Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Product Sivanto Prime 200 SL Insecticide

APVMA Product Number 84727

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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 the 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's website.

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 section 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of Sivanto Prime 200 SL Insecticide should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health,

occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade, and efficacy and target crop or animal safety. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on 12 July 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

Bayer CropScience Pty Ltd has applied to the APVMA for registration of the new product Sivanto Prime 200 SL Insecticide, a soluble concentrate that contains 200 g/L of the approved active constituent, flupyradifurone. It is proposed that the product be used for the control of macadamia lace bugs, banana and fruit spotting bugs and scirtothrips in macadamias.

This publication provides a summary of the information reviewed and an outline of the regulatory considerations for the proposed registration of Sivanto Prime 200 SL Insecticide.

1.1 Product claims and use pattern

Sivanto Prime 200 SL Insecticide is intended for the control of macadamia lace bug, banana spotting bug, fruit spotting bug and suppression of scirtothrips in macadamias. The product may be applied to racemes, foliage and macadamia nuts, once per season. The product is proposed to be applied at 50 mL to 100 mL/100 L as a dilute foliar spray.

1.2 Mode of action

Flupyradifurone is a butenolide systemic insecticide that acts as an insect nicotinic acetylcholine receptor agonist, this disrupts nerve transmissions resulting in the death of the treated insects.

For insect resistance management, the product is a Group 4D insecticide.

1.3 Overseas registrations

The formulation of Sivanto Prime 200 SL Insecticide is registered for use in the USA, Trinidad, Tobago, Kuweit, Jordan, Nicaragua, Georgia, Kenya, Cuba, Iran, Tunisia, El Salvador, Guatemala, Canada, Honduras, Dominican Republic, Panama, Guatemala, Ecuador, Columbia, Mexico, Netherlands, Peru, Brazil, Korea and India. Registrations include use in various crops such as tree crops, vegetable crops and cereals for the control of a range of insect pests.

2 CHEMISTRY AND MANUFACTURE

2.1 Active Constituent

Flupyradifurone is a white powder with an uncharacteristic weak odour, with slight solubility in water (3.2 g/L, pH 4, 20°C) and a melting point of 69°C. Flupyradifurone is a butenolide systemic insecticide that binds to insect nicotinic acetylcholine receptors a class of neurotransmitter-gated cation channels involved in excitatory neurotransmission. Binding of flupyradifurone to the receptor protein induces a depolarising ion current and subsequent excitation of the nerve cell. This disrupts the nervous system of insects resulting in death of the treated insects.

The APVMA has evaluated the chemistry (manufacturing process, quality control procedures, batch analysis results and analytical methods, physio-chemical properties and spectroscopic data) and toxicology aspects of flupyradifurone active constituent, and found them to be acceptable. Based on the assessment of data provided by the applicant, the APVMA is satisfied that the chemistry and manufacture aspects of flupyradifurone are acceptable. The active constituent was approved on 30 August 2016 under the approval number 68328.

Table 1: Nomenclature of flupyradifurone

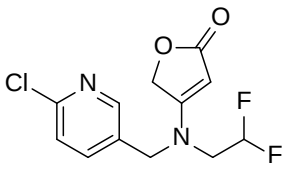
COMMON NAME:	Flupyradifurone
IUPAC NAME:	4-[[(6-chloropyridin-3-yl)methyl](2,2-difluoroethyl)amino]furan-2(5H)-one.
CAS REGISTRY NUMBER:	951659-40-8
MANUFACTURER'S CODES:	BYI 02960
MOLECULAR FORMULA:	$C_{12}H_{11}ClF_2N_2O_2$
MOLECULAR WEIGHT:	288.68
STRUCTURE:	
CHEMICAL FAMILY:	Butenolide insecticides
MODE OF ACTION:	Flupyradifurone binds to insect nicotinic acetylcholine receptors, a class of neurotransmitter-gated cation channels involved in excitatory neurotransmission. Binding of flupyradifurone to the receptor protein induces a depolarising ion current and subsequent excitation of the nerve cell. This disrupts the nervous system of insects resulting in death of the treated insects.

Table 2: Physiochemical properties of flupyradifurone

APPEARANCE:	White powder with an uncharacteristic weak odour.
MELTING POINT:	69°C
BOILING POINT:	Decomposition at 270°C - no boiling point at ambient conditions.
RELATIVE DENSITY:	1.43 g/mL at 20°C
SOLUBILITY IN WATER:	3.2 g/L (at 20°C, pH 4 and 7) 3.0 g/L (at 20°C, pH 9)
SOLUBILITY IN ORGANIC SOLVENTS:	n-Heptane: 0.0005 g/L Toluene: 3.7 g/L Methanol: >250 g/L Dichloromethane: >250 g/L Ethyl acetate: >250 g/L Acetone: >250 g/L DMSO: >250 g/L
OCTANOL/WATER PARTITION COEFFICIENT:	log POW = 1.2 (at 25°C, pH 4, 7 and 9)
MEDIAN PARTICLE SIZE:	24.7 µm
HENRYS LAW CONSTANT: (VOLATILITY)	8.2 × 10-8 Pa m^3 mol^{-1} (at pH 4 and 7) 8.8 × 10-8 Pa m^3 mol^{-1} (at pH 9)
FLAMMABILITY:	Not flammable.
EXPLOSIVE PROPERTIES:	Not explosive.
OXIDISING PROPERTIES:	Not oxidizing.
VAPOUR PRESSURE:	9.1 × 10^{-7} Pa (at 20°C)
COMPLEX FORMATION:	Cobalt ions were weakly complexed while cadmium, copper, chromium, lead and zinc ions did not provide any complex in water.
STABILITY:	Stable for two years under ambient conditions. Stable when stored at 54°C for 14 days. Stable when stored in contact with aluminium, iron, ferric citrate, or aluminium acetate at 54°C for 14 days.
PHOTOLYSIS: (QUANTUM YIELD)	Stable for 1 year in absence of light. [^{14}C] flupyradifurone was irradiated for 35 hours with artificial sunlight at an intensity of 680 W/m^2 and showed degradation with a half-life of 13.8 h in a sterile potassium phosphate buffer (pH 7) but essentially no degradation upon storage of the dark control sample.

On the basis of the data provided, and the toxicological assessment, the following APVMA Active Constituent Standard has been established for flupyradifurone active constituent.

CONSTITUENT	SPECIFICATION	LEVEL
Flupyradifurone	Flupyradifurone	960 g/kg minimum

2.2 Formulated Product

Sivanto Prime 200 SL Insecticide is a soluble concentrate (SL) formulation containing the new active flupyradifurone. The product Sivanto Prime 200 SL Insecticide will be manufactured in Australia or overseas and imported into Australia in 1 L to 110 L high density polyethylene (HDPE) containers. Suitable details of the product formulation, specifications for the ingredients, manufacture process and quality control, product specifications, stability data for the product when stored in the proposed packaging, analytical methods for the active constituents in the product, and details of the packaging, were provided and evaluated.

Based on the assessment, the APVMA is satisfied that the product will remain stable for at least 2 years under normal conditions in the proposed commercial packaging.

