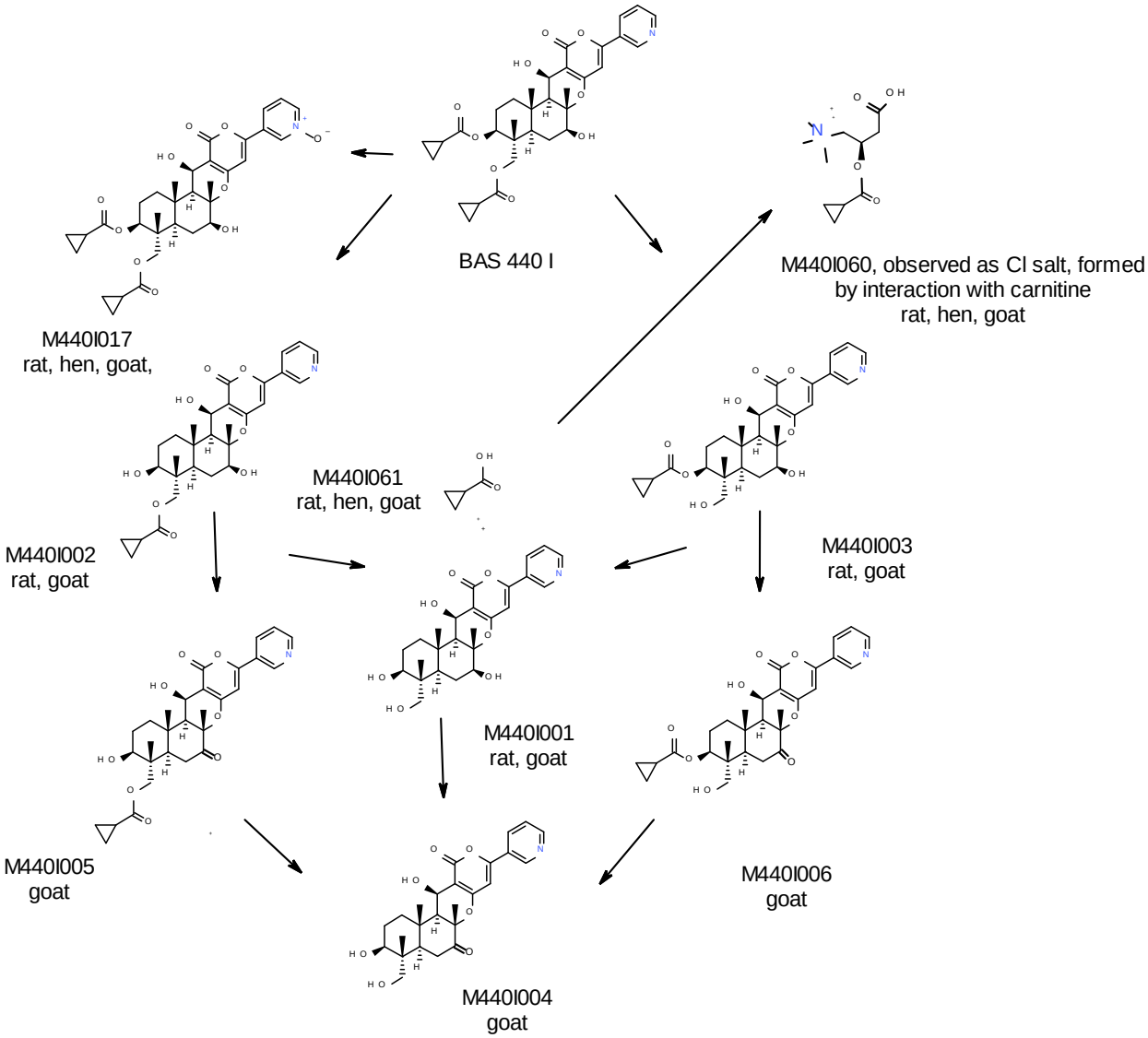
Livestock

The metabolism of afidopyropen was investigated in the laying hen and lactating goat. One goat study was conducted with ^{14}C-afidopyropen with the label on the pyranone-4-C. The hen study and a second goat study were conducted with the ^{14}C label on the carbonyl of both cyclopropane carboxylic acid groups.

In the hen study, components of the residue exceeding 10% TRR were unchanged parent afidopyropen in all matrices (46.5-96.6%, 0.021 – 0.355 mg/kg), metabolite M440I017 in liver (20.9%, 0.085 mg/kg) and M440I060 (CPCA-carnitine) in muscle (37.7%, 0.017 mg/kg).

Based on the goat study performed with the Pyranone label, components of the residue exceeding 10% TRR were unchanged parent afidopyropen (16.6–35.0%, 0.002–0.068 mg/kg) and metabolites M440I003 (4.4–22.4%, 0.002–0.009 mg/kg) and M440I001 (23.5-65.8%, 0.002–0.089 mg/kg) in tissues liver, kidney, muscle, parent in fat (49.3%, 0.002 mg/kg) and metabolites M440I001 (45%, 0.002 mg/kg) and M440I005 (17.1%, 0.001 mg/kg) in milk and cream. Based on the goat study performed with the CPCA label, components of the residue exceeding 10% TRR were unchanged parent afidopyropen (18.5%, 0.038 mg/kg) and metabolites M440I003 (12.4%, 0.026 mg/kg) and cyclopropanecarboxylic acid (CPCA, M440I061) (27.8%, 0.057 mg/kg) in liver, and M440I061 in kidney (64.1%, 0.31 mg/kg). Metabolite M440I060 was a significant residue in muscle (91%, 0.28 mg/kg). In the study with the CPCA label, an unidentified component or components related to CPCA were present in milk and cream (up to 67.6%, 0.16 mg/kg).

The proposed metabolic pathway for afidopyropen in animals is shown below:



Summary of metabolism of afidopyropen (BAS 440 I) in animals

4.2 Analytical methods

Plant commodities were analysed by BASF analytical method D1103/1. Residues of afidopyropen (BAS 440 I) and its metabolite M440I007 in crop samples were extracted by shaking with acetonitrile, or with acetonitrile and water for dry plant matrices. Residues in the extract were cleaned-up and partitioned by shaking in the presence of a mixture of salts (sodium chloride, magnesium sulfate and citrate buffering agents) into the organic layer, and centrifuged. The residues in the acetonitrile layer were further purified with the addition of a second salt mixture (containing magnesium sulfate to remove residual water and primary secondary amine, PSA sorbent, to remove sugars and fatty acids) and centrifuged. An aliquot of the organic phase was diluted with acidified water, further diluted to a specific volume with acetonitrile:water (1:1, v/v), and then analyzed by HPLC-MS/MS or UPLC-MS/MS. The LOQ for afidopyropen and M440I007 in crop commodities was 0.01 mg/kg. The LOD for afidopyropen and M440I007 was set at 0.002 mg/kg, which was 20% of the defined LOQ. Recoveries from fortified control samples of various plant matrices were within acceptable limits.

BASF Analytical Method No. D1507/01 was used for the determination of residues of afidopyropen (BAS 440 I) and its metabolites M440I001, M440I003, M440I005, and CPCA carnitine in livestock commodities by LC-MS/MS. Following solvent extraction, residues of afidopyropen in livestock commodities are cleaned up by solid phase extraction (SPE). The residues were determined by LC-MS/MS. The validated LOQ for residues in livestock tissues (bovine muscle, fat, liver) and poultry egg is 0.01 mg/kg each for afidopyropen, M440I001 and M440I003, and 0.05 mg/kg for CPCA carnatine. The validated LOQ for residues in milk (bovine) is 0.001 mg/kg each for afidopyropen, M440I001 and M440I005, and 0.005 mg/kg for CPCA carnatine. Average recoveries from fortified control samples were generally within acceptable limits, with the exception of the recoveries for CPCA carnitine from eggs with average recoveries in the range of 66–74%.

Storage stability

The applicant has provided a storage stability study, which indicates that residues of afidopyropen and its metabolite M440I007 are stable in barley grain, lettuce, navy bean, soybean oil, orange fruit, soybean hay and soybean seed for at least 24 months when stored frozen at -20 °C. The commodities cover the range of required categories as follows: lettuce (high water), soybean oil, soybean seed (high oil), navy bean (high protein), orange (high acid) and barley grain (high starch).

In the residue trials submitted, all samples were maintained under freezer conditions, (ie -18 °C) prior to analysis and tested within 468 days (~16 months) of collection. This is acceptable for the purposes of the current application.

4.3 Residue definition

Plant commodities

The proposed residue definition for commodities of plant origin is afidopyropen. This definition is suitable for both enforcement and for dietary risk assessment, noting that parent afidopyropen was present in all tomato, cabbage and soybean commodities (except soybean seed) in the metabolism studies.

M440I007 (>10% TRR in tomatoes, cabbage and soybean commodities except seed) is considered to be of lower toxicological significance than parent afidopyropen by the draft toxicological assessment and will not be included in the residue definition for commodities of plant origin.

Trigonelline is a naturally occurring plant alkaloid that the applicant has indicated may be found at levels from 4 mg/kg in corn seed to 554 mg/kg in white beans. For these reasons analysis of trigonelline was excluded in the crop field trials. Trigonelline will not be included in the residue definition for commodities of plant origin.