Table 3: Identification of the proposed product

DISTINGUISHING NAME:	Sivanto Prime 200 SL Insecticide
FORMULATION TYPE:	Soluble Concentrate (SL)
ACTIVE CONSTITUENT CONCENTRATION:	Flupyradifurone (200 g/L)

Table 4: Physiochemical properties of Sivanto Prime 200 SL Insecticide

APPEARANCE:	Clear brown, weak characteristic odour
PH:	5.4 (1% aqueous solution)
SPECIFIC GRAVITY:	1.174
SURFACE TENSION:	34 mN/m (undiluted at 25°C)
DYNAMIC VISCOSITY:	0.1323 Pa.s (20 s^{-1}, 20 °C) 0.1323 Pa.s (100 s^{-1}, 20 °C)
EXPLOSIVE PROPERTIES:	Not explosive
OXIDISING PROPERTIES:	Not oxidising
FLAMMABILITY:	Not applicable

FLASH POINT:	>100 °C
AUTO-FLAMMABILITY:	420 °C
CORROSIVE HAZARD:	Not corrosive
PACK SIZES:	1 L – 110 L
PACKAGING MATERIAL:	High density polyethylene (HDPE)
PRODUCT STABILITY:	The product should remain within specifications for at least 2 years under normal conditions in HDPE packaging

2.3 Recommendations

The APVMA has evaluated the chemistry aspects of Sivanto Prime 200 SL Insecticide (manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable. The available storage stability data indicate that the technical active and formulated product are expected to remain stable for at least two years when stored under normal conditions.

Based on a review of the chemistry and manufacturing details provided by the applicant, the registration of Sivanto Prime 200 SL Insecticide is supported from a chemistry perspective.

3 TOXICOLOGICAL ASSESSMENT

3.1 Evaluation of toxicology

The toxicological data submitted on the active flupyradifurone is considered sufficient to characterise its toxicity and establish health-based-guidance values for the purpose of determining the dietary risk posed by the presence of residues in treated crops. The submitted data included metabolism studies, acute toxicity studies (active constituent and product), short-term toxicity studies (oral and dermal), long-term oral toxicity studies (including carcinogenicity), reproductive and developmental toxicity studies, genotoxicity studies, acute and repeat dose neurotoxicity studies, and other information to address the human safety criteria. Toxicity studies on the metabolites, immunotoxicity study on the active constituent and dermal absorption studies on the formulation were also included in the submission.

3.2 Mode of activity

Flupyradifurone acts by interfering with insect nicotinic acetylcholine receptors. Acetylcholine receptors are involved in neurotransmission in the nervous system of insects.

3.3 Toxicokinetics and metabolism

Flupyradifurone was rapidly absorbed, moderately metabolised, widely distributed and excreted primarily in the urine. Excretion was rapid and extensive, with the majority of the administered dose excreted within 24 hours indicating a low probability of bioaccumulation of either the parent compound or metabolites. The main metabolic pathway for flupyradifurone involves hydroxylation followed by conjugation with glucuronic acid.

3.4 Acute toxicity

In rats, flupyradifurone displayed low acute oral toxicity ($300 < LD_{50} < 2000$ mg/kg bw), low acute dermal toxicity ($LD_{50} > 2000$ mg/kg bw) and low acute inhalational toxicity ($LC_{50} > 4671$ mg/m^3). Flupyradifurone was not a skin irritant, but was a slight eye irritant in rabbits. No determination could be made on its skin sensitisation potential because the submitted local lymph node assay (LLNA) was not considered to be sufficiently robust.

3.5 Repeat-dose toxicity

The main effects of flupyradifurone in repeat dose dietary studies in rats, mice and dogs consisted primarily of reduced body weight gain and liver toxicity, shown by centrilobular hepatocellular hypertrophy with associated clinical chemistry changes. Thyroid effects (e.g. follicular cell hypertrophy) were generally only observed at higher dose levels. The available data indicated that the dog was the most sensitive species to adverse effects with myofiber degeneration of skeletal muscle occurring at relatively low dose levels. No treatment-related adverse effects were observed at the highest tested dose of 500 mg/kg bw/d in a repeat dose dermal toxicity study in rats.

Flupyradifurone was not genotoxic in a series of *in vitro* and *in vivo* tests or carcinogenic in mouse or rat bioassays. Flupyradifurone was not immunotoxic or a reproductive toxicant. Additionally, the available data indicate the flupyradifurone has some neurotoxic potential following a single dose, this could not be confirmed with repeat dose exposure.

3.6 Product toxicity

The formulated product, Sivanto Prime 200 SL Insecticide, containing 200 g/L flupyradifurone, has low acute oral toxicity (LD_{50} >2000 mg/kg bw), dermal toxicity (LD_{50} >2000 mg/kg bw) and inhalational toxicity in rats (LC_{50} >2000 - < 3496 mg/m^3). It was not a skin irritant in rabbits but was a slight eye irritant in rabbits. Sivanto Prime 200 SL Insecticide was a weak skin sensitiser in mice in a LLNA study.

3.7 Public health

Poisons scheduling

On 23 July 2015, the Delegate to the Secretary of the Department of Health published a final scheduling decision to list flupyradifurone in Schedule 6 without schedule exemptions and confirmed an implementation date of 1 October 2015. The reasons for the Delegate's decision to list flupyradifurone in Schedule 6 were due to its acute oral toxicity and skin sensitisation potential of the active constituent and the formulated product. Sivanto Prime 200 SL Insecticide containing 20% flupyradifurone will be subject to control under Schedule 6 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

Acceptable Daily Intake (ADI)

The Acceptable Daily Intake (ADI) is that quantity of a chemical compound that can safely be consumed on a daily basis for a lifetime. An ADI for flupyradifurone was established at 0.08 mg/kg bw/d using a NOAEL of 7.8 mg/kg bw/d for skeletal muscle myofiber degeneration at higher doses in a 52-week dietary study in dogs. This ADI was supported by a NOAEL of 7.7 mg/kg bw/d for reduced bodyweight gain in dams in a two-generation reproduction study in rats.

Acute Reference Dose (ARfD)

The Acute Reference Dose (ARfD) is the maximum quantity of a chemical that can safely be consumed over a short period of time, usually in one meal or during one day. An ARfD for flupyradifurone was established at 0.35 mg/kg bw/d using a NOAEL of 35 mg/kg bw for an increased incidence of piloerection and pupil dilation at the next higher dose in an acute neurotoxicity study.

4 RESIDUES ASSESSMENT

4.1 Introduction

Sivanto Prime 200 SL Insecticide is a soluble concentrate formulation containing the new active constituent flupyradifurone (Figure 1). It is to be used to control various insect pests on macadamia nuts.

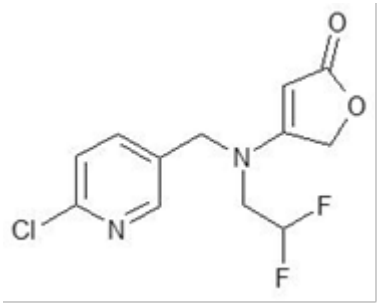


Figure 1: Flupyradifurone (BYI 02960)

4.2 Metabolism

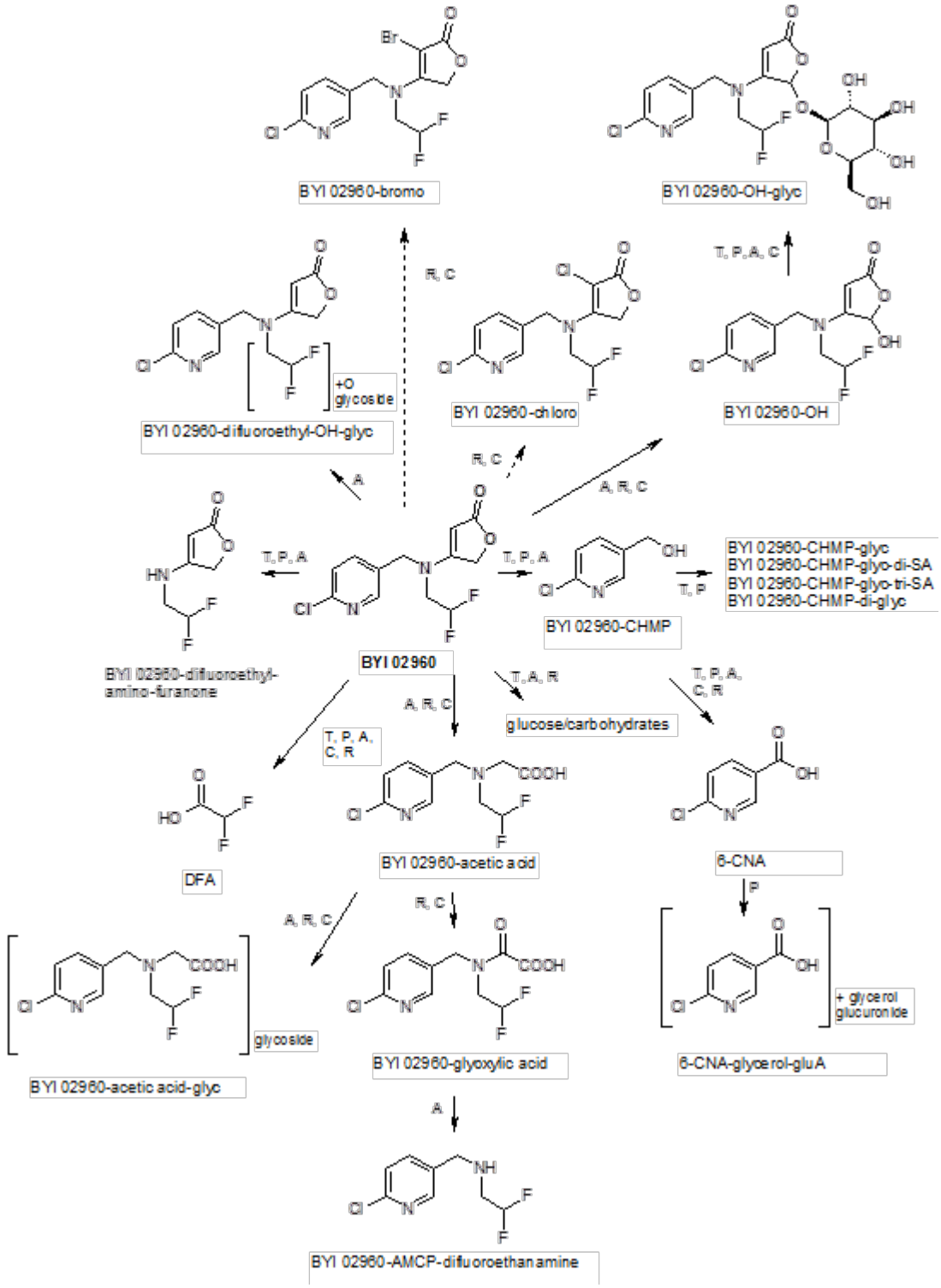
Plants

The metabolism of flupyradifurone (BYI 02960) has been investigated in apple, cotton, rice, tomato and potato using different application techniques (foliar application, soil application, seed piece treatment and granular application). A confined rotational crop study has also been conducted on wheat, Swiss chard and turnips grown after three plant back intervals. All studies used flupyradifurone labelled with ^{14}C in either the pyridinyl or furanone ring. An additional tomato study was conducted with flupyradifurone labelled with ^{14}C in the ethyl side chain.

The major portion of the radiolabelled residue from the application of [Furanone-4-^{14}C]-flupyradifurone or [Pyridinylmethyl-^{14}C]-flupyradifurone to several crops was parent flupyradifurone. In only tomato and potato did any radiolabelled residue component except flupyradifurone exceed 10% of the total radioactive residue, excluding natural products (glucose). In tomato (soil drench treatment), radiolabelled glucose and CHMP-di-glyc/6-CNA were significant (>10%). Glucose represents extensive metabolism and reincorporation of the radiolabelled carbon. CHMP degradates would be formed by cleavage of the pyridinyl moiety. In potato (seed piece treatment), 6-CNA was significant (22% total radioactive residue or TRR, 0.016 mg/kg). The remaining crops (rice, apple, and cotton) represent foliar applications and had no significant metabolites except apple with radiolabelled glucose.

These two radiolabels would not reflect the fate of the difluoroethyl portion of flupyradifurone. A single study was conducted with tomato and [ethyl-^{14}C]-flupyradifurone. Difluoroacetic acid (DFA) comprised the vast majority of the radiolabelled residue in tomato fruit (87%). Moreover, DFA was a significant component of the residue in most crop field trials.

A metabolic pathway for flupyradifurone in plants is shown below in Figure 2.



T = tomato, P = potato, A = apple, R = rice, C = cotton

Figure 2: Proposed metabolic pathway of flupyradifuone (BYI 02960) in plants.

Confined rotational crops

The metabolites observed in confined rotational crops from soil treatment with [Furanone-4-^{14}C]-flupyradifurone or [Pyridinylmethyl-^{14}C]-flupyradifurone were generally the same as those observed in the primary crops. Some were further degradates or derivatives of the primary crop metabolites. Flupyradifurone was the major portion of the radiolabelled residue in all commodities (Swiss chard, wheat forage and hay and straw and grain, and turnip tops and roots) at all plantback intervals (29, 135, and 296 days).

Radiolabelled studies for the determination of DFA were not conducted, but soil metabolism studies indicate that DFA is a major metabolite. Also, DFA was found at levels in excess of flupyradifurone in many limited field rotational crop samples of carrot, turnip, lettuce, and barley commodities, but concentrations were below those from use on primary crops.

Livestock

The major portion of the radiolabelled residue from oral administration of [Furanone-4-^{14}C]-flupyradifurone or [Pyridinylmethyl-^{14}C]-flupyradifurone to lactating goats was flupyradifurone. The only major metabolite encountered was lactose in milk (67% TRR). The radiolabel positions did not allow for determination of DFA. A lactating cow feeding study did show that DFA was about 10 - 30% of the flupyradifurone concentration in milk and tissues.

The metabolism in poultry was more complex. Parent flupyradifurone was generally a minor component in hen matrices with the exception of fat (15% of the TRR) and eggs (20% of the TRR) for the pyridinyl label only. Fatty acids were the major metabolic product with the furanone label for eggs, fat, and liver, indicating extensive metabolism and reincorporation of the radiolabel into natural products. With the pyridinylmethyl label, acetyl-AMCP, from cleavage of both the furanone and difluroethyl groups, was the major residue in eggs, and the major residue in liver was BYI 02960 OH-SA from hydroxylation of the furanone. The radiolabel positions did not allow for determination of DFA.

The poultry feeding study showed that DFA was the major component in all commodities, typically tenfold the concentration of flupyradifurone.

A metabolic pathway for flupyradifurone in livestock is shown below in Figure 3.