Animal commodities

CPCA-Carnitine (M440I060) was the most significant residue in goat muscle (91%, 0.283 mg/kg) from the CPCA label study so would be a suitable indicator of mis-use for the enforcement definition. The lactating cow transfer study confirmed a higher potential for CPCA than parent in muscle and also milk. It was also observed in poultry muscle at 37.7% TRR (0.017 mg/kg) in the CPCA-label study. Parent afidopyropen was also significant at up to 96.6% TRR (in egg yolk) in the poultry study and up to 35% TRR (in liver) in the goat study with the pyranone label. A residue definition of afidopyropen and M440I060 (CPCA-carnitine) is suitable for enforcement for both ruminants and poultry. A validated analytical method (D1507/15) is available for the determination of both parent afidopyropen and CPCA-carnitine in animal tissues, eggs and milk. Given the proposed use of afidopyropen does not include any significant animal feeds, this definition is also suitable for dietary risk assessment at this time.

4.4 Residue trials

The maximum proposed use pattern for afidopyropen on vegetables (except potatoes) allows for two applications for control of aphids at 10 g ai/ha and to the same crop another two applications for whitefly control at 35 g ai/ha. The re-treatment interval is 14 days for control of aphids and not specified for control of whitefly. The proposed withholding period for vegetables (except potatoes) is 1 day. As no residue data for vegetables grown in protected situations is available at this time, the following restraint is recommended for the label: ‘DO NOT use in protected cropping situations’.

Brassica vegetables

Australian trials were conducted on broccoli, cabbage and Brussels sprouts (one trial on each). This is supported by 10 US trials on broccoli and 10 on cabbage.

In the residue trials, the treated plots received two foliar applications of afidopyropen (100.0 g a.i./L DC, formulation code, BAS 440 00 I) targeting 10 + 10 g a.i./ha/application followed by another two foliar applications of afidopyropen targeting 50 + 50 g a.i./ha/application, with 7-day retreatment intervals.

In Australian trials, residues at 0 DALA were 0.06 mg/kg in broccoli, 0.03 mg/kg in cabbage and 0.01 mg/kg in Brussels sprouts.

In US trials, residues in broccoli at 0 DALA were 0.05, 0.05, 0.10, 0.11, 0.12, 0.13, 0.13, 0.20, 0.20 and 0.24 mg/kg.

In US trials, residues in cabbage heads w/o wrapper leaves at 0 DALA were <0.002 (2), <0.01 (6), 0.02 and 0.03 mg/kg.

Based on the combined dataset for Brassica vegetables (using cabbage w/o wrapper leaves) the OECD Maximum Residue Limit (MRL) calculator recommends a MRL of 0.4 mg/kg. The Standard Trial Median Residue (STMR) is 0.03 mg/kg. A MRL of 0.5 mg/kg is recommended for afidopyropen on VB 0040 Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead brassicas. This MRL should be conservative as it is based on data immediately after the last application when a 1 day WHP is proposed, also application rates were up to 1.4× that proposed.

Leafy vegetables (including brassica leafy vegetables) and parsley

Australian trials on Chinese cabbage and leafy lettuce (one each) are supported by US trials on mustard greens (eight trials), head lettuce (eight trials), leaf lettuce (eight trials) and spinach (eight trials).

In the residue trials, the treated plots received two foliar applications of afidopyropen (100.0 g a.i./L DC, formulation code, BAS 440 00 I) targeting 10 + 10 g a.i./ha/application followed by another two foliar applications of afidopyropen targeting 50 + 50 g a.i./ha/application, with 7-day retreatment intervals.

In Australian trials, residues at 0 days after last application (DALA) residues were 1.12 mg/kg in leafy lettuce and 0.086 mg/kg in Chinese cabbage.

In US trials, residues in head lettuce (w/o wrapper leaves) at 0 DALA were <0.01 (3), 0.02, 0.03 (2), 0.06 and 0.28 mg/kg.

In US trials, residues in leaf lettuce at 0 DALA were 0.05, 0.18, 0.29, 0.49, 0.64, 0.72, 0.82 and 0.97 mg/kg.

In US trials, residues in spinach at 0 DALA were 0.10, 0.56, 0.63, 0.63, 0.72, 0.85, 1.06 and 1.17 mg/kg.

In US trials, residues in mustard greens at 0 DALA were 0.14, 0.73, 1.11, 1.13, 1.36, 1.85, 2.12 and 3.14 mg/kg.

Based on the combined dataset for leafy vegetables (using head lettuce w/o wrapper leaves) the OECD MRL calculator recommends a MRL of 4 mg/kg. The median residue is 0.63 mg/kg, the High Residue (HR) is 3.14 mg/kg. MRLs of 5 mg/kg are recommended for afidopyropen on VL 0053 Leafy vegetables and by extrapolation HH 0740 Parsley. These MRLs should be conservative as they are based on data immediately after the last application when a 1 day WHP is proposed, also application rates were up to 1.4× that proposed.

Celery

Nine US trials on celery have been provided in support of the application. The treated plots received two foliar applications of afidopyropen (100.0 g a.i./L DC, formulation code, BAS 440 00 I) targeting 10 + 10 g a.i./ha/application followed by another two foliar applications of afidopyropen targeting 50 + 50 g a.i./ha/application, with 7-day retreatment intervals.

The trials did not sample celery at the proposed 1 day WHP. At 0 DALA residues in celery were 0.03, 0.13, 0.13, 0.29, 0.45, 0.53, 1.05, 1.12 and 1.89 mg/kg. The STMR is 0.45 mg/kg. The OECD MRL calculator recommends a MRL of 3 mg/kg. This MRL will likely be conservative as it is based on data immediately after the last application when a 1 day WHP is proposed, also application rates were up to 1.4× that proposed.

Cucurbits

Twenty-seven field trials were conducted on cucurbits grown in the USA during the 2014 growing season. Nine trials were conducted on cucumber, eight on cantaloupe and ten on squash.

The treated plots received two foliar applications of afidopyropen (100.0 g a.i./L DC, formulation code, BAS 440 00 I) targeting 10 + 10 g a.i./ha/application followed by another two foliar applications of afidopyropen targeting 50 + 50 g a.i./ha/application, with 7-day retreatment intervals.

In general the trials did not sample cucurbits at the proposed 1 day withholding period.

At 0 DALA residues in cucumber were 0.06, 0.09, 0.10, 0.12, 0.13, 0.18, 0.19, 0.39 and 0.44 mg/kg.

At 0 DALA residues in cantaloupe were <0.002, 0.01, 0.02, 0.02, 0.02, 0.02, 0.02 and 0.03 mg/kg.

At 0 DALA residues in squash were <0.01 (3), 0.01, 0.01, 0.02, 0.02, 0.03, 0.04 and 0.04 mg/kg.

Based on the combined dataset for cucurbits the OECD MRL calculator recommends a MRL of 0.6 mg/kg. The STMR is 0.02 mg/kg, and the HR is 0.44 mg/kg. An MRL of 0.7 mg/kg is recommended for afidopyropen on VC 0045 Fruiting vegetables, Cucurbits. The MRL should be sufficient as it is based on data immediately after the last application when a 1 day WHP is proposed, also application rates were up to 1.4× that proposed.

Fruiting vegetables, other than cucurbits

Two Australian residue trials (one each on tomato and pepper) are supported by 20 overseas trials on tomatoes (including cherry tomato) and 10 overseas trials on peppers (including chilli peppers).

In the residue trials, the treated plots received two foliar applications of afidopyropen (100.0 g a.i./L DC, formulation code, BAS 440 00 I) targeting 10 + 10 g a.i./ha/application followed by another two foliar applications of afidopyropen targeting 50 + 50 g a.i./ha/application, with 7-day retreatment intervals.

The residue trials for fruiting vegetables, other than cucurbits, did not sample at the proposed 1 day WHP.

In Australian trials, residues in tomatoes and peppers at 0 DALA were 0.013 and 0.006 mg/kg respectively.

In US trials, residues in tomatoes at 0 DALA were <0.01 (2), 0.01, 0.01, 0.01, 0.02, 0.02, 0.02, 0.02, 0.02, 0.02, 0.03, 0.03, 0.04, 0.04, 0.05, 0.06, 0.07, 0.07 and 0.10 mg/kg.

In the US trials, residues in peppers at 0 DALA were <0.01, 0.01, 0.02, 0.03, 0.03, 0.03, 0.05, 0.06, 0.06 and 0.06 mg/kg.

Based on the combined dataset the OECD MRL calculator recommends a MRL of 0.15 mg/kg. The HR is 0.10 mg/kg, and the STMR is 0.03 mg/kg. An MRL of 0.2 mg/kg is recommended for afidopyropen on VO 0050 fruiting vegetables, other than cucurbits. This MRL will likely be conservative as it is based on data immediately after the last application when a 1 day WHP is proposed, also application rates were up to 1.4× that proposed.

Tomato pomace from processed tomatoes can be used as a feed for livestock. In a tomato processing study provided by the applicant the average processing factor for dry tomato pomace was 17.6×. Based on a HR in tomatoes of 0.103 mg/kg, the HR-P for dry tomato pomace is 1.81 mg/kg. The STMR-P for dry tomato pomace is 0.37 mg/kg (0.021 × 17.6). An MRL of 3 mg/kg is recommended for afidopyropen on Tomato pomace, dry.

Potato, sweet potato, ginger

The maximum proposed use of afidopyropen on potato, sweet potato and ginger is for two applications at 35 g ai/ha in conjunction with a 7 day WHP. The re-treatment interval is not specified for this use pattern.

Two Australian residue trials on potatoes are supported by 20 trials conducted in the USA. A potato processing study involving application at exaggerated rates has also been conducted.

In the residue trials, the treated plots received two foliar applications of afidopyropen (100.0 g a.i./L DC, formulation code, BAS 440 00 I) targeting 10 + 10 g a.i./ha/application followed by another two foliar applications of afidopyropen targeting 50 + 50 g a.i./ha/application, with 7-day retreatment intervals.