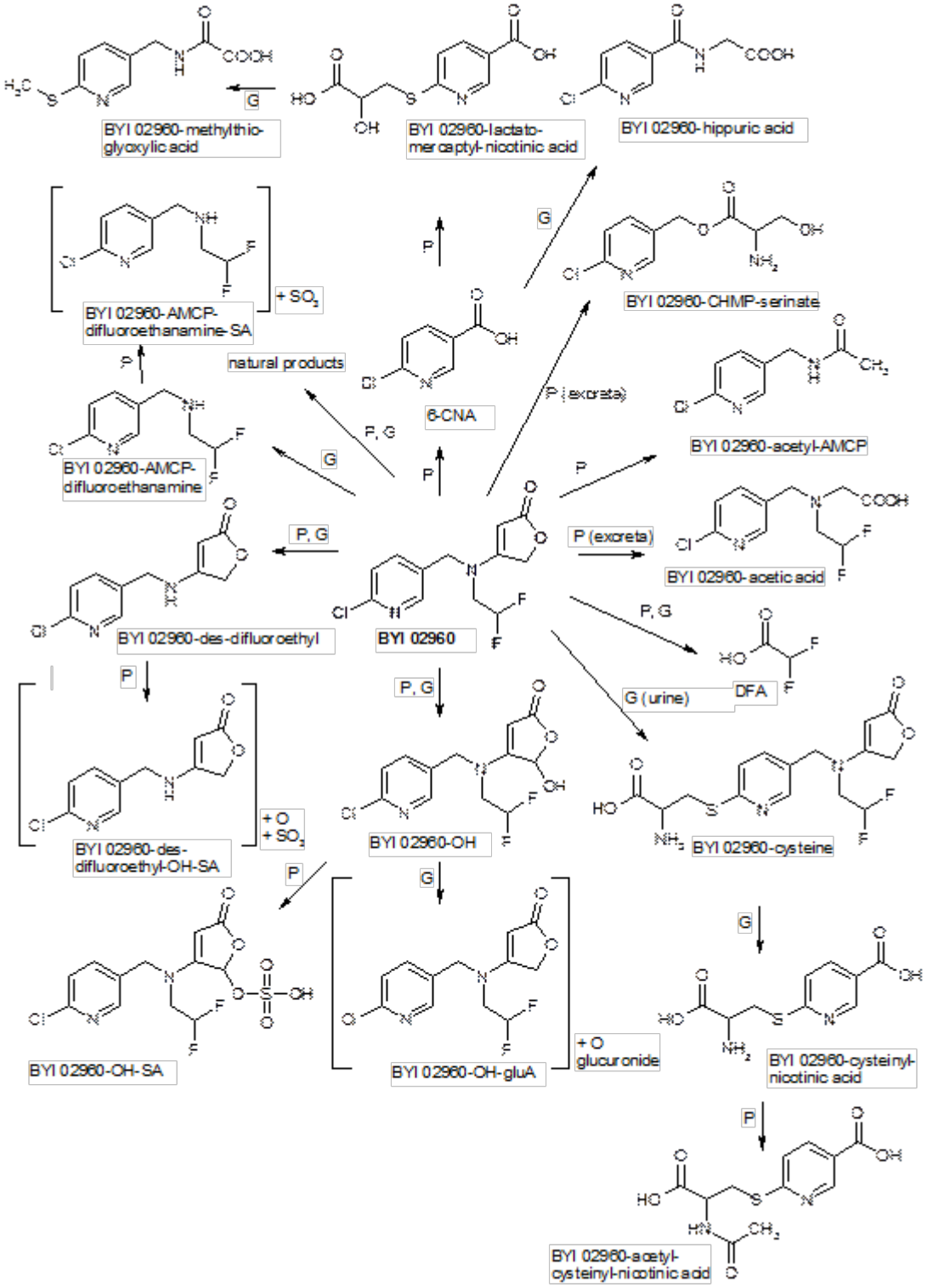


Figure 3: Proposed metabolic pathway for flupyradifurone (BYI 02960) in lactating goats and laying hens.

4.3 Analytical methods

Plant commodities

In macadamia residue trials, residues of flupyradifurone and the metabolites 6-CNA, DFEAF and DFA were extracted with acetonitrile/water containing formic acid. The extract was filtered. For analysis of DFA an aliquot was taken and diluted with acetonitrile. For analysis of flupyradifurone, 6-CNA and DFEAF an aliquot of the extract was reduced to its aqueous remainder and partitioned against ethyl acetate. The ethyl acetate was reduced to dryness and the sample reconstituted in acetonitrile. Analysis was by HPLC coupled to a triple quadrupole mass spectrometer using MRM for analyte detection. Quantitation was achieved with matrix matched analytical standards for all analytes and stable labelled internal standards for 6-CNA and DFEAF. The limit of quantification (LOQ) for flupyradifurone, DFEAF and 6-CNA was 0.01 mg/kg for each component except DFA, for which it was 0.02 mg/kg. Recoveries of flupyradifurone and its metabolites from fortified samples of macadamia kernels were within acceptable limits.

Animal commodities

In a dairy cattle transfer study provided with the application, residues of flupyradifurone, BYI02960-OH, BYI02960-AMCP, and DFA were extracted from cow matrices by diluting liquid matrices (milk, whey, cream, and urine) or blending tissue matrices (fat, muscle, kidney, and liver matrices) with acetonitrile/water/formic acid. Extracts were purified and amended with a mixture of stable, isotopically labelled internal standards prior to analysis by high performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS). The LOQ was 0.01 mg/kg for all analytes (parent compound, BYI 02960-acetyl-AMCP, and BYI 02960-OH) except DFA, for which it was 0.02 mg/kg (0.05 mg/kg in whey).

Although mean recoveries of DFA fortified at 0.05 mg/kg in cow liver and at 0.50 mg/kg in cow muscle averaged 68% and 66%, respectively, the overall mean recoveries for each analyte in all matrices was within the acceptable range of 70 to 120%.

In a poultry transfer study residues (flupyradifurone, DFA, BYI 02960-acetyl-AMCP and BYI 02960-OH) were extracted from poultry eggs, liver, and muscle samples by blending the sample with acetonitrile/water/formic acid. Residues in fat samples were extracted by shaking the sample with acetonitrile/water/formic acid and then centrifuging. For all matrices, a mix of isotopically labelled internal standards was added to an aliquot and was cleaned up on a C-18 Bond Elut cartridge. The sample was analysed by high performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS). The overall mean of the recoveries for each analyte in all matrices was within the acceptable range of 70 to 120%.

Stability of residues in stored analytical samples

Storage stability of residues has been demonstrated to be satisfactory for orange fruit (high acid content), spinach leaves and tomato fruit (high water content), wheat grain (high starch content), bean seed (high protein content), coffee bean and soybean seed (high oil content), and sugar cane for at least one year when stored frozen.

4.4 Residue definition

Plant commodities

It is noted that the Joint FAO/WHO Meeting on Pesticide Residues or JMPR (2016) considered a similar metabolism dossier to that provided in the applicants submission but considered residue trials for a number of additional crop groups. The JMPR residue definition for compliance with the MRL for plant commodities is flupyradifurone. The JMPR residue definition for estimation of dietary intake for plant commodities is the sum of flupyradifurone, difluoroacetic acid (DFA) and 6-chloronicotinic acid (6-CNA), expressed as parent equivalents.

Parent flupyradifurone is a suitable marker for enforcement purposes as it is present in all plant commodities at significant levels. The recommended residue definition for plant commodities for compliance with MRLs is the parent only.

Given the comparable toxicities of parent flupyradifurone and DFA, and the major relative amounts of both found in plant metabolism and crop field trials, a residue definition of the sum of flupyradifurone and DFA acid expressed as flupyradifurone is recommended for commodities of plant origin for dietary exposure assessment.

The metabolite 6-CNA will not be included in the residue definition at this time as it was not observed in the available macadamia residue trials, but may be considered in the future if uses are extended to crops where this metabolite is significant.

Animal commodities

The JMPR residue definition for compliance with the MRL and for estimation of dietary intake for animal commodities is the sum of flupyradifurone and DFA, expressed as parent equivalents.

Parent flupyradifurone was the major portion of the residue in the goat metabolism study and is considered a suitable marker for commodities of mammalian origin. A residue definition of parent only is recommended for compliance with MRLs for commodities of animal origin at this time noting the potential exposure to livestock and poultry associated with the proposed use on macadamia nuts is negligible.

Given the comparable toxicities of parent flupyradifurone and DFA and the major relative amounts of both found in the feeding studies, a residue definition of the sum of flupyradifurone and DFA, expressed as flupyradifurone is recommended for commodities of animal origin for dietary exposure assessment.

The inclusion of DFA into the compliance residue definition for animal commodities in line with the JMPR definition may be considered in the future should a use pattern that may result in animal exposure be proposed for Australia.

4.5 Residue trials

The proposed use of flupyradifurone on macadamias is for a single application at up to 20 g a.i./100 L. The proposed harvest withholding period is 20 days with a restraint preventing grazing of treated orchards. The applicant submitted several Australian residue studies on macadamias involving multiple application rates and timings.

Residues of flupyradifurone at 18 – 20 days after the last of 3 applications at the proposed maximum concentration of 20 g a.i./100 L were <0.01 (n = 6) mg/kg. An MRL of *0.01 mg/kg is appropriate for flupyradifuone on TN 0669 Macadamia nuts.

For dietary exposure assessment, residues of DFA at 18 or more days after the last of 3 applications at the proposed maximum concentration of 20 g a.i./100 L were <0.02, 0.02 (3), 0.04 and 0.08 mg/kg (as DFA). In parent equivalents, the highest residue (HR) is 0.24 mg/kg, the Supervised Trials Median Residue (STMR) is 0.06 mg/kg.

Additional studies demonstrate that DFA residues may occur in macadamias following application of flupyradifurone in previous seasons. The highest residue of DFA in macadamias after multiple seasons applications was 0.21 mg/kg after two applications per season at 15 + 20 g a.i./100 L over two seasons (parent and 6-CNA residues were <LOQ). The DFA residue should be conservative as two applications were made per season when only one is proposed for the label. In parent equivalents the HR is 0.63 mg/kg. This HR will be used for dietary exposure assessment.

6-Chloronicotinic acid (6-CNA)

It is noted that 6-CNA acid is also a metabolite of imidacloprid and is the target analyte for many imidacloprid methods. However, 6-CNA was not detected in macadamia nuts in the available residue trials. It is not necessary to establish a separate imidacloprid MRL for macadamias to cover the proposed use of flupyradifurone.

4.6 Animal commodity MRLs

Macadamia nuts are not a significant feed for livestock and treated macadamia orchards will not be grazed. It is not necessary to establish animal commodity MRLs for flupyradifurone at this time.

4.7 Bioaccumulation potential

The log P_{ow} for flupyradifurone is 1.2 at pH 4, 7 or 9 suggesting low fat solubility. The potential for bioaccumulation is considered to be low. The log P_{ow} of DFA is -3.5 at pH 5 and 7, and -3.5 at pH 9.

4.8 Spray drift

The product may be applied by ground application only. Based on the estimated residues in pasture downwind from the application area from airblast application and the results of the animal transfer study, it is proposed that downwind mandatory no-spray zones are not required for protection of international trade.

4.9 Estimated dietary intake

The chronic dietary exposure to flupyradifurone 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 flupyradifurone is equivalent to <20% of the ADI. It is concluded that the chronic dietary exposure to flupyradifurone 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 intake was estimated at <1% of the ARfD. It is concluded that the acute dietary exposure is acceptable.

4.10 Recommendations

The following amendments are recommended to the MRL Standard:

TABLE 1

COMPOUND		FOOD	MRL (mg/kg)
ADD:			
Flupyradifurone			
TN	0669	Macadamia nuts	*0.01

TABLE 3

COMPOUND	RESIDUE
ADD:	
Flupyradifurone	For enforcement for commodities of plant and animal origin: Flupyradifurone For dietary exposure assessment for commodities of plant and animal origin: Sum of flupyradifurone and difluoroacetic acid, expressed as flupyradifurone

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

The proposed use does not involve treatment of major trade commodities and significant residues are not expected to arise in livestock feeds as a result of the proposed use. The applicant has proposed the following risk mitigation statement which is acceptable:

> *Export of treated produce*
>
> *Growers should note that suitable MRLs or import tolerances do not exist in all markets for produce treated with Sivanto Prime 200 SL. If you are growing produce for export, please check with Bayer CropScience Pty Ltd or your industry body for the latest information on any potential trade issues and their management before using Sivanto Prime.*

It is also noted that a no-spray zone is not required for protection of international trade for the use on macadamia nuts by ground equipment.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Use pattern

Sivanto Prime 200 SL Insecticide will be applied to macadamia *via* open-cab air-blast application. It will be applied at the maximum recommended application rate of 400 g a.i./ha (active flupyradifurone) only once over a 12 month period.

6.2 Risk during use

The product is intended for professional use (farmers and commercial spray operators). Workers may be exposed to the product when opening containers, mixing and loading, using the product, cleaning up spills, maintaining equipment and entering treated areas. The main routes of exposure to the product will be dermal and inhalation (during application).

Since the NOAEL for systemic effects in a rat dermal toxicity study was 500 mg/kg bw/d (highest tested dose) and the likely occupational exposure by inhalation is less than 1/10th of the overall exposure, a quantitative occupational risk assessment was not considered necessary as workers are unlikely to be exposed at these levels. Consequently, the proposed use and mode of application (air-blast) of the product for the control of lace bugs, banana and fruit spotting bugs and scirtothrips in macadamia was considered acceptable without the use of personal protective equipment (PPE). The risk for by-standers or members of the public are also considered to be low.

6.3 Risk with re-entry

The risk associated with re-entering treated areas is expected to be limited to exposure *via* the dermal route; exposure to dried spray may occur with activities such as the inspection of treated plants. Workers re-entering treated areas will not be at any greater risk than the applicators, hence a re-entry statement will not be required.

6.4 Recommendations for safe use

The following first aid instructions and safety directions are recommended for inclusion on the product label:

First aid instructions

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126.

Safety directions

Harmful if inhaled. May irritate the eyes. Avoid contact with eyes. Do not inhale spray mist. Wash hands after use.

6.5 Conclusion

The registration of Sivanto Prime 200 SL Insecticide, containing 200 g/L of flupyradifurone in a soluble concentrate (SL) formulation for control of lace bugs, banana and fruit spotting bugs and scirtothrips in macadamia, is supported from a human health perspective.

7 ENVIRONMENTAL ASSESSMENT

7.1 Fate and behaviour in soil

Aerobic metabolism studies of flupyradifurone were conducted in twenty soils from Europe, the United States or Brazil in four different radiolabelled positions at 20°C in the laboratory. The two main degradation products were difluoroacetic acid (DFA, up to 34%) and 6-chloronicotinic acid (6-CNA, up to 22%). After 120 days, mineralisation ranged 2.2 - 59%, and bound residues ranged 11 - 34%. Degradation tended to follow bi-phasic kinetics with DT_{50} values ranging 33 - 401 days (geomean 82 days). The geomean of the representative DT_{50} values for modelling was 137 days (determined as per NAFTA degradation kinetics tool Pest DF[2]).