Residues of afidopyropen and M440I007 in potato tubers in the Australian trials at 7 days after the last application at 50 g ai/ha (1.4×) were each <0.003 mg/kg (n = 2). Residues were also not detectable at any other time point 0–14 DALA.

Residues of afidopyropen and M440I007 in potato tubers in the US trials at 7 days after the last application at 50 g ai/ha (1.4×) were each <0.002 mg/kg (n = 20). Residues were also not detectable at any other time point 0–14 DALA.

MRLs of *0.01 mg/kg are recommended for afidopyropen on each of VR 0589 Potato, VR 0508 sweet potato and by extrapolation HS 0784 Ginger, root.

Cotton

The maximum proposed use of afidopyropen on cotton is for two applications at 35 g ai/ha in conjunction with a 7 day WHP. The re-treatment interval is not specified for this use pattern.

Three Australian residue trials on cotton are supported by 12 trials conducted in the USA.

In the Australian and US trials, the treated plots received two foliar applications of afidopyropen (100.0 g a.i./L DC, formulation code, BAS 440 00 I) targeting 10 + 10 g a.i./ha/application followed by another two foliar applications of afidopyropen targeting 50 + 50 g a.i./ha/application, with 7-day retreatment intervals.

In the Australian trials, residues in cotton seed at 7 DALA were <0.003 (n = 3) mg/kg.

In the US trials, residues in cotton seed at 7 DALA were <0.002, <0.01 (6), 0.01, 0.02, 0.03, 0.04 and 0.06 mg/kg.

Based on the combined dataset the OECD MRL calculator recommends a MRL of 0.09 mg/kg. The HR is 0.06 mg/kg, the STMR is <0.01 mg/kg. An MRL of 0.1 mg/kg is recommended for afidopyropen on SO 0691 Cotton seed. It is noted that the rate in the trials was up to 1.4× that proposed.

The applicant has provided details of a cotton processing study conducted at three sites in the USA. At one of the sites residues were not observed in the seed RAC or the processed fractions. At the other sites processing factors for cotton seed meal were 0.29× and 0.31×. Processing factors for hulls were 0.29× and 1.03×. Processing factors for cotton seed oil were 0.02× and 0.06×. As residues of afidopyropen did not concentrate on processing to cotton seed meal, hulls or oil, it is not necessary to establish separate MRLs for these commodities. For livestock feeding, the STMR-P for cotton seed meal is 0.003 mg/kg (0.01 × 0.30), the STMR-P for hulls is 0.0066 (0.01 × 0.66).

4.5 Crop rotation

In the confined rotational crop studies discussed in section 4.1, afidopyropen (BAS 440 I) was not detected in any sample of confined rotational crops. One metabolite of afidopyropen, M440I003, was detected in trace amounts (0.9% TRR, 0.001 mg/kg) in spring wheat straw planted 31 days after treatment at 125 g ai/ha (Nicotinic acid label). Uptake was generally low, and afidopyropen was metabolised to a number of low level polar and nonpolar metabolites, all occurring at ≤0.008 mg/kg. A significant amount of radiolabel was not extractable using methanol or water. Enzyme treatment released a range of polar components, each comprising ≤0.008 mg/kg, indicating incorporation or inclusion of the radiolabel into plant biomolecules.

The risk of residues of afidopyropen or its metabolites occurring in rotational or following crops as a result of the proposed use involving a total seasonal application rate of up to 90 g ai/ha is low.

4.6 Animal commodities and Maximum Residue Limits (MRLs)

Ruminants

Animal transfer studies were considered for lactating cattle where the animals were dosed with afidopyropen at target dose levels corresponding to 1.5 ppm, 4.5 ppm and 15.0 ppm in the feed (dry weight basis) daily for 29 consecutive days. For cattle the estimated maximum livestock dietary burden is 0.042 ppm based on a diet containing cotton seed, cotton seed meal and hulls and tomato pomace. The expected residues and proposed MRLs are summarised below:

Table 5: Cattle commodities

FEEDING LEVEL (ppm)	MILK	MUSCLE	LIVER	KIDNEY	FAT
AFIDOPYROPEN + CPCA RESIDUE (mg/kg)					
1.5	<0.012	<0.114	0.041	<0.024	<0.024
0.042, estimated burden	<LOQ	<0.003	0.001	<LOD	<LOD
Recommended MRLs	*0.01	*0.1	*0.1		-

LOQ is 0.001 mg/kg for afidopyropen and 0.005 mg/kg for CPCA-carnitine in milk
LOQ is 0.01 mg/kg for afidopyropen and 0.05 mg/kg for CPCA-carnitine in tissues
LOD is 0.002 mg/kg for afidopyropen and 0.01 mg/kg for CPCA-carnitine in tissues
CPCA-cartinine multiplied by 2.23 to convert to parent equivalents

Estimated residues in animal commodities will be below method LOQs. MRLs for afidopyropen are recommended at the combined LOQs for parent and the CPCA metabolite as below:

MO 0105 Edible offal (Mammalian)	*0.1 mg/kg
MM 0095 Meat [mammalian]	*0.1 mg/kg
ML 0106 Milks	*0.01 mg/kg

Poultry

An animal transfer study for poultry has not been provided. However, the estimated dietary burden (from cotton seed meal) is significantly below the threshold of 0.1 ppm where a feeding study is required.

Using the hen metabolism study, which involved dosing at 12 ppm, predicted residues in eggs and tissues from feeding at the estimated livestock dietary burden 0.0003 ppm are estimated below:

Table 6: Poultry commodities

FEEDING LEVEL (ppm)	EGGS	MUSCLE	LIVER	FAT	
AFIDOPYROPEN + CPCA RESIDUE (mg/kg)					
12	0.355 (yolk)	0.038	0.241	0.097	
0.0003, estimated burden	<LOQ	<LOQ	<LOQ	<LOQ	
Recommended MRLs	*0.1	*0.1	*0.1		-

LOQ is 0.01 mg/kg for afidopyropen and 0.05 mg/kg for CPCA-carnitine in tissues and eggs.

Poultry animal commodity MRLs for afidopyropen are recommended at the combined LOQs for parent and the CPCA metabolite as below:

PE 0112 Eggs	*0.1 mg/kg
PO 0111 Poultry, Edible offal of	*0.1 mg/kg
PM 0110 Poultry meat	*0.1 mg/kg

4.7 Fat solubility and potential for bioaccumulation

The log P_{ow} for afidopyropen is 3.45 suggesting moderate fat solubility. In the goat metabolism studies, residues of afidopyropen were at similar levels in muscle and fat. In the goat study with the CPCA-label, the CPCA-carnitine metabolite (M440I060) was found at higher levels in muscle than in fat. In the lactating cattle animal transfer study, residues of afidopyropen or its CPCA-carnitine metabolite were not detected in fat after feeding at up to 15 ppm in the diet. The MRLs for afidopyropen in meat will not be established in the fat at this time.

4.8 Spray drift

In the animal transfer study feeding at 1.5 ppm gave a maximum residue of 0.019 mg/kg (parent) in liver, with the metabolite <0.01 mg/kg. The estimated feeding level for residues of parent to be at the LOQ of 0.01 mg/kg is 0.79 ppm. Assuming pasture consists of 1500 kg DM/ha this corresponds to an allowable drift of 1.185 g ai/ha, or 0.034× the maximum label field rate of 35 g ai/ha.

A coarse droplet size is specified for the product.

Using the APVMA standard scenario for ground application with a high boom with a coarse droplet size, drift will drop to below 0.034× of the field rate by 4 metres downwind from the application area.

Given the insignificant size of this buffer it is recommended that mandatory no spray zones are not required for protection of international trade for either ground application.

4.9 Dietary risk assessment

The chronic dietary exposure to afidopyropen is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived primarily from the 2011-12 National Nutritional and Physical Activity Survey. The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for afidopyropen is equivalent to 1% of the ADI.

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

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived primarily from the 2011-12 National Nutritional and Physical Activity Survey. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. The highest acute dietary exposure was <50% of the ARfD.

It is concluded that the acute dietary exposure of afidopyropen is acceptable.

4.10 Recommendations

In considering the application, and section 5A(3)(b)(iii) of the schedule to the Code Act, the following amendments will be made to the APVMA MRL Standard should the application be approved:

Table 7: Proposed changes to APVMA MRL Standard

TABLE 1

COMPOUND		FOOD	MRL (mg/kg)
ADD:			
Afidopyropen			
VB	0040	Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead brassicas	0.5
VS	0624	Celery	3
SO	0691	Cotton seed	0.1
MO	0105	Edible offal (Mammalian)	*0.1
PE	0112	Eggs	*0.1
VC	0045	Fruiting vegetables, Cucurbits	0.7
VO	0050	Fruiting vegetables, other than Cucurbits	0.2
HS	0784	Ginger, root	*0.01
VL	0053	Leafy vegetables	5
MM	0095	Meat [mammalian]	*0.1
ML	0106	Milks	*0.01
HH	0740	Parsley	5
VR	0589	Potato	*0.01
PO	0111	Poultry, Edible offal of	*0.1
PM	0110	Poultry meat	*0.1
VR	0508	Sweet potato	*0.01

TABLE 3

COMPOUND	RESIDUE
ADD:	
Afidopyropen	Commodities of plant origin: Afidopyropen Commodities of animal origin: Afidopyropen and the carnitine conjugate of cyclopropanecarboxylic acid (M440I060), expressed as afidopyropen

TABLE 4

COMPOUND	ANIMAL FEED COMMODITY	MRL (mg/kg)
ADD:		
Afidopyropen		
	Tomato pomace, dry	3

MRL amendments recommended for Tables 1 and 3 above will be considered for inclusion in Schedule 20 of the Australia New Zealand Food Standards Code.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Cotton seed and its derived oils and meals are considered to be major export commodities[2], as are commodities of animal origin, such as meat, offal and dairy products, which may be derived from livestock fed feeds produced from treated cotton seed meal and tomato pomace. Residues in these commodities resulting from the use of Versys may have the potential to unduly prejudice trade.