Anaerobic metabolism studies of flupyradifurone were conducted in three soils. DT_{50} values ranged 392 - 693 days indicating flupyradifurone is expected to be relatively stable under flooded soil conditions.

Photolysis is not expected to be a significant route of degradation of flupyradifurone in soil. DT_{50} values ranged 100 - 109 days in laboratory soil under continuous irradiation.

In terrestrial field dissipation studies conducted on bare soil in twelve locations across North America and Europe, DT_{50} values ranged 8.3 - 310 days, with a geomean DT_{50} of 51 days and a representative geomean DT_{50} of 314 days determined for modelling. Residue carryover into the next growing season ranged from 8 - 59%.

K_{FOC} values for flupyradifurone in ten soils ranged 75 - 270 mL/g (mean 130 mL/g) indicating moderately mobility in soil, which is supported by soil column leaching studies. It was also demonstrated that adsorption of flupyradifurone was time-dependent and increased by a factor of 3.3 after 120 days. 6-CNA had K_{FOC} values ranging 18 - 151 mL/g (mean 62 mL/g) indicating it is mobile in soil. The K_{FOC} for DFA in five soils ranged from 1.7 - 9.5 mL/g (mean 6.8) indicating it is highly mobile.

The key regulatory endpoints selected for risk assessment were the soil DT_{50} 314 days (geomean of representative half-lives from 12 field trials) and K_d 1.6 (predicted value at 1% OC based on the regression of ten soil values).

7.2 Fate and behaviour in water

Flupyradifurone is stable to hydrolysis. Aqueous photolysis DT_{50} values were 14 hours in buffered or natural water, which suggests that photolysis can contribute to the degradation of flupyradifurone in the non-turbid water near the surface.

After 120 days in six aerobic water/sediment systems in the laboratory, 11 - 37% flupyradifurone remained in the water phase while 39 - 59% partitioned to sediment. Mineralisation ranged 3.9 - 8.5% and bound

[2] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-calculate-representative-half-life-values

residues ranged 14 - 27%. The DT_{50} values ranged 193-285 days (geomean 228 days). No major metabolites were formed.

After 102 days in two anaerobic water/sediment systems, 32-72% flupyradifurone remained in the water phase while 16 - 2% partitioned to the sediment. The geomean DT_{50} was 239 days in the anaerobic systems. No major metabolites were formed.

In an outdoor microcosm study, the mean DT_{50} of flupyradifurone was 81 days in the water phase due to partitioning into the sediment and degradation. The DT_{50} was 95 days in the whole system was faster under the prevailing outdoor conditions in comparison to the laboratory water/sediment studies. Considering that flupyradifurone is rapidly degraded by photolysis, there may be enhanced degradation effect of sunlight under field conditions.

In two aerobic water/sediment systems, the dissipation of the major soil metabolite DFA from the supernatant water phase was characterised by translocation into the sediment and by slow degradation (geomean DT_{50} 239 days). The geomean DT_{50} value for DFA in the entire water/sediment systems was 339 days.

The key regulatory endpoint selected for risk assessment was the whole system DT_{50} 95 days (mean value from outdoor microcosm study).

7.3 Fate and behaviour in air

Flupyradifurone is not expected to persist in the atmosphere with modelled half-lives of 4.4 to 13 hours. As a consequence of the short half-life in air, no long-range transport of flupyradifurone in the atmosphere is likely to occur nor an accumulation of flupyradifurone in the environmental compartment air. Based on its low vapour pressure, it is concluded that very low, if any, quantities of flupyradifurone are expected to enter the atmosphere from volatilisation of soil residues.

7.4 Risk to terrestrial vertebrates

Flupryadifurone is not considered to be acutely toxic to mammals (LD_{50} >2000 mg/kg bw); however, reduced growth of offspring was observed following long-term exposure to 39 mg/kg bw/d (NOEL 7.7 mg/kg bw/d). Flupyradifurone was moderately toxic to birds (lowest acute LD_{50} 232 mg/kg bw); reproductive effects were observed following long-term exposure to 154 mg/kg bw/d (NOEL 40 mg/kg bw/d).

Terrestrial vertebrates could be directly exposed to residues of flupyradifurone if oversprayed food sources are consumed immediately after application. Acute risks to birds and mammals and reproductive risks to birds were determined to be acceptable at the screening level. Reproductive risks to mammals were determined to be acceptable at the Tier 1 level of assessment, which considers growth stage of crop and generic focal species for orchard situations. No hazard or risk mitigation labelling is required for terrestrial vertebrates.

7.5 Risk to aquatic species

Flupyradifurone is not acutely toxic to fish (LC_{50} >100 mg/L), but reduced fry survival was observed following long-term exposure to 8.4 mg/L (NOEC mg/L). Flupyradifurone is highly toxic to some species of aquatic invertebrates (lowest LC_{50} 0.25 mg/L), and reproductive effects were observed following long-term exposure to concentrations as low as 0.024 mg/L (NOEC 0.013 mg/L). Flupyradifurone is also highly toxic to sediment dwellers (acute LC_{50} 0.064 mg/L), and reduced emergence and rate of development were observed at 0.021 mg/L (NOEC 0.011 mg/L). Algae and aquatic plants are not sensitive to flupyradifurone (E_rC_{50} >80 mg/L).

Aquatic organisms could be directly exposed to residues of flupyradifurone immediately after application as a result of spray drift or run off from treated areas. Risks were determined to be acceptable to fish, algae, and aquatic plants at the screening level. Spray drift risks to aquatic invertebrates and sediment dwellers were determined to be acceptable with a mandatory no-spray zone of 25 metres. Runoff risks to aquatic invertebrates and sediment dwellers were considered to be acceptable at the Tier 3 level of assessment which considered dilution from a large catchment into a relatively small water body. Precautionary labelling is advised to minimise risks of runoff to aquatic systems.

7.6 Risk to bees

Flupyradifurone has relatively low toxicity to bees following contact exposure (LD_{50} 16 µg/bee) and it is moderately toxic following oral exposure (LD_{50} 1.2 µg/bee). No adverse effects on adults or larvae were observed following chronic exposure at the highest doses tested (045-0.44 µg/bee/day).

For the proposed foliar applications, bees foraging in a field may be exposed through contact with direct spray or through consumption of residues in pollen and nectar. Macadamia nut trees are attractive to bees and require bee pollination. Therefore, bees are expected to be present during flowering. In Australia, macadamia will start flowering in August and September and the flowers produce both pollen and nectar. Flowers are visited by a range of insects including honey bees. Most honey bees collect nectar in the morning and some honey bees collect pollen in the afternoon. The flowers are attractive to bees for three days after opening. Each flower produces relatively small amounts of nectar. The pollen gatherers are reported to be better pollinators than nectar foragers as they are more likely to contact the stigma. Since the macadamia is native to Australia, the flowers are also visited by native stingless bee and solitary bees such as *Trigona* sp. However, as stingless bees are only managed on a small scale, honey bees and unmanaged stingless bees are probably the most important pollinators of macadamia.

The proposed application rate of flupyradifurone is 400 g a.i./ha post-flower (contact exposure) or limited to 200 g a.i./ha during flowering (oral or contact exposure). Risks of contact toxicity were determined to be acceptable at the screening level for either application timing. Acute mortality of adult bees following oral exposure was determined to be of greatest concern for the 200 g a.i./ha treatment during flowering. Higher tier tests were considered to determine the likely effects under real-world conditions. Field and semi-field studies at relevant rates (2× 200 g a.i./ha) in blooming *Phacelia tanacetifolia* and oil seed rape indicated that application during flowering can result in short-term effects such as reduced flight intensity and behaviour anomalies but does not have any overall adverse impact on colony performance or survival.

The weight of evidence suggests that risks of the use of Sivanto Prime 200 SL Insecticide to bees are considered to be acceptable under field conditions, but mitigation measures are recommended to minimise oral exposure.

7.7 Risk to other non-target arthropods

In a full suite of testing in laboratory, extended laboratory, semi-field aged residue and field trials using a representative suspension concentrate (SL) formulation of flupyradifurone, it was demonstrated that flupyradifurone is toxic to beneficial (predatory and parasitic) arthropods.

Beneficial arthropods could be directly exposed to flupyradifurone during treatment of orchards or as a result of spray drift. Unacceptable adverse effects could not be ruled out following Tier I or Tier II assessments. However, available semi-field suggest field residues are safe within 49 days to the most sensitive species *Aphidius rhopalosiphi* (on maize seedlings) and 42 days for another sensitive species *Orius laevigatus* (on apple trees). This also suggests there is potential for recolonisation. In off-crop field tests to simulate spray drift exposure scenarios, no adverse effects on communities were observed at the highest dose (NOER 21 g a.i./ha). Although population effects were observed in some species, these recovered within 1 - 2 months. The rates in the field study were too low to confirm acceptable impacts of the 400 g a.i./ha rate on off-field communities. Therefore, a precautionary statement is recommended to minimise spray drift.

7.8 Risk to earthworms and other soil macro-organisms

Flupyradifurone was slightly acutely toxic to earthworms with an LC_{50} value as low as 121 mg/kg dry soil for the SL formulation. Reproductive effects were observed in earthworms and springtails at concentrations as low as 1.5 mg/kg dry soil (NOEC 1.4 mg/kg dry soil).

Earthworms and other soil macro-organisms could be directly exposed to residues of flupyradifurone in over-sprayed soil within the treatment area. Risks of the proposed use of Sivanto Prime 200 SL Insecticide to earthworms and other soil macro-invertebrates were determined to be acceptable at the screening level. As a result, no hazard or risk mitigation labelling is required.

7.9 Risk to soil micro-organisms

Laboratory data examining soil processes (carbon mineralisation and nitrogen transformation) indicate that soil micro-organisms were not negatively impacted at the highest doses tested (up to 4.0 mg/kg dry soil), which is considerably higher than environmentally relevant concentrations.

Soil micro-organisms could be directly exposed to residues of flupyradifurone in over-sprayed soil within the treatment area. Considering there was no impact on soil processes at tenfold the application rate, risks of the proposed use of Sivanto Prime 200 SL Insecticide to soil micro-organisms were determined to be acceptable. As a result, no hazard or risk mitigation labelling is required.

7.10 Risk to non-target terrestrial plants

Tier 1 testing with a representative suspension concentrate (SL) formulation on 11 species of non-target terrestrial plants indicate that flupyridifurone is not phytotoxic following pre- or post-emergent exposure (ER_{25} >410 g a.i./ha; ER_{50} >410 g a.i./ha). Considering no phytotoxicity is expected at the maximum application rate of 400 g a.i./ha, risks of the proposed use of Sivanto Prime 200 SL Insecticide to non-target terrestrial plants were determined to be acceptable. As a result, no hazard or risk mitigation labelling is required.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed use pattern

Sivanto Prime 200 SL Insecticide is intended for the control of macadamia lace bug, banana spotting bug, fruit spotting bug and suppression of scirtothrips in macadamias. The product may be applied to racemes, foliage and macadamia nuts, once per season. The proposed application rate is 50 mL to 100 mL/100 L to be applied as a dilute spray.

8.2 Summary of efficacy and crop safety

A total of 26 efficacy (including 16 crop safety trials) were provided for Sivanto Prime 200 SL Insecticide.

Macadamia lace bug (Ulonemia concava or Ulonemia decoris)

A total of two laboratory trials and six field trials (a total of 8 trials) were provided to evaluate the efficacy and crop safety for Sivanto Prime 200 SL Insecticide against label claims for use against the Macadamia lace bug at the proposed label rate of 50 mL/100L. All trials were conducted from 2011 to 2013 in the Northern NSW areas of Lismore, Dunoon, Tregeagle, Casino and Wollongbar. Efficacy claims at the proposed label rate were supported in most trials.

Banana spotting bug (*Amblypelta lutescens* ssp. *lutescens*) and Fruitspotting bug (*Amblypelta nitida*)

One laboratory trial and fourteen field trials (a total of 15 trials) were provided to evaluate efficacy and crop safety for Sivanto Prime 200 SL Insecticide against label claims for use against Banana spotting bugs and Fruit spotting bugs at the proposed label rate of 75 – 100 mL/100L. All trials were conducted from 2010 to 2014 in NSW (Tregeagle and Wollongbar) and Queensland (Glasshouse Mountains, South Johnstone, Goomboorain, Bundaberg and Gympie). Efficacy claims at the proposed label rate were supported in most trials.

Scirtothrips (Scirtothrips dorsalis)

Three trials were provided to evaluate suppression of scirtothrips and crop safety in macadamias at the proposed label rate of 100 mL/100L. The trials were conducted in Queensland in 2013 (Bundaberg and Thebine). The label claim of suppression was supported in most trials.

Crop safety

Crop safety was assessed in 16 trials in 9 macadamia varieties. There were no negative crop safety effects recorded in any trials when Sivanto Prime 200 SL Insecticide was applied at the recommended label rates to macadamias.

8.3 Conclusions

Sivanto Prime 200 SL Insecticide is expected to control Macadamia lace bug and Banana spotting bug, provide suppression of Scirtothrips and will be safe to macadamias when used as directed.

9 LABELLING REQUIREMENTS

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

Sivanto® Prime 200 SL

INSECTICIDE

ACTIVE CONSTITUENT: 200 g/L FLUPYRADIFURONE

GROUP	4D	INSECTICIDE

For the control of macadamia lace bug, banana spotting bug, fruit spotting bug and suppression of scirtothrips in macadamias as specified in the DIRECTIONS FOR USE table

Net Contents: 1-110 L

DIRECTIONS FOR USE

RESTRAINTS
DO NOT apply by aircraft.
DO NOT apply if heavy rain or storms are forecast within 3 days.
DO NOT irrigate to the point of run-off for at least 3 days after application.
DO NOT apply more than one application of Sivanto Prime to a macadamia block in a twelve-month period.

SPRAY DRIFT RESTRAINTS

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.

DO NOT direct the spray above trees during airblast applications. TURN OFF outward pointing nozzles at row ends and outer rows during airblast applications.

Users of this product **MUST make an accurate written record** of the details of each spray application within 24 hours following application and **KEEP** this record for a minimum of 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/situation and weed/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 and wetland areas, including aquacultural ponds, surface streams and rivers within **25 metres** downwind from the application area.