Detectable residues are not expected to occur in animal commodities from livestock fed on cotton seed meal and tomato pomace from treated crops. The risk to trade in animal commodities does not require further consideration.

The vegetable crops on the label are not considered to be major export commodities so will also not be considered further. The trade advice statement on the label is appropriate for the vegetable uses:

Growers should note that MRLs or import tolerances do not exist in all markets for labelled crops treated with VERSYS Insecticide. Additionally, some export markets have established MRLs different to those in Australia. If you are growing crops for export, please check with BASF Australia Ltd for the latest information on MRLs and import tolerances BEFORE using this product.

5.2 Destination and value of exports

In 2015–16 Australia exported 146.7 kt of cottonseed, 5.22 kt of cotton seed oil and 0.17 kt of cotton seed meal (22.5 kt in 2014–15) (Agricultural Commodity Statistics, ABARES 2016). The major markets for cotton seed were Japan, Republic of Korea, Saudi Arabia and the United States. The major markets for cotton seed meal were New Zealand and the Republic of Korea (2014–15). Markets for Australian cotton seed oil were not specified by ABARES.

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

5.3 Overseas registration and approved label instructions

The applicant indicated that there are no current registrations of afidopyropen overseas. Submissions for registration have been made in Canada, India, Mexico and the USA.

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

5.4 Comparison of Australian MRLs with Codex and overseas MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods. Afidopyropen has not been considered by Codex. The applicant indicated that afidopyropen has been scheduled for consideration by the JMPR with expected submission in 2018 and nomination of CXLs in 2020.

No overseas MRLs have been established for afidopyropen at this time.

5.5 Potential risk to trade

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

Detectable residues (up to 0.06 mg/kg) may be present in cotton seed, which is a major export commodity, and MRLs have yet to be established overseas. However, the STMR in cotton seed from the available trials was <0.01 mg/kg, and residues were reduced on processing to oil and meal, hence the risk is considered to be low. Comment is sought from the relevant industry groups on the potential risk to trade in cotton from the proposed use.

6 WORKPLACE HEALTH AND SAFETY ASSESSMENT

6.1 Summary

Farmers, agricultural workers and professional spray operators will be the main users of Versys Insecticide. Workers may be exposed to the product or its active constituent, afidopyropen, when opening containers, mixing / loading, applying the spray mixture, maintaining equipment, cleaning up spills and equipment, and when performing work activities in treated crops. The main route of exposure to the product and active will be the skin, although exposure via inhalation and eye contact is also possible.

Versys Insecticide is of low acute oral and dermal toxicity and moderate inhalation toxicity, is a slight eye and moderate skin irritant, but does not cause skin sensitisation. Based on the use pattern and this acute hazard profile, workers handling and preparing the product will need to wear coveralls and gloves for protection from skin irritation.

In the absence of exposure monitoring data from persons preparing and applying Versys Insecticide under field conditions, dermal and inhalation exposure were estimated using the Pesticide Handler Exposure Database (PHED). Relative to the workplace health and safety (WHS) NOAEL for repeat-dose toxicity of afidopyropen in laboratory animals, the assessment indicated an acceptable margin of exposure (MOE) of greater than 100 for mixer / loaders preparing the product while wearing coveralls and gloves without respiratory protective equipment (RPE). There were also acceptable MOEs for spray operators using groundboom sprayers (without cabs), hand-held high- or low-pressure handwands and backpack sprayers without the use of personal protective equipment (PPE).

Using the US EPA Re-Entry Interval Calculator, acceptable MOEs were also estimated for re-entry workers to foliar residues of afidopyropen while performing agricultural activities in treated crops on or after the day of application. The only risk management measure needed to protect re-entry workers is a label statement directing them not to enter treated crops until the spray has dried. When used to estimate the exposure of a child playing in an area adjacent to a treated crop, the US EPA Bystander Exposure model indicated an exposure level below the ADI for afidopyropen via the diet.

Based on the hazard, exposure and risk assessments for mixer / loaders, applicators and re-entry workers, First Aid Instructions and Safety Directions (including warnings, precautions and PPE) have been recommended for inclusion on the product label. With these hazard and exposure mitigation measures in place, it was considered that there should be no adverse effects on workplace health and safety from the use of Versys Insecticide in accordance with the label directions.

6.2 Health hazards

Exposure during use

Farmers, agricultural workers and professional spray applicators will be the main users of Versys Insecticide. Workers may be exposed to the concentrate when opening containers; pouring, diluting or mixing the product; and cleaning up spills and equipment. Exposure to afidopyropen in the finished spray mixture may also occur during loading, application and equipment clean-up or maintenance. The main potential route of exposure is the skin, with some further potential for eye contact. Additional exposure via inhalation of respirable aerosols could occur during spray application.

Acute toxicological hazards of the product

Versys Insecticide is of low acute oral and dermal toxicity in rats (LD50s were >2000 and >5000 mg/kg bw via the respective routes), but of moderate inhalation toxicity, with an LC50 between 600 and 1130 mg/m3 in rats when administered as a respirable aerosol. The product is a slight eye and moderate skin irritant in rabbits, but does not cause skin sensitisation in Guinea pigs.

Based on this hazard profile, workers handling the product are at risk from inhalation toxicity and irritation to the eyes and skin, requiring the inclusion of suitable hazard and precaution statements on the product label together with directions to wear coveralls and protective gloves when opening containers and preparing the spray mixture. Respiratory protective equipment (RPE), however, is not considered necessary because of the low potential for the formation of respirable aerosols when pouring, mixing or loading the concentrate, and the low concentration of the formulation constituents when present in the diluted spray mixture.

Repeat-dose hazards of the active, afidopyropen

Versys Insecticide is expected to be applied on a seasonal basis, as required by crop growth stage, environmental conditions and pest pressure. Consequently, occupational exposure to afidopyropen will probably be discontinuous, occurring repeatedly during a growing season but followed by an exposure-free interval between harvest and commencement of the next growth season. A NOAEL for assessment of occupationally exposed persons was therefore chosen from among the short-term repeat-dose, subchronic and developmental toxicity studies with afidopyropen. In the absence of a suitable study by dermal administration, the WHS assessment was based on route-to-route extrapolation from a study performed via the oral route. The lowest NOAEL from among the eligible studies was 15 mg/kg bw/d, set in a 90-day dog study on the basis of histological evidence of toxicity to the liver, reduced bodyweight gain and vomiting at and above the next highest dose of 30 mg/kg bw/d. Adjusting for the incomplete (70%) oral absorption of afidopyropen in rats, the final value of the WHS NOAEL became 10.5 mg/kg bw/d. The acceptable margin of exposure (MOE) from the WHS NOAEL was set at 100 to allow for differences in toxicokinetics, toxicodynamics and sensitivity between and within species.

6.3 Exposure

Exposure during mixing, loading and application

In the absence of exposure monitoring studies on workers preparing and applying Versys Insecticide, dermal and inhalation exposure to afidopyropen was estimated using the US EPA Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998). The assessment indicated an acceptable MOE of greater than 100 for workers during open pour mixing and loading of Versys Insecticide, while wearing coveralls and protective gloves without RPE. There were also acceptable MOEs for application by groundboom sprayer (without cab), hand-held high- or low-pressure handwand and backpack sprayer without the use of personal protective equipment (PPE). Therefore, PPE is not required during application of the product.

Exposure during re-entry to treated crops

In addition to becoming exposed to pesticides during their preparation for use and application, agricultural workers may also experience exposure to pesticide residues when re-entering previously treated crops to perform activities such as harvesting, thinning, scouting for pests and irrigation. The principal route of exposure is via the skin, through direct contact with contaminated foliage. Re-entry workers' exposure to foliar residues of afidopyropen were estimated using the US EPA Re-Entry Interval Calculator (March, 2013), covering all re-entry activities in each crop group nominated by the applicant. The assessment included exposures after one, two or four successive applications of afidopyropen at the maximum label rate specified for each crop.

For all crop/activity combinations investigated, the estimated exposure levels were acceptable with MOEs of greater than 100 on the day of treatment, once the spray has dried. Therefore, no risk management measures are required for the protection of re-entry workers, other than a label statement directing them not to enter treated crops until the spray has dried.

Exposure of bystanders and the public

The US EPA Bystander Exposure model was used to estimate exposure under worst-case conditions (a child exposed via the dermal and oral routes while playing on turf contaminated by spray drift from an adjacent treated crop). As the assessment indicated that the potentially absorbed dose of afidopyropen would be significantly less than the dietary ADI (see Section 3.8), no additional risk management measures are required for the protection of bystanders.

Given that Versys Insecticide is expected to be used only by professional horticulturalists and spray operators, the product is unlikely to enter the public domain except during transport. If the concentrate is released accidentally in a public place, the emergency procedures detailed on the draft Safety Data Sheet would ensure that spills are contained and disposed of without exposure of or risk to the public.

Recommendations for safe use

Taking into consideration the potential toxicological hazards, use pattern and likelihood of user exposure, persons handling and applying Versys Insecticide should follow the directions for use (including the following First Aid Instructions and Safety Directions) on the product label:

First aid instructions

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 0800 764 766.

Safety directions

Harmful if inhaled. Will irritate the eyes and skin. Avoid inhaling vapour or spray mist. Avoid contact with eyes and skin. If product on skin, immediately wash area with soap and water. When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist and a washable hat and elbow-length PVC gloves. Wash hands after use. After each day's use, wash gloves and contaminated clothing.

Re-entry statement

Do not re-enter treated crops until the spray has dried.

6.4 Conclusion

The registration of Versys Insecticide, containing 100g/L afidopyropen, for the control of aphids and silverleaf whitefly in cotton, ornamental plants and vegetables as proposed in the directions for use is supported. The product can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product Safety Data Sheet.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

The environmental assessment considered the proposed use of Versys Insecticide for control of aphids and suppression of silverleaf whitefly in cotton and a range of horticultural crops. To support the application environmental fate and toxicity data were provided for afidopyropen and several of its metabolites. For more information about metabolic pathways of afidopyropen in plants and animals refer to 4.1 Metabolism.

7.2 Fate and behaviour in soil

Non-sterile and sterile soil studies were conducted. Photolytic degradation of afidopyropen in soil did not result in unique major metabolites (photoproducts), nor did the influence of light appear to be an important dissipation pathway in/on soil. Metabolites observed in the soil photolysis study, including the dark control, were consistent with those from the aerobic soil metabolism study. The only major metabolite was M440I003 (max 13.4% TAR) observed in the non-sterile dark control. In non-sterile soil the DT_{50} was 32.1 days in light and 8.4 days in the dark. In sterile soil the DT_{50} of afidopyropen was 43.8 days under light and 40.7 days in the dark, indicating no effect of light on the degradation.

Degradation of afidopyropen in four aerobic soils proceeded readily, with DT_{50} values ranging from 2.7 to 18.6 days and with a mean 8.8 days at 20ºC. Where biphasic degradation was observed, DT_{50} values ranging from 2.46 days (fast phase) to 65.3 days (slow phase). Four metabolites exceeding 10% of the applied radioactivity (TAR) from afidopyropen were observed. These major metabolites were M440I002 (max 11.3% TAR), M440I003 (max 14.1% TAR), M440I024 (max 12.1% TAR), and M440I057 (max 36.5% TAR). No other soil metabolites exceeding 10% were observed. Mineralization was observed with levels of CO_2 reaching a maximum value of approximately 28.1% TAR after 120 days of incubation, demonstrating further degradation of the primary degradation products. Bound residues reached maximum levels of 51.0% TAR by 120 days. The major metabolites were not persistent and demonstrated some decline from peak levels in all soils by the end of the 120-day aerobic soil incubations. In some cases, calculation of metabolite DT_{50} values was possible. The degradation DT_{50} values (pathway fitting starting from afidopyropen) ranged from 0.3 to 5.5 days for M440I002, 9.3 to 36.1 days for M440I003, and 3.5–9.9 days for M440I057. For M440I024 only a simple dissipation DT_{50} (fit from the peak onward) in a single soil was determined, and was 28.4 days.

In soils dosed with afidopyropen and incubated for approximately one half-life aerobically, then flooded and purged with nitrogen to facilitate anaerobic, reducing conditions, six metabolites exceeding 10% of the applied radioactivity were observed. These major metabolites were M440I001 (max 35.2% TAR), M440I002 (max 18.4% TAR), M440I003 (max 17.2% TAR), M440I046 (max 16.6% TAR), M440I047 (max 17.1% TAR), and M440I057 (37.3% TAR). Metabolites M440I002, M440I003, and M440I057 began forming during the aerobic portion of the incubation, while M440I001, M440I046, and M440I047 appeared to form primarily during the flooded portion of the incubation. Where possible, dissipation (peak forward regression) times of metabolites during the flooded phase of the study were determined. The DT_{50} values ranged from 5.2 to 188 days for M440I002 in four soils, 58.1 to 84.7 days for M440I003 in three soils, and 66.0 days for M440I057 in one soil.

The adsorption of afidopyropen was determined in six soils with a range of pH (5.5–7.8), organic carbon (0.81–1.4%), clay (5–26%), and texture (loamy sand to silt loam). The adsorption distribution coefficient, Kd, ranged from 4.5 to 20.2 mL/g with a median of 12.9 mL/g for the highest concentration tested. There was an approximately linear inverse relationship between the reported soil pH, determined in water, and the adsorption Kd. The organic carbon corrected adsorption coefficient, KOC, ranged from 516–2439 mL/g with a mean of 1251 mL/g. There did not appear to be a clear relationship between adsorption Kd and organic carbon. The desorption Kd values of afidopyropen in the six soils ranged from 9.8–35.1 mL/g with a mean of 20.5 mL/g. Sorption was concentration dependent with increased sorption as concentration decreased. The Freundlich sorption coefficients for afidopyropen had 1/n values <1 and a regressed Kd was calculated based on expected environmental concentrations to apply in the risk assessment. This value was derived from the soil with the lowest Kf and the resultant Kd for the risk assessment was determined to be 41.8 L/kg.

The adsorption of afidopyropen metabolites M440I001 (mean Kd 12.8 L/kg), M440I002 (mean Kd 13.0 L/kg), M440I003 (mean Kd 974 L/kg), M440I005 (isomer of M440I057, mean Kd 3882 L/kg), and M440I024 (mean Kd 25.8 L/kg) was determined in the six same or similar soils as used for afidopyropen. Desorption Kd values were not determined for some metabolites in soils where the direct method (solvent extraction of soil after the adsorption phase) was used to establish the equilibrium Kd.

Under terrestrial field dissipation conditions (dispersible concentrate formulation, 4 applications, 7-day interval, total 125 g ac/ha) at five widely distributed US trial sites, afidopyropen degraded to form the metabolites expected from the laboratory studies. Afidopyropen dissipation was rapid with DT_{50} values ranging from 1.5 to 7.9 days with a mean of 4.7 days. In many instances, there was significant rainfall or irrigation (>10 mm) shortly after the final application which may decrease residues faster than in conditions with no rainfall/irrigation. The APVMA re-calculated the kinetics for degradation of the parent compound using a SFO model for residues after 10 mm precipitation to derive a degradation DT_{50} value. DT_{50} values ranged from 11.6 to 24.0 days and the geometric mean value of 15.3 days was applied in the risk assessment.

In the field studies, metabolite M440I001, formed mainly under anaerobic conditions, reached a maximum of only 1.2%. Metabolite M440I002 reached a maximum of 10.5%, M440I003 reached 5.7%, M440I024 reached 3.5%, and M440I057 (isomer of M440I005) reached 3.9%. Metabolite M440I016 was also observed (maximum 1.0%). Metabolite M440I016 was a minor metabolite observed between 5 and 10% TAR in the aerobic soil laboratory study, but was included in the analytical method. These metabolites were not persistent with median (n=5) dissipation DT_{50} values (fit from peak onward) of 34.3 days for M440I002, 28.4 days for M440I003, 52.1 days for M440I024 and 53.0 days for M440I057. Further, residues did not exceed the LOD (0.0002 mg/kg) below the 15–30 cm sampling depth at any site, despite favourable leaching conditions.

7.3 Fate and behaviour in water

Afidopyropen was stable in pH 4 and pH 7 sterile buffer for at least 5 days at 50ºC in the dark (Button, 2014). In pH 9 buffer the DT_{50} values were 1261 days at 10ºC, 133 days at 25ºC and 9.84 days at 50ºC. The kinetic data rate constants were used to generate an Arrhenius plot for afidopyropen in pH 9 buffer. Estimated DT_{50} values at pH 9 for 20ºC and 25ºC were 294 days and 157 days, respectively, when calculated by the Arrhenius equation. In pH 9 buffer at 10 and 25ºC, no degradation products were observed that exceeded 10% of the total applied radioactivity (TAR). However, at 50ºC in pH 9 buffer, M440I001, M440I002, and nicotinic acid exceeded 10% TAR. The product M440I003 was also identified, but at levels <10% TAR.

Hydrolysis is unlikely to be an important degradation process at most environmentally relevant pH and temperature levels.

Under aqueous conditions, afidopyropen was susceptible to photolysis. In sterile pH 7 buffer afidopyropen DT_{50} values of 17–28 days (40ºN latitude) were observed while in sterile natural water DT_{50} values of 10–12 days (40ºN latitude) were observed. No degradation was observed in dark controls. The only product reaching 10% TAR or higher was nicotinic acid, which had a replicate average maximum value of 21.5% TAR in natural water. Metabolite M440I007, a dimer of the parent BAS 440 I, was also observed, but at a replicate average maximum of 5.4% TAR.

In aerobic aquatic (water/sediment) systems, afidopyropen quickly redistributed from the water to the sediment phase (water phase dissipation DT_{50} 2–3 days). Degradation of afidopyropen occurred with total system DT_{50} values of 76–86 days, though no metabolites were observed in the water phase at the 10% TAR level or greater. In sediment of the aerobic aquatic study, one metabolite exceeded 10% TAR. Metabolite M440I024 reached a maximum of 10.8% TAR in the sediment.

Under anaerobic aquatic conditions, afidopyropen redistributed quickly from the water phase to sediment (water phase DT_{50} 9–13 days). Degradation of afidopyropen occurred with total system DT_{50} values of 35–45 days. Metabolite M440I001 was observed above 10% TAR in the water phase with a maximum of 14.8%. In anaerobic aquatic sediment, M440I001 reached a replicate average maximum of 30.2% TAR and M440I002 reached 12.6% TAR.

In a flow-through bioconcentration study, carp were exposed to afidopyropen at nominal concentrations of 0.018 and 0.18 mg ac/L for an uptake period of 28 days. The bioconcentration steady state factor for afidopyropen was determined to be 0.059. Based on this result, bioaccumulation of afidopyropen in aquatic organisms, is unlikely.

7.4 Risk to terrestrial vertebrates

Afidopyropen was moderately toxic to birds by dietary consumption or through oral administration. Afidopyropen appeared to have repellent effects on both quail and ducks at the highest concentrations tested. The lowest acute oral LD_{50} for birds is 366 mg ac/kg bw for zebra finch. The lowest acute dietary LC50 in bobwhite quail at 527 mg ac/kg diet. The lowest avian reproductive NOEC occurred in mallard and bobwhite quail at 80 mg ac/kg diet (6.7 mg/kg bw/d for bobwhite quail and 10.1 mg/kg bw/d for mallard duck).

The risk to mammals and birds was determined by considering relevant Australian species. This was done on a dose basis by taking into account the species' energy requirements and hence food intake, and the amount of afidopyropen predicted to be present on that food. This dose was then compared with the studied acute and chronic effects of afidopyropen on birds and mammals. In all cases the risk was found to be acceptable.

7.5 Risk to aquatic species

Acute toxicity of afidopyropen to fish was tested on three species under static and semi-static conditions. The 96 h LC_{50} ranged from 18.0 mg ac/L to carp to >21.3 mg/L (the limit of solubility in the test media) to rainbow trout.

Freshwater and an estuarine/marine fish species were tested in ELS (early life-stage) studies. In the study with sheepshead minnow, which lead to the lower endpoints of both studies, fish were exposed to afidopyropen at mean measured concentrations of 0.082 to 2.7 mg ac/L. There were no statistically significant treatment-related effects on hatching success or survival at concentrations ≤2.7 mg ac/L. Growth (measured as total length, wet and dry weight) was the most sensitive biological endpoint measured in this study. Based on a statistically significant decrease in wet weight at the 0.20 mg ac/L test concentration, the NOEC was determined to be 0.082 mg ac/L.

The formulation was significantly more toxic to fish based on acute toxicity testing with rainbow trout with a 48 h EC_{50} of 1.08 mg formulation/L, equating to 0.11 mg ac/L.

Afidopyropen is moderately toxic to aquatic invertebrates based on acute results. The 48 h EC_{50} to *Daphnia magna* was 8.0 mg ac/L while 96 h $L(E)C_{50}$ results to the saltwater species, mysid shrimp and eastern oyster, were 4.4 mg ac/L and 2.17 mg ac/L respectively.

Aquatic invertebrates *Daphnia magna*, *Moina macrocopa* and in particular the mysid shrimp, were the most sensitive taxa to afidopyropen with NOEC values between 0.004 and 0.448 µg ac/L. Saltwater mysids (*Americamysis bahia*) were exposed to afidopyropen at mean measured concentrations of 2.0 to 30 ng ac/L under flow-through conditions for 28 days, and were evaluated for survival, reproduction, and growth. Reproduction was the most sensitive biological endpoint measured. There was a statistically significant decrease in the mean percent of surviving females producing young in the 7.1, 14 and 30 ng ac/L treatment groups. Consequently, the NOEC, based on reproduction, was 4.0 ng ac/L.

The formulation was significantly more toxic to aquatic invertebrates based on acute toxicity testing with *Daphnia magna* with a 48 h EC_{50} of 1.17 mg formulation/L, equating to 0.12 mg ac/L.

The toxicity of afidopyropen was tested with 4 different algae species as well as with the aquatic macrophyte, *Lemna gibba*. The ER_{10} values were calculated from the dose/response data applying a non-linear regression dose response model. The most sensitive species is the marine diatom *Skeletonema costatum* with a 72 h ErC_{10} = 2.35 mg ac/L (initial measured concentration). The 7 day ErC_{10} to *Lemna gibba* was 3.78 mg ac/L.

Again, the formulation exhibited significantly higher toxicity. Based on the green algae, *Pseudokirchneriella subcapitata*, the active constituent 72 h ErC_{10} was calculated to be 18.9 mg ac/L. In comparison, testing with the formulation resulted in a 72 h ErC_{10} = 0.056 mg ac/L.

Several studies have been performed with afidopyropen on aquatic sediment organisms. The studies were conducted as spiked sediment. In order to assess the acute toxicity studies were conducted with three different species (i.e. *Chironomus tentans, Hyalella azteca* and *Leptocheirus plumulosus*). For all species, the 10 d LC_{50} was >800 µg ac/kg.

One study was conducted as spiked water (OECD 218) and is provided as additional information. It was not applied in the risk assessment as more sensitive results were available for pelagic organisms exposed through the water column.

In a chronic study the 28-day NOEC value for afidopyropen was ≥ 37.2 µg ac/L (initial concentration, spiked water). In the 40-d spiked sediment study, there were no statistical differences observed on survival, growth or on any of the emergence or reproductive endpoints when the treatment groups were compared to the pooled control. Based on the results of this study, the NOEC was 24.9 µg ac/kg which is the highest concentration tested

The risk to aquatic species from spray drift was determined using the standard APVMA scenario for high boom and COARSE spray quality. The downwind no spray zone was determined by calculating the fraction of the proposed spray rate required to achieve a concentration in a 3 m wide 15 cm deep water body, below the regulatory acceptable level.

The risk to aquatic species from run-off water containing afidopyropen from treated fields entering the aquatic environment was also considered. The predicted concentration was calculated using an OECD proposed model, which takes into account afidopyropen's degradation and mobility from soil characteristics. The APVMA's method to refine estimates of pesticide runoff to waterways (Regulatory update #212) was applied in refining the risk assessment, based on real world data for topography, rainfall, soil type and river flows for the regions relevant for cotton, potatoes and horticulture. The probability of a rainfall event sufficient to produce runoff was also considered when seasonal risks could not be ruled out within specific regions. Runoff risks were determined to be acceptable.

7.6 Risk to bees and other non-target arthropods

Afidopyropen did not demonstrate toxicity to honey bees with an adult acute oral LD50 >100 µg/bee, adult acute contact LD50 >200 µg/bee and a larvae oral LD50 of 55.9 µg/bee. A number of higher tier studies were provided. The risk to bee brood and general hive health was determined to be acceptable. However, short term effects on bees exposed following application appear possible. The overall risk to bees was found to be acceptable with instruction to not apply the product while bees are foraging.

Tier 1 toxicity tests to standard non-target arthropods were available with an LR50 = 78.1 g ac/ha for the parasitic wasp and 140.4 g ac/ha for the predatory mite. The in-field and off-field risk to these organisms was found to be acceptable.

7.7 Risk to soil organisms

Afidopyropen did not exhibit significant toxicity to earthworms (acute LC_{50} >1000 mg/kg soil; chronic NOEC = 476 mg/kg soil) or other soil macro-organisms (Collembola chronic NOEC = 154.3 mg/kg soil). Risk to earthworms and other soil macro-organisms was found to be acceptable.

Afidopyropen did not adversely affect soil functions of nitrogen turnover and respiration at concentrations up to 20 mg/kg soil and the risk to soil microorganisms was found to be acceptable.

7.8 Risk to non-target terrestrial plants

Afidopyropen did not exhibit toxicity to a range of standard terrestrial plants in both vegetative vigour and seedling emergence studies and the risk to non-target terrestrial plants was found to be acceptable.

7.9 Conclusion

The registration of Versys Insecticide, containing 100g/L afidopyropen, for the control of aphids and silverleaf whitefly in cotton, ornamental plants and vegetables as proposed in the directions for use is supported. Versys Insecticide, when used according to instruction, would not be likely to have an unintended effect that is harmful to animals, plants, or things or to the environment.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed product use pattern

Versys Insecticide is intended for the control of green peach aphid (*Myzus persicae*), cabbage aphid (*Brevicoryne brassicae*), currant lettuce aphid (*Nasonovia ribis-nigri*) and cotton/melon aphid (*Aphis gossypii*); and for the suppression of silverleaf whitefly in brassica vegetables, celery, cucurbits, fruiting and leafy vegetables (including brassica leafy vegetables), parsley, potato, sweet potato, ginger and cotton. The product is also intended for the control of aphids in ornamentals.

The product is to be applied at rates of 100 mL/ha for aphid control and 350 ml/ha plus Hasten Spray Adjuvant at 0.2% v/v for suppression of silverleaf whitefly. The product should be applied in sufficient water to ensure thorough coverage of the target crop at a minimum of 200 Lwater/ha.

Afidopyropen disrupts feeding and other behaviours in target insects leading to death by starvation. As a result, Versys Insecticide, does not provide immediate knockdown, although cessation of feeding will occur within hours of application.

8.2 Evaluation of efficacy

Thirty-nine replicated small plot field studies were provided in support of the application. In all cases, trials used a randomised complete block design with 4 replicates. The number of treatments varied between 5 and 12, depending on how many standard or other experimental products were included, consideration of different rates and single or repeated application. For each pest a broadly similar protocol was followed for assessment of the impacts on the pest, adjusted for the particular crop and pest situation (e.g. pest levels prior to treatment and numbers per leaf/plant and incidence of affected plants at intervals after spraying).

The studies were conducted in a range of vegetable crops, cotton, two ornamental species, and in one case, canola. The crops were grown at various sites in Queensland, New South Wales, Victoria, Tasmania and Western Australia. The trials were conducted during 2010 to 2015 and explored effects of different application rates, addition of adjuvants and different formulations of afidopyropen, culminating in the final Versys formulation.

Eleven of the 12 trials provided for cotton/melon aphid (*Aphid gossypii*) found that appropriate afidopyropen treatments were significantly different from the untreated control ($P = 0.05$) in controlling aphid nymphs and adults and reached a similarly high level of control (≥ 85%) to the standard treatments against which they were compared (pirimicarb, spirotetramat, clothianidin, diafenthiuron, sulfoxaflor and/or imidacloprid). Activity at the first assessment after application was sometimes inferior to standard treatments with insecticides having knockdown activity. However, knockdown activity is not expected with afidopyropen due to its action in disrupting insect behaviour and feeding.

In four of 7 studies with cabbage aphid (*Brevicoryne brassicae*), suitable afidopyropen treatments were significantly different from the untreated control in controlling aphid nymphs and adults and reached a similar level of control to the standard treatments against which they were compared (>85% control in three of the studies). A moderate level of control was reached in two other studies, and no treatment was found to differ significantly from the control in the other study.

In two studies, high efficacy against Currant lettuce aphids (*Nasonovia ribis-nigri*) equivalent to industry standard treatments was obtained, based on results after two applications. In a third study, high efficacy was obtained against adult aphids, but for nymphs both the standard and the afidopyropen treatment only reached a moderate level of control with a single or repeated application. In a fourth study, a moderate level of control was obtained with the afidopyropen formulations tested and any differences from the standard treatments were not statistically significant.

Seven of the 8 trials provided for green peach aphid (*Myzus persicae*) found that appropriate afidopyropen treatments were significantly different from the untreated control in controlling aphid nymphs and adults and reached a similarly high level of control (≥ 85%) to the pirimicarb or spirotetramat +Hasten standard treatment.

The trial results are considered sufficient to demonstrate that Versys Insecticide when applied at 100 mL/ha will be efficacious against these aphid species.

Results from the 9 trials provided for Silverleaf whitefly (*Bemisia tabaci*) demonstrated varied level of control, but overall indicated that suitable afidopyropen treatments had useful suppression activity against this pest. In all 9 trials, two applications were made at an interval of 7-9 days. In 7 of the trials, statistically significant differences were not found in observations prior to the second application, however, given the mode of action, cumulative efficacy is expected. For this pest, the proposed label indicates that only a single spray should be applied before rotating to an alternative insecticide for whitefly control and the product is expected to contribute to subsequent efficacy of a following treatment from a different activity group. The Silverleaf whitefly studies indicated that an application rate of 35 g ac/ha (350 mL/ha of the Versys formulation) is appropriate for the proposed cropping situations, and that addition of adjuvant is important for optimum efficacy.

8.3 Evaluation of crop safety

Observations for phytotoxicity were made in all 39 trials and included applications of up to two times the label rate of both the final formulation and developmental formulations of afidopyropen, including SC and EC formulations, with and without various surfactants/adjuvants. No phytotoxicity was observed following application of Versys Insecticide.

8.4 Resistance management

For resistance management purposes, Versys Insecticide is a group 9D insecticide. Group 9D is a new subgroup in the TRPV modulator and exhibits no cross-resistance to other insecticides in other Group 9 sub-groups.

The proposed use of Versys Insecticide for control of aphids is limited to 2 applications (with a 14 day interval) at a rate of 100 mL/ha) before rotating to an alternative insecticide, with a maximum of 4 applications per crop.

When used for suppression of silverleaf whitefly, a single application is made at 350 mL/ha before rotating to an alternative insecticide. For this use pattern, the product is limited to a maximum of 2 applications in any one crop and, if using for whitefly suppression in conjunction with aphid control, no more than 2 additional applications at the 100 mL/ha rate for aphid control may be made.

8.5 Conclusion

The claims on the proposed label that Versys Insecticide provides control of various aphid species and suppression of silverleaf whitefly in certain vegetable crops, cotton and ornamentals when used as directed, are supported by Australian trials. The directions for use are appropriate and consistent with insecticide use in commercial agriculture in Australia. Acceptable crop safety is also expected when the product is used as directed.

The application for registration of Versys Insecticide is supported on efficacy and crop safety when used in accordance with label instructions.

9 LABELLING REQUIREMENTS

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

VERSYS Insecticide

ACTIVE CONSTITUENT: 100 g/L AFIDOPYROPEN

GROUP	9D	INSECTICIDE

For the control of Green peach aphid (*Myzus persicae*), Cabbage aphid (*Brevicoryne brassicae*), Currant lettuce aphid (*Nasonovia ribis-nigri*), Cotton aphid / Melon aphid (*Aphis gossypii*) and suppression of silverleaf whitefly (*Bemisia tabaci* Biotype B) in certain vegetable crops, cotton and ornamentals.

IMPORTANT: READ THE ATTACHED LEAFLET BEFORE USING THIS PRODUCT

CONTENTS: 1 L, 5 L, 10 L

BASF Australia Ltd ABN 62 008 437 867
Level 12, 28 Freshwater Place Southbank VICTORIA 3006
Website: crop-solutions.basf.com.au

DIRECTIONS FOR USE

RESTRAINTS
DO NOT apply by aircraft.
DO NOT apply more than a total of 900mL/ha in any one crop.
DO NOT feed cotton fodder, stubble or trash to livestock.
DO NOT use the product in protected cropping situations.

SPRAY DRIFT RESTRAINTS
DO NOT apply with spray droplets smaller than a COARSE spray droplet size category according to 'APVMA compliance instructions for mandatory COARSE or larger droplet size categories' located under this title in the GENERAL INSTRUCTIONS section of this label.
DO NOT apply when wind speed is less than 3 or more than 20 kilometres per hour, as measured at the application site.
DO NOT apply during surface temperature inversion conditions at the application site.
Users of this product MUST make an accurate written record of the details of each spray application within 24 hours following application, and must KEEP this record for at least 2 years. The spray application details that must be recorded are:
1 date with start and finish times of application; 2 location address and paddock(s) sprayed; 3 full name of this product; 4 amount of product used per hectare and number of hectares applied to; 5 crop or situation and weed or pest; 6 wind speed and direction during application; 7 air temperature and relative humidity during application; 8 nozzle brand, type, spray angle, nozzle capacity and spray system pressure measured during application; 9 name and address of person applying this product. (Additional record details may be required by the state or territory where this product is used.)
MANDATORY NO-SPRAY ZONES
DO NOT apply if there are aquatic or wetland areas including aquacultural ponds, surface streams and rivers downwind from the application area and within the mandatory no-spray zones shown in the table below:

Table 1 – No-spray zones for protection of the aquatic environment	
	Downwind Mandatory No-Spray Zone
For ground application	
From 3 to 20 kilometres per hour	250 metres

CROP	PEST	RATE	WHP	CRITICAL COMMENTS
Brassica vegetables (including broccoli, broccolini, Brussels sprouts, cabbage, cauliflower, kohlrabi) Celery Cucurbits Fruiting vegetables, excluding cucurbits (capsicum, chilli, eggplant, okra, tomato) Leafy vegetables and Brassica Leafy Vegetables including chard (silver beet), cress spinach, lettuce (head and leafy), bok choy, Chinese cabbage, choy sum, gai lan, kale, leafy mustard, pak choy, rocquette Parsley	Green peach aphid (*Myzus persicae*) Cabbage aphid (*Brevicoryne brassicae*) Currant lettuce aphid (*Nasonovia ribis-nigri*) Cotton aphid / Melon aphid (*Aphis gossypii*)	100mL/ha	1 day	Versys Insecticide disrupts insect behaviour and feeding and will provide slow knockdown. Monitor crops and commence applications as local threshold levels are reached. Versys Insecticide will provide residual control of aphids out to 21 days. Continue to monitor crops and make subsequent applications after 14 days where necessary. Apply a maximum of 2 sprays before rotating to an alternative insecticide for aphid control. Do Not apply more than 4 applications per crop. If using for whitefly control, do not apply more than 2 additional applications at the 100mL/ha rate for aphids. Apply in sufficient water to ensure thorough coverage of the target crop. Addition of an adjuvant may aid in speed of knockdown and the overall control. For suitable adjuvants refer to the Adjuvant section in Compatibility.
	Suppression of – Silverleaf whitefly (*Bemisia tabaci* Biotype B)	350 mL/ha + 0.2% v/v Hasten		When local thresholds are reached, apply a single spray before rotating to an alternative insecticide for whitefly control. Do not apply more than 2 applications for whitefly control in any one crop. If using for whitefly control, do not apply more than 2 additional applications at the 100mL/ha rate for aphids. Versys Insecticide will provide suppression of both adult and nymph stages of whitefly, however it is recommended to target the nymph

				stage as better activity is seen against nymphs. A general decline in population will occur over time as nymph numbers are suppressed.
Cotton potato, sweet potato, ginger	Green peach aphid (*Myzus persicae*) Cabbage aphid (*Brevicoryne brassicae*) Currant lettuce aphid (*Nasonovia ribis-nigri*) Cotton aphid / Melon aphid (*Aphis gossypii*)	100mL/ha	7 days	Versys Insecticide disrupts insect behaviour and feeding and will provide slow knockdown. Monitor crops and commence applications as local threshold levels are reached. Versys Insecticide will provide residual control of aphids out to 21 days. Continue to monitor crops and make subsequent applications after 14 days where necessary. Apply a maximum of 2 sprays before rotating to an alternative insecticide for aphid control. Do Not apply more than 4 applications per crop. Apply in sufficient water to ensure thorough coverage of the target crop. Addition of an adjuvant may aid in speed of knockdown and the overall control. For suitable adjuvants refer to the Adjuvant section in Compatibility.
	Suppression of – Silverleaf whitefly (*Bemisia tabaci* Biotype B)	350 mL/ha + 0.2% v/v Hasten		When local thresholds are reached, apply a single spray before rotating to an alternative insecticide for whitefly control. Do not apply more than 2 applications for whitefly control in any one crop. Versys Insecticide will provide suppression of both adult and nymph stages of whitefly, however it is recommended to target the nymph stage as better activity is seen against nymphs. A general decline in population will occur over time as nymph numbers are suppressed.

Ornamentals	Green peach aphid (*Myzus persicae*) Cabbage aphid (*Brevicoryne brassicae*) Currant lettuce aphid (*Nasonovia ribis-nigri*) Cotton aphid / Melon aphid (*Aphis gossypii*)	100 mL/ha	-	Versys Insecticide disrupts insect behaviour and feeding and will provide slow knockdown. Monitor crops and commence applications as local threshold levels are reached. Versys Insecticide will provide residual control of aphids out to 21 days. Continue to monitor crops and make subsequent applications after 14 days where necessary. Apply a maximum of 2 sprays before rotating to an alternative insecticide for aphid control. Do Not apply more than 4 applications per crop. Apply in sufficient water to ensure thorough coverage of the target crop. Addition of an adjuvant may aid in speed of knockdown and the overall control. For suitable adjuvants refer to the Adjuvant section in Compatibility.

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

WITHHOLDING PERIOD:

Brassica vegetables, celery, cucurbits, fruiting vegetables (other than cucurbits), leafy vegetables (including brassica leafy vegetables), parsley: DO NOT harvest for 1 day after application.

Cotton, ginger, potato, sweet potato: DO NOT harvest for 7 days after application.

TRADE ADVICE:

Export of treated commodities

Growers should note that Maximum Residue Limits (MRLs) or import tolerances do not exist in all markets for labeled crops treated with VERSYS Insecticide. Additionally, some export markets have established MRLs different to those in Australia. If you are growing crops for export, please check with BASF Australia Ltd for the latest information on MRLs and import tolerances BEFORE using this product.

GENERAL INSTRUCTIONS

VERSYS Insecticide is an insecticide which acts by inhibiting behaviour in target insects. This disrupts insect orientation and the ability to feed, resulting in death. As a result, VERSYS Insecticide will only provide slow knockdown, although cessation of feeding will occur within hours of application. Monitor crops and apply

VERSYS Insecticide as threshold levels are reached. VERSYS Insecticide has low toxicity to beneficial insects and is suitable for use in Integrated Pest Management programs.

APPLICATION

To be effective, thorough crop coverage is required. Apply in a minimum of 200L water/ha. Adjust water volumes according to the crop growth stage to ensure thorough coverage. Always mix with Hasten Spray Adjuvant at 0.2% v/v when applying for suppression of silverleaf whitefly.

Instructions for Ground Application

These instructions inform those using this chemical product how to lawfully comply with the requirement of a COARSE or larger spray droplet size category for spray application.

Spray droplet size categories are defined in the ASAE S572 Standard (newer name may also be shown as ASABE) or the BCPC guideline. Nozzle manufacturers may refer to one or both of these documents, to identify droplet size categories; however, for a nozzle to comply with this requirement, the manufacturer must refer to at least one.

Complying with the label requirement to use a specific droplet size category means using the correct nozzle that will deliver that droplet size category under the spray operation conditions being used. The APVMA has approved only the following specific methods for choosing the correct nozzle. Use one of the methods specified in these instructions to select a correct nozzle to deliver a COARSE or larger droplet size category.

USE ONLY nozzles that the nozzles' manufacturer has rated to deliver a COARSE, a VERY COARSE or an EXTREMELY COARSE droplet size category, as referenced in ASAE S572 or BCPC. Choose a nozzle that is specified to provide the droplet size category required in the label Spray Drift Restraints.

DO NOT use a higher spray system pressure than the maximum the manufacturer specifies for the selected nozzle to deliver the droplet size category required in the label Spray Drift Restraint.

IPM compatibility

VERSYS Insecticide has low toxicity to insect predators and is suitable for use where IPM is practiced.

COMPATBILITY

Versys Insecticide has been tested and is compatible with the following adjuvants; Hasten Spray Adjuvant, Agral Spray Adjuvant and Agridex Non-ionic Surfactant.

INSECTICIDE RESISTANCE WARNING

GROUP 9D INSECTICIDE

For insecticide resistance management VERSYS is a Group 9D insecticide. Some naturally-occurring insect biotypes resistant to VERSYS and other Group 9D insecticides may exist through normal genetic variability in any insect population. The resistant individuals can eventually dominate the insect population if VERSYS or other Group 9D insecticides are used repeatedly. The effectiveness of VERSYS on resistant individuals could be significantly reduced. Since occurrence of resistant insects is difficult to detect prior to use, BASF Australia Ltd accepts no liability for any losses that may result from the failure of VERSYS to control resistant insects. VERSYS may be subject to specific resistance management strategies. For further information contact your local supplier, BASF Australia Ltd representative or local agricultural department agronomist.

RE-ENTRY PERIOD

Do not re-enter treated crops until spray has dried

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product or used containers.

PROTECTION OF HONEY BEES AND OTHER POLLINATORS

DO NOT apply while bees are actively foraging. Risk to bees is reduced by spraying in early morning and late evening when bees are not foraging.

STORAGE AND DISPOSAL:

Store in the closed, original container in a dry, cool, well-ventilated area out of direct sunlight. Triple rinse containers before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and deliver empty packaging to an approved waste management facility. If an approved waste management facility is not available, bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose, clear of waterways, desirable vegetation and tree roots, in compliance with relevant local, state or territory government regulations. DO NOT burn empty containers or product.

SAFETY DIRECTIONS:

Harmful if inhaled. Will irritate the eyes and skin. Avoid inhaling vapour or spray mist. Avoid contact with eyes and skin. When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist, a washable hat and elbow-length PVC gloves. If product on skin, immediately wash area with soap and water. Wash hands after use. After each day's use wash gloves and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Telephone 131126 Australia-wide.

SDS
Additional information is listed in the Material Safety Data Sheet.

CONDITIONS OF SALE
All conditions and warranties rights and remedies implied by law or arising in contract or tort whether due to the negligence of BASF Australia Ltd or otherwise are hereby expressly excluded so far as the same may legally be done provided however that any rights of the Buyer pursuant to non- excludable conditions or warranties of the Competition and Consumer Act 2010 or any relevant legislation of any State are expressly preserved but the liability of BASF Australia Ltd or any intermediate Seller pursuant thereto shall be limited if so permitted by the said legislation to the replacement of the goods sold or the supply of equivalent goods and all liability for indirect or consequential loss or damage of whatsoever nature is expressly excluded. This product must be used or applied strictly in accordance with the instructions appearing hereon. This product is solely sold for use in Australia and must not be exported without the prior written consent of BASF Australia Ltd.

APVMA Approval No:

Batch No:
Date of Manufacture:
Website: crop-solutions.basf.com.au
= Registered trademark of BASF

BASF
We create chemistry

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

ABBREVIATIONS

ac	active constituent
ACCS	Advisory Committee on Chemical Scheduling
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ARfD	Acute Reference Dose
bw	bodyweight
°C	degrees celsius
CIPAC	Collaborative International Pesticides Analytical Council
CPCA	cyclopropanecarboxylic acid
d	day
DALA	Days After Last Application
DAT	Days After Treatment
DC	Dispersible Concentrate
DT_{50}	time taken for 50% of the concentration to dissipate
EC_{50}	concentration at which 50% of the test population are immobilised
EI	Export Interval
ESI	Export Slaughter Interval
g	gram
GAP	Good Agricultural Practice
h	hour
ha	hectare
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
IPM	Integrated Pest Management

in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
Kd	soil adsorption coefficient
Kf	soil Freunlich sorption coefficient
kg	kilogram
K_{oc}	organic carbon partitioning coefficient
Kt	kilotonne
L	litre
LC_{50}	concentration that kills 50% of the test population of organisms
LC-MS/MS	Liquid Chromatography- Mass Spectrometry
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
L(E)Cx	concentration of impart lethality (L) or effect (E) on x% of the test population
LOD	Limit of Detection – level at which residues can be detected
LOEL	Lowest Observable Adverse Effect Level
Log_{10}	logarithm base 10
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
mN	milliNewton
MOE	Marign of Exposure
mol	molecular mass (usually expressed in grams)
MRL	Maximum Residue Limit
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
NOEC/NOEL	No Observable Effect Concentration Level
OC	organic carbon
Pa	pressure

PBI	Plant Back Interval
P_{ow}	partition coefficient (ratio of the equilibrium concentrations of a dissolved substance)
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
PSA	Primary-Secondary Amine
Q-value	Quotient-value
s	second
sc	subcutaneous
SC	suspension Concentrate
SFO	single first order
STMR/STMR-P	Supervised Trials Median Residue/Supervised Trials Median Residue in Processed Commodity
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TAR	total applied radioactivity
TGA	Therapeutic Goods Administration
TRR	Total Radioactive Residues
TRVP	family of transient receptor potential cation channels in animals
µg	microgram
WHP	Withholding Period

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Carcinogenic	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxic	The ability to damage genetic material
Immunotoxic	Toxicity to the immune system
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
Mutagenic	The capacity to induce mutation
Neurotoxic	Poisonous to nerve tissue
Photolysis	Breakdown of chemicals due to the action of light
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons
Vacuolation	Formation of a space or vesicle within the cytoplasm of a cell, enclosed by a membrane and typically containing fluid.

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