CROP	PEST	RATE	CRITICAL COMMENTS
Macadamias	Macadamia lace bug (*Ulonemia concava* or *Ulonemia decoris*)	50 mL/100 L	Monitor crops from early flowering and apply once local thresholds are reached. **Apply a maximum of 1 application of Sivanto Prime to a macadamia block in a 12-month period. DO NOT exceed 1 L of Sivanto Prime per hectare per application for macadamia lace bug during flowering.** Concentrate spraying is not appropriate for this use. Ensure thorough coverage of all racemes, foliage and macadamia nuts using dilute spraying equipment. Refer to "Application" section in GENERAL INSTRUCTIONS for more information.
	Banana spotting bug (*Amblypelta lutescens*) and fruit spotting bug (*Amblypelta nitida*)	75 or 100 mL/100 L	Monitor crops and apply once local thresholds are reached from early nut set. Where applicable, use the higher rate during periods of high pest pressure or when longer residual control is desired. **Apply a maximum of 1 application of Sivanto Prime to a macadamia block in a 12-month period. DO NOT exceed 2 L of Sivanto Prime per hectare per application for spotting bug.** Concentrate spraying is not appropriate for this use. Ensure thorough coverage of foliage and macadamia nuts using dilute spraying equipment. Refer to "Application" section in GENERAL INSTRUCTIONS for more information.
	Scirtothrips (*Scirtothrips dorsalis*) (suppression only)	100 mL/100 L	Monitor crops and apply once local thresholds are reached, but only after flowering. **Apply a maximum of 1 application of Sivanto Prime to a macadamia block in a 12-month period. DO NOT exceed 2 L of Sivanto Prime per hectare per application for scirtothrips.** Concentrate spraying is not appropriate for this use. Ensure thorough coverage of foliage and macadamia nuts using dilute spraying equipment. Refer to "Application" section in GENERAL INSTRUCTIONS for more information.

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

WITHHOLDING PERIODS (WHP)

Harvest (H):

Macadamias DO NOT HARVEST FOR 20 DAYS AFTER APPLICATION

Grazing (G):

Macadamias DO NOT GRAZE TREATED ORCHARD

EXPORT OF TREATED PRODUCE

Growers should note that suitable MRLs or import tolerances do not exist in all markets for produce treated with Sivanto Prime 200 SL. If you are growing produce for export, please check with Bayer CropScience Pty Ltd or your industry body for the latest information on any potential trade issues and their management before using Sivanto Prime.

GENERAL INSTRUCTIONS

INSECTICIDE RESISTANCE WARNING

Mixing

Shake the container well before using. Partially fill the spray tank with clean water and add the required volume of product to the water whilst agitating. Top up the tank with clean water to the required volume.

Application

- Use a sprayer designed to apply high volumes of water up to the point of run-off and matched to the crop being sprayed.
- Thorough coverage of the target area is essential. Set up and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient water to cover the crop to the point of run-off. Avoid excessive run-off.
- The required water volume may be determined by applying different test volumes, using different settings on the sprayer, from industry guidelines or expert advice.
- Add the amount of product specified in the Directions for Use table for each 100 L of water. Spray to the point of run-off, but do not exceed a maximum of 2000 L/ha for macadamia crops. Do not apply more than one application of Sivanto Prime to macadamias in a twelve month period.
- The required dilute spray volume will change and the sprayer set up and operation may also need to be changed, as the crop grows.
- Concentrate spraying is not appropriate for this use.

GROUP 4D INSECTICIDE

For insecticide resistance management Sivanto Prime 200 SL Insecticide is a Group 4D insecticide. Some naturally occurring insect biotypes resistant to Sivanto Prime and other Group 4D insecticides may exist through normal genetic variability in any insect population. The resistant individuals can eventually dominate the insect population if Sivanto Prime or other Group 4D insecticides are used repeatedly. The effectiveness of Sivanto Prime on resistant individuals could be significantly reduced. Since occurrence of resistant individuals is difficult to detect prior to use, Bayer CropScience Pty Ltd accepts no liability for any losses that may result from the failure of Sivanto Prime to control resistant insects.

Sivanto Prime may be subject to specific resistance management strategies. For further information contact your local supplier, Bayer CropScience representative or local agricultural department agronomist.

COMPATIBILITY

Sivanto Prime may be mixed with the following crop protection products: Blue Shield® DF Copper Fungicide, Kocide® Blue Xtra Fungicide, Spin Flo® Systemic Fungicide, Cabrio® Fungicide, Agridex® Non-ionic Surfactant, Maxx Organosilicone Surfactant™. For the latest information on the compatibility of Sivanto Prime with other products, contact your local Bayer CropScience representative.

INTEGRATED PEST MANAGEMENT

Toxic to beneficial arthropods. In-crop residues are expected to be safe for beneficial arthropods within 49 days after the last application. Minimise spray drift to reduce harmful effects on beneficial arthropods in non-crop areas.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with the chemical or used containers.

PROTECTION OF HONEY BEES AND OTHER INSECT POLLINATORS

Moderately toxic to bees. Flupyradifurone has a systemic action. The use pattern as per the Directions for Use is not expected to result in adverse impact on colony performance or survival, but may have transient effects on honey bee behaviour for a short period after application. In order to protect insect pollinators, refer to the Directions for Use for pest-specific application restrictions.

STORAGE AND DISPOSAL

Store in the closed, original container in a cool, well-ventilated area. Do not store for prolonged periods in direct sunlight.

(non-returnable packs)

Triple rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace caps 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. DO NOT re-use empty containers for any other purpose.

(60, 110 litre pack)

If tamper evident seals are broken prior to initial use then the integrity of the contents cannot be assured. Empty container by pumping through the dry-break connection system. Do not attempt to unscrew the valve or breach the locked filling point. Do not contaminate the container with water or other foreign material. Ensure that the coupler, pump, meter and hoses are disconnected, triple rinsed with clean water and drained after each use. Contact point of purchase to arrange return or collection of empty containers. This container remains the property of Bayer CropScience Pty Ltd. DO NOT re-use empty containers for any other purpose.

SAFETY DIRECTIONS

Harmful if inhaled. May irritate the eyes. Avoid contact with eyes. Do not inhale spay mist. When opening the container, mixing and loading and using the prepared spray, wear cotton overalls (or equivalent clothing) buttoned to the neck and wrists and elbow-length chemical resistant gloves. 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 13 11 26).

SAFETY DATA SHEET

Additional information is listed in the Safety Data Sheet, which can be obtained from www.crop.bayer.com.au.

EXCLUSION OF LIABILITY

This product must be used strictly as directed, and in accordance with all instructions appearing on the label and in other reference material. So far as it is lawfully able to do so, Bayer CropScience Pty Ltd accepts no liability or responsibility for loss or damage arising from failure to follow such directions and instructions.

Sivanto®, Agridex® and Blue Shield® are Registered Trademarks

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APVMA Approval No.: 84727/111236

FOR 24 HOUR SPECIALIST ADVICE
IN EMERGENCY ONLY
PHONE 1800 033 111

ABBREVIATIONS

6-CNA	6-Chloronicotinic acid
ac	active constituent
ACCS	Advisory Committee on Chemicals Scheduling
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
d	day
DAT	Days After Treatment
DFA	Difluoroacetic acid
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
ER_{25}	Effective rate, 25th percentile
ER_{50}	Effective rate, median
ESI	Export Slaughter Interval
EUP	End Use Product
Fo	original parent generation
g	gram

GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Heamatocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
K_d	Adsorption constant
K_{FOC}	Freundlich organic carbon absorption coefficient
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre

MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NAFTA	North American Free Trade Agreement
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
NOER	No Observable Effect Rate
OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SL	Soluble Concentrate
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter

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.
Carcinogenicity	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
Genotoxicity	The ability to damage genetic material
Hydrophobic	repels water
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
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES