Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of pydiflumetofen in the product Miravis Fungicide

APVMA Product Number 82484

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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 and Ageing, Office of Chemical Safety (OCS), Department of Sustainability, Environment, Water, Population and Communities (DSEWPaC), 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 in the APVMA's publications *Ag MORAG: Manual of Requirements and Guidelines* and *Vet MORAG: Manual of Requirements and Guidelines*.

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 approval of the active pydiflumetofen and registration of the product Miravis Fungicide 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 27 March 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

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

1 INTRODUCTION

1.1 Applicant

Syngenta Australia Pty Ltd

1.2 Purpose of application

Syngenta Australia Pty Ltd has applied to the APVMA for registration of the new product Miravis Fungicide containing 200 g/L pydiflumetofen in a suspension concentrate (SC) formulation.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of MIRAVIS FUNGICIDE, and approval of the new active constituent pydiflumetofen.

The active pydiflumetofen as well as the end-use product will be manufactured overseas and imported into Australia.

1.3 Product claims and use pattern

Miravis Fungicide is proposed for use as a broad-spectrum fungicide in canola, grapes and potatoes.

The proposed product use pattern is for control of Black leg (*Leptosphaeria maculans*) and White leaf spot (*Mycosphaerella capsellae*) of canola, applied at a rate of 300 to 450 mL/ha when combined with use of a seed treatment or in-furrow treatment, or at a rate of 450 to 600 mL/ha without prior use of seed treatment or in-furrow treatment. The product is also proposed for control of Powdery mildew (*Uncinular necator*) of grapes (wine, table and dried fruit production) applied at a rate of 20 mL/100L using either dilute or concentrate methods, and applied as part of a regular spray program for powdery mildew control until pre-flowering, and for control of Target spot/early blight (*Alternaria solani*) of potatoes, applied at a rate of 250 to 375 mL/ha when used in a protectant program.

1.4 Mode of Action

Pydiflumetofen is a new broad-spectrum fungicide of the chemical group of N-methoxy-(phenyl-ethyl)-pyrazole-carboxamides. The mode of action of the active substance is respiration inhibition at complex II (Succinate-Dehydrogenase) in mitochondria of phytopathogenic fungi, thus pydiflumetofen belongs to the SDHI fungicide group (Group 7).

1.5 Overseas registrations

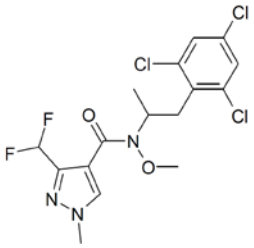
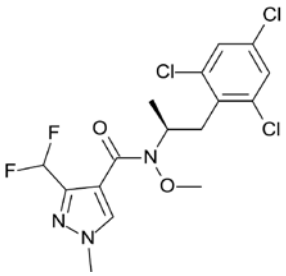
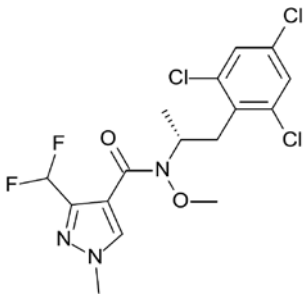
Miravis Fungicide is registered for use in potatoes and grapes in New Zealand, and products containing pydiflumetofen in combination with difenoconazole are approved for use in soybean, peanuts, tomatoes, peppers and grapes in Argentina. Submissions for registration of products containing pydiflumetofen have also been made in a number of other overseas countries.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

The active constituent pydiflumetofen will be manufactured overseas, and imported into Australia as the fully formulated end use product.

Pydiflumetofen is a white powder at room temperatures, with low volatility. It has very low solubility in water, while being slightly soluble in aliphatic hydrocarbon solvents, and very soluble in polar organic solvents. It is not explosive, flammable or oxidising, and is stable on storage.

COMMON NAME (ISO):	Pydiflumetofen
CHEMICAL NAME (IUPAC):	3-(Difluoromethyl)-*N*-methoxy-1-methyl-*N*-[(*RS*)-1-methyl-2-(2,4,6-trichlorophenyl)ethyl]pyrazole-4-carboxamide
MANUFACTURER'S CODES:	Pydiflumetofen: SYN545974 S-enantiomer: SYN546968 R-enantiomer: SYN546969
CAS REGISTRY NUMBER:	1228284-64-7
EMPIRICAL FORMULA:	$C_{16}H_{16}Cl_3F_2N_3O_2$
MOLECULAR WEIGHT:	426.7
STRUCTURAL FORMULA:	 Pydiflumetofen consists of two enantiomers: *S*-isomer and *R*-isomer, present in a 1:1 ratio *S*-isomer:  *R*-isomer: 
CHEMICAL FAMILY:	Pyrazole-carboxamide

PHYSICO-CHEMICAL PROPERTIES OF PYDIFLUMETOFEN ACTIVE CONSTITUENT

PHYSICAL FORM:	Purified active: White powder Technical active: Off-white powder
ODOUR:	No odour detected for purified or technical active
MELTING POINT:	112.7 °C for purified active
RELATIVE DENSITY AT 20^{O}C:	1.55 for technical active
VAPOUR PRESSURE	0.185 µPa at 20 °C; 0.530 µPa at 25 °C for purified active
PH (1% W/V IN DISTILLED WATER)	5.12 at 25 °C for technical active
PARTITION COEFFICIENT	log Pow = 3.8 at 25 °C for purified active
SOLUBILITY IN WATER	1.5 mg/L at 25 °C for purified active
SOLUBILITY IN SOLVENTS (FOR TECHNICAL ACTIVE)	Dichloromethane: >500 g/L Acetone: 220 g/L Ethyl acetate: 130 g/L Toluene: 67 g/L Methanol: 26 g/L Octanol: 7.2 g/L Hexane: 0.27 g/L
FLAMMABILITY	Not highly flammable for purified or technical active
EXPLOSIVE PROPERTIES	Not explosive under thermal, shock or frictional stimuli for purified or technical active
SELF-IGNITION TEMPERATURE	No self-ignition observed under the conditions of the test for purified or technical active
OXIDISING PROPERTIES	Not oxidizing for purified or technical active
STABILITY:	Stable at 54°C for 2 weeks when stored in a lacquered steel or HDPE containers; Stable in the presence of metals and metal ions (aluminium flakes and iron granules, aluminium acetate and iron acetate)

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

On the basis of the chemistry data provided, and the toxicological assessment, it is proposed that the following APVMA Active Constituent Standard be established for pydiflumetofen:

APVMA ACTIVE CONSTITUENT STANDARD FOR PYDIFLUMETOFEN

CONSTITUENT	SPECIFICATION	LEVEL
Pydiflumetofen	Pydiflumetofen	980 g/kg minimum

Approval of pydiflumetofen active constituent is supported from a chemistry perspective.

2.2 Formulated product

The product Miravis Fungicide will be manufactured overseas. It is a suspension concentrate formulation containing 200 g/L pydiflumetofen as the only active constituent. Miravis Fungicide will be packaged in high density polyethylene (HDPE) or polyethylene terephthalate (PET) containers ranging from 1–20 L. Suitable details of the product formulation, specifications for the ingredients, formulation and quality control processes, product specifications, stability data for the product when stored in the proposed packaging, analytical methods for the active constituent in the product, and details of the proposed containers, were provided and evaluated.

The stability data indicates that the product will remain stable for up to two years when stored under normal conditions.

PRODUCT NAME:	Miravis Fungicide
FORMULATION TYPE:	Suspension concentrate (SC)
ACTIVE CONSTITUENT CONCENTRATION:	200 g/L Pydiflumetofen

Physical and chemical properties of product

PHYSICAL FORM:	Off-white liquid
ODOUR:	No particular odour
PH VALUE:	pH: 7.2 (undiluted at 25 °C); pH: 7.5 (1% in DI water at 25 °C)
SURFACE TENSION:	36.0 mN/m (1% in water, 20 °C)
VISCOSITY (AT 20°C):	212 mPa.s at 20 s^{-1}; 80.8 mPa.s at 100 s^{-1};
SAFETY PROPERTIES	Not explosive, oxidising, reducing or flammable, compatible with water and a common dry powder fire extinguishing agent (mono-ammonium phosphate)
CORROSIVE HAZARD:	Not corrosive to HDPE or PET containers
PACK SIZES:	1 L – 20 L
PACKAGING MATERIAL:	HDPE or PET
PRODUCT STABILITY:	Stable at 54 °C for 2 weeks, or at - 10 °C for 2 weeks

2.3 Recommendations

Based on a review of the chemistry and manufacturing details provided by the applicant, registration of *Miravis Fungicide* is supported from a chemistry perspective.

3 TOXICOLOGICAL ASSESSMENT

3.1 Evaluation of toxicology

The toxicological data submitted on the active pydiflumetofen is considered sufficient to determine its toxicology profile and to characterise the risk to humans. The 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, repeat dose neurotoxicity study, and other information to address the human safety criteria.

In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels.

Chemical class

Pydiflumetofen belongs to the N-methoxy-(phenyl-ethyl)-pyrazole-carboxamide chemical group of fungicides. Pydiflumetofen acts on succinate dehydrogenase (or Electron Transport Chain Complex II) in the mitochondria and inhibits respiration in phytopathogenic fungi. The active ingredient is a mixture of R and S isomers of pydiflumetofen.

Toxicokinetics and metabolism

In rats, mass balance studies showed that orally administered pydiflumetofen is well absorbed at low doses and the pharmacokinetic (AUC) data confirms that the presence of radiolabelled compound (ie parent + metabolites) in the systemic circulation is not dose proportional. Due to extensive first pass metabolism, the bioavailability of pydiflumetofen is low and is further reduced after repeat dosing. This reduction in bioavailability of radiolabelled compound was most apparent at doses greater than 30 mg/kg bw/d due to very substantial autoinduction of hepatic xenobiotic metabolising enzymes after only a few days of dosing. Elimination of parent pydiflumetofen was rapid ($t_{1/2}$ approx 1.5 h; iv) but that of its metabolites was moderately slow with an apparent half-life between 20 and 51 h indicating that modest plasma accumulation of metabolites is likely to occur in repeat dose studies. The predominant route of excretion in both sexes was via bile which accounted for between 2 and 80% of the administered dose (dose dependent) with urine accounting for less than 20%. At lower doses, very little pydiflumetofen was present in faeces but at higher doses unabsorbed pydiflumetofen was a substantial contributor in faeces. Excretion was largely complete within the first 72 h. Residual radiolabel in the carcass accounted for less than 0.5% of the administered dose indicating a low potential for bioaccumulation, and negligible amounts were recovered in expired air.

Metabolism of pydiflumetofen involved both phase I and phase II pathways including oxidation, glucuronidation and sulphation plus cleavage at the amide bond to form pyrazole related metabolites and cleavage of the parent molecule to form 2,4,6-trichlorophenol related metabolites. Similar kinetics were observed in the mouse and pregnant rabbit.

Acute toxicity

Pydiflumetofen has low to very low acute oral toxicity (LD_{50} >5000 mg/kg), dermal toxicity (LD_{50} >5000 mg/kg) and inhalational toxicity (LC_{50} >5110 mg/m^3) in rats. It was not a skin irritant in rabbits but was a slight eye irritant in rabbits. Pydiflumetofen is not a sensitiser in mice in a Local Lymph Node Assay (LLNA).

Repeat-dose toxicity

The predominant effects of pydiflumetofen in repeat dose studies were generally confined to increased liver weight, & hepatocellular hypertrophy, secondary to adaptive induction of xenobiotic metabolising enzymes (XME), reductions in bodyweight gains and occasionally increased thyroid weights or thyroid follicular cell hyperplasia secondary to XME induction. Mortality was not increased at the top doses in any of the studies.

Pydiflumetofen was not carcinogenic in a rat chronic study but did increase the incidence of hepatic carcinoma and adenoma in male mice. The mechanism of action of pydiflumetofen in the production of mouse hepatic cancers was examined in a series of studies that demonstrated a mode of action that is not relevant to humans (a phenobarbital like activation of Constitutive Androstane Receptor – CAR – with a consequent induction of Cyp450, increased cell proliferation, hepatomegaly and hepatocyte hypertrophy). Toxicity studies of NOA449410, a metabolite in lactating goats and laying hens (see residues assessment) but not identified in rats, were negative in an acute toxicity study and a battery of genotoxicity assays.

Pydiflumetofen was neither a reproductive toxin in rats nor a developmental toxin in rats and rabbits. The compound was tested in a battery of *in vivo* and *in vitro* genotoxocity studies. With the exception of a positive after 22 h of exposure in the absence of S9 in a human lymphocyte clastogenicity assay, all assays were negative. The overall weight of evidence is that pydiflumetofen does not present a genotoxic risk to humans.

Product toxicity

The formulated product, MIRAVIS FUNGICIDE, containing 200 g/L pydiflumetofen, has low acute oral toxicity (LD_{50} >2958 mg/kg), dermal toxicity (LD_{50} >5000 mg/kg) and inhalational toxicity in rats (LC_{50} >3500 mg/m^3). It was not a skin irritant in rabbits but was a slight transient eye irritant in rabbits. Miravis Fungicide was not a skin sensitiser in mice in a LLNA study.

3.2 Public health standards

Poisons scheduling

On 31 October 2017 the Delegate of the Secretary of the Department of Health published a final Scheduling decision to exempt pydiflumetofen from Scheduling in the Poisons Standard. The reasons for the Delegate's decision to create a new Appendix B entry for pydiflumetofen were: due to its low acute oral and dermal toxicity and lack of demonstrable skin irritation or sensitisation. An implementation date of 1 February 2018 for pydiflumetofen in the Poisons Standard was adopted. Miravis Fungicide containing 20% pydiflumetofen will not be subject to control under the Poison Standard.

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 of 0.1 mg/kg bw/d was established for pydiflumetofen based on a NOAEL of 10 mg/kg bw/d for reduced, bodyweight gain, feed consumption and feed conversion efficiency at the next higher dose tested in a 52–week dietary rat study and using an uncertainty factor of 100.

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. The establishment of an ARfD for pydiflumetofen was not considered necessary, based on its low acute toxicity and the absence of any other toxicologically relevant effect that might be attributable to a single dose.

4 RESIDUES ASSESSMENT

4.1 Introduction

Miravis Fungicide is proposed for use as a broad-spectrum fungicide in canola, grapes and potatoes. Plant and animal metabolism studies, supervised residue trials, analytical methodology, fate in storage and processing data and residues in trade information related to the active pydiflumetofen were considered.

4.2 Metabolism

Plants

Plant metabolism studies for pydiflumetofen (SYN545974) were conducted on wheat, canola, tomatoes and confined rotational crops (lettuce, wheat and turnip). Spring wheat grown outdoors was treated with 2 foliar applications of either [Phenyl-U-^{14}C] or [Pyrazole-5-^{14}C] - SYN545974, each at a nominal application rate of 125 g ai/ha. The first application was made at BBCH 32-34 and the second at BBCH 58. Oilseed rape grown outdoors was treated once post emergence with either [Phenyl-U-^{14}C] or [Pyrazole-5-^{14}C] - SYN545974, at a nominal application rate of 150 g ai/ha. The application timing was at BBCH 65. Tomato plants grown in a glasshouse were treated with 2 foliar spray applications of either [Phenyl-U-^{14}C] or [Pyrazole-5-^{14}C] - SYN545974 at growth stages BBCH 83 and BBCH 86. The nominal application rate was 200 g ai/ha per application. A separate group of tomato plants grown in a glasshouse were treated with a single application of 20 mg ai/plant direct to the soil.

The metabolism of pydiflumetofen was also investigated in the succeeding crops of lettuce, spring wheat and turnip following application to bare soil. [Phenyl-U-^{14}C] or [Pyrazole-5-^{14}C] - SYN545974 was applied to soil (sandy loam) as a single spray application at the nominal rate of 400 g ai/ha. The soil containers were maintained outdoors until 28 days after application when they were moved into a glasshouse for the remainder of the experiment. The rotational crops were sown 30, 120 and 270 days after application.

The major component of the radioactive residue found in primary and rotational crops was parent compound:

- In wheat, the highest levels of parent were detected in straw (1.08–1.17 mg/kg, 76–84%Total Radioactive Residue (TRR)), and the lowest in grain (0.030–0.046 mg/kg, ≥ 81.5% TRR). Only 2 other metabolites were identified: SYN545547 and SYN547891 (see metabolic pathway for plants below). Residues of SYN545547 accounted for ≤ 3.9% TRR with the largest residue detected in straw (0.059 mg/kg, 3.9% TRR). Residues of SYN547891 accounted for ≤ 8.3% TRR with the highest residue in straw (0.065 mg/kg, 4.3% TRR).

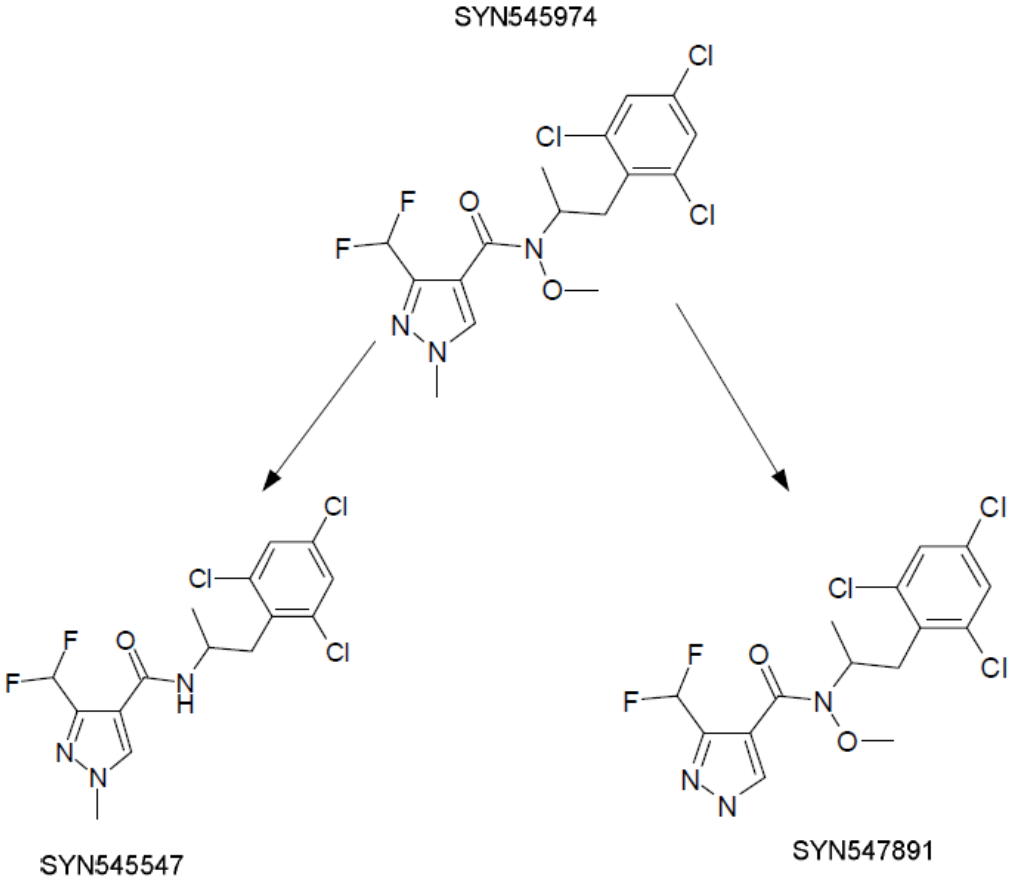
- In canola, the highest residues of parent were detected in trash (0.018–0.032 mg/kg, 30–51%TRR); lower parent residues were detected in seed (0.007- 0.012 mg/kg, 39 - 63% TRR). Low residues of SYN545547 (≤ 0.002 mg/kg, ≤ 3.7% TRR) and SYN547891 (≤ 0.003 mg/kg, ≤ 5.1% TRR) were detected in trash. Low residues of SYN545547 (≤ 0.001 mg/kg, ≤ 6.1% TRR) and SYN547891 (≤ 0.001 mg/kg, ≤ 2.7% TRR) were detected in seed.

- Parent was the major component in all foliar treated tomato fruit samples. The highest residues were detected in fruit collected 14 days after the second application (0.592–0.611 mg/kg, 92–97%TRR). Residues of SYN545547 and SYN547891 accounted for a maximum of 3.6% and 1.6% TRR respectively. In the soil treated experiment, fruit total radioactive residues were low (≤ 0.013 mg/kg), with only SYN545974 (0.001 mg/kg, 4.1% TRR) identified from the pyrazole label.

- In confined rotational crops, parent represented the major proportion of the residue in all commodities, declining between the 30 and 270 day plant back intervals. The highest absolute residue of parent was detected in 120 day PBI pyrazole wheat straw of 0.063 mg/kg, (29% TRR), declining to 0.030 mg/kg (19% TRR) by 270 day PBI. Parent SYN545974 again represented the major component in both immature lettuce and turnip foliage at 30 day PBI (maximum of 77% TRR and 77% respectively) equating to maximum residue levels of 0.015 mg/kg and 0.008 mg/kg respectively. Metabolites SYN547891 and SYN545547 were detected in all commodities. Residues of SYN545547 accounted for ≤ 5.6% TRR with the largest residue detected in 30 day PBI and 120 day PBI pyrazole labelled straw (0.005 mg/kg, 2.2–2.3% TRR). Residues of SYN547891 accounted for ≤ 13% TRR with the highest residue detected in 30 day PBI pyrazole labelled straw (0.012 mg/kg, 5.5% TRR).

The proposed metabolic pathway of pydiflumetofen (SYN545974) in plants is shown below and involves the following steps.

- Demethylation of the pyrazole ring to produce SYN547891.
- Reduction of the parent molecule to produce SYN545547.



Proposed Metabolic Pathway for Pydiflumetofen (SYN545974) in plants

Livestock

In livestock, metabolism studies were conducted on lactating goats and laying hens:

Lactating goats

Two lactating goats, one per radiolabel, were orally dosed with [phenyl-U-^{14}C]-SYN545974 or [pyrazole-5-^{14}C]-SYN545974 for 7 days at a nominal rate of 100 mg ai equiv/kg dietary dry matter intake. Actual dose rates based on measured food consumption were approximately 205 and 144 mg ai equiv/kg dry matter intake for the phenyl and pyrazole label respectively (corresponding to 4.6 and 4.6 mg ai equiv/kg bw respectively). Milk, urine and faeces were collected daily. The goats were sacrificed approximately 11 hours after administration of the final dose and samples of tissues taken (liver, kidneys, peritoneal fat, perirenal fat, subcutaneous fat, flank muscle, loin muscle, GI tract and contents, blood, bile and carcass). Residues in milk achieved a plateau concentration of approximately 0.091 mg/kg (phenyl) and 0.126 mg/kg (pyrazole), after 2 days.

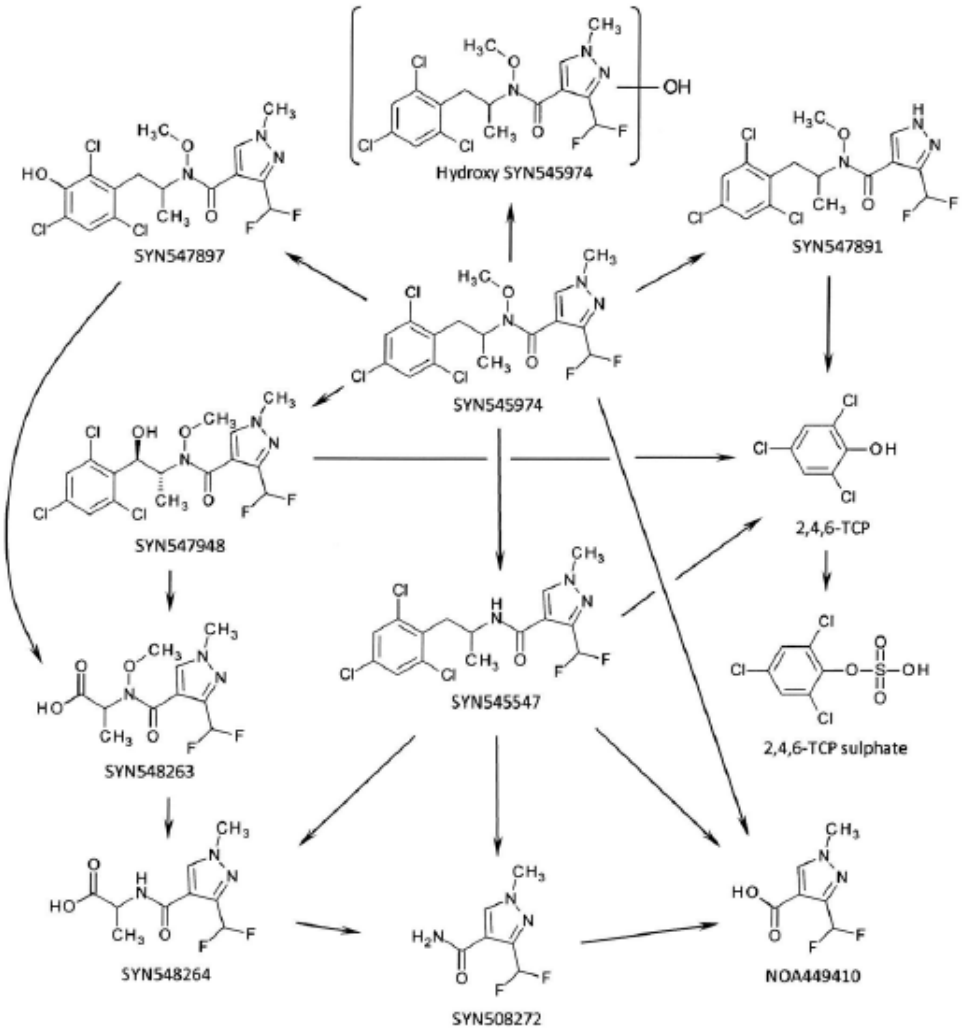
Parent pydiflumetofen was identified in milk and all tissues. Parent % TRRs were greatest in fat (67–74% TRR), muscle (13–24% TRR), milk (8.7–16% TRR) and liver (2.0–8.2% TRR) with much smaller % TRRs being found in kidney (0.5–0.8% TRR). Absolute residues of parent were greatest in liver (≤ 0 .570 mg/kg) and fat (≤ 0.206 mg/kg) with lower residues (0.011 to 0.025 mg/kg) present in muscle, milk and kidney.

The most prominent metabolites of pydiflumetofen identified in goat tissues and milk were:

- 2,4,6-TCP sulphate conjugate (milk: 42% TRR; 0.051 mg/kg, phenyl label)
- SYN548264 (milk: 29% TRR; 0.038 mg/kg, pyrazole label)
- SYN508272 (muscle: 18% TRR; 0.024 mg/kg, milk: 11%TRR; 0.014 mg/kg, pyrazole label)
- SYN548263 (kidney: 17% TRR; 0.389 mg/kg, milk: 14% TRR; 0.019 mg/kg, pyrazole label)

The proposed metabolic pathway for pydiflumetofen in lactating goats is summarised below. The observed metabolites of pydiflumetofen were formed by:

- N-demethylation of the pyrazole ring
- N-demethoxylation of the amide nitrogen
- monohydroxylation of the benzyl methylene functionality
- monohydroxylation of the trichlorophenyl ring
- cleavage at the benzylic methylene, N-alkyl and amide linkages between the phenyl and pyrazole rings
- conjugation of metabolites to form their glucuronide and/or sulphate ester analogues (all except hydroxy SYN545974).



Proposed Metabolic Pathway for Pydiflumetofen (SYN545974) in lactating goats

Laying hens

Six laying hens per radiolabelled treatment were dosed orally with [phenyl-U-^{14}C]-SYN545974 or [pyrazole-5-^{14}C]-SYN545974 for 14 days at a nominal rate of 30 mg ai equiv/kg dry matter intake. Actual dose rates based on measured food consumption were approximately 56.3 and 56.9 mg ai equiv/kg dry matter intake for the phenyl and pyrazole label respectively (3.3 and 3.6 mg ai equiv/kg bw). Excreta and eggs were collected daily, with eggs separated into yolk and white. The hens were sacrificed approximately 11 hours after administration of the final dose and tissues (liver, muscle, fat) taken for analysis.

Mean residues in egg yolks achieved a plateau concentration of approximately 0.344 mg/kg (phenyl) and 0.116 mg/kg (pyrazole) after 10 and 7 days of dosing, respectively. Mean residues in egg whites achieved a plateau concentration of approximately 0.064 mg/kg (phenyl) and 0.062 mg/kg (pyrazole) after 6 and 7 days of dosing, respectively.

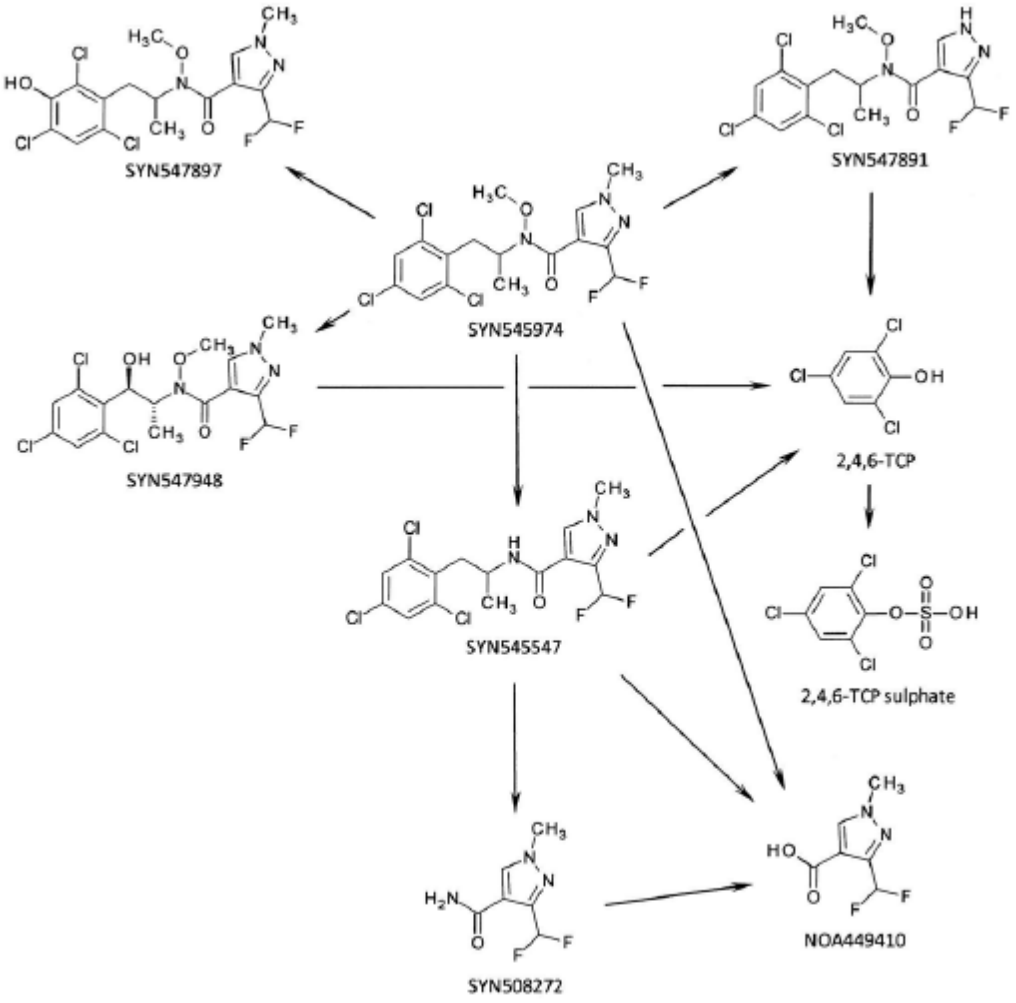
Parent pydiflumetofen was identified in eggs and all tissues. The proportion of TRR as parent was greatest in egg white (27–47% TRR) and fat (17–31% TRR) with much smaller proportions being found in muscle (5–9% TRR), egg yolk (3–11% TRR) and liver (0.5–5% TRR). Absolute residues of parent were greatest in egg white (≤ 0.025mg/kg), liver (≤ 0.021 mg/kg) and fat (0.017 mg/kg) with lower residues present in egg yolk (0.011 to 0.012 mg/kg) and muscle (0.001 to 0.002 mg/kg).

The most prominent metabolites of pydiflumetofen identified in chicken tissues and eggs were:

- 2,4,6-TCP sulphate conjugate (egg yolk: 67.8% TRR; 0.242 mg/kg, muscle: 48.4% TRR; 0.013 mg/kg, fat: 26.5% TRR; 0.027 mg/kg, egg white: 14.5% TRR; 0.008 mg/kg, phenyl label)
- SYN508272 (muscle: 46.3% TRR; 0.010 mg/kg, egg white: 34.3% TRR; 0.018 mg/kg, pyrazole label)
- NOA449410 (egg white: 15.4% TRR; 0.008 mg/kg, pyrazole label)

The proposed metabolic pathway for pydiflumetofen in laying hens is summarised below. The observed metabolites of pydiflumetofen were formed by:

- N-demethylation of the pyrazole ring
- N-demethoxylation of the amide nitrogen
- monohydroxylation of the benzyl methylene functionality
- monohydroxylation of the trichlorophenyl ring
- cleavage at the benzylic methylene, N-alkyl and amide linkages between the phenyl and pyrazole rings
- conjugation of metabolites to form their glucuronide and/or sulphate ester analogues (all except hydroxy SYN545974).



Proposed Metabolic Pathway for Pydiflumetofen (SYN545974) in laying hens

4.3 Analytical methods

Plant commodities

For high water content and dry crop categories, the representative sample was extracted twice with acetonitrile/water using a homogenizer at high speed. The extracts were combined after removal of solids by centrifugation. An aliquot of sample extract was diluted and processed via SPE procedures prior to final reconstitution and subjected to residue determination. Alternatively, an aliquot of sample extract was filtered or treated with C18 via dispersive SPE procedure and diluted prior to final analysis if instrument sensitivity allowed with minimum matrix interferences. Residue determination was achieved by high performance liquid chromatography with triple quadrupole mass spectrometric detection (LC-MS/MS) using electrospray ionization techniques. The limit of quantification (LOQ) of the method has been established at 0.01 mg/kg for pydiflumetofen in crop commodities.

Animal commodities

A method was provided for the determination of pydiflumetofen in bovine fat, muscle, liver, kidney, milk, blood and hens eggs. The LOQ for the method was 0.01 mg/kg. Bovine muscle, liver, kidney, milk, blood and hens eggs were extracted by homogenizing in acetonitrile/water. For the extraction of bovine fat the sample was dissolved in hexane before liquid/liquid partitioning into acetonitrile/water. Samples were centrifuged and an aliquot diluted with water for final determination by LC-MS/MS. Alternatively, samples may be cleaned up by Solid Phase Extraction (SPE) prior to analysis.

For the determination of 2,4,6-trichlorophenol (2,4,6-TCP) in bovine fat, muscle, liver, kidney, milk, blood and hen eggs, an enzyme hydrolysis procedure is employed to release 2,4,6-TCP from conjugates. The LOQ for the method was 0.01 mg/kg. Bovine muscle, liver, kidney, milk, blood and hens eggs were extracted by homogenizing in acetonitrile/water. For the extraction of bovine fat the sample was dissolved in hexane before liquid/liquid partitioning into acetonitrile/water. Samples were centrifuged (except fat samples) and an aliquot concentrated to the aqueous remainder. Samples were buffered with sodium acetate containing β-glucuronidase and diluted with water prior to incubation. Samples were cleaned up by Solid Phase Extraction (SPE) prior to analysis by LC-MS/MS.

A method was provided for the determination of SYN548264 and SYN508272 in bovine milk. The LOQ for the method was 0.01 mg/kg. SYN548264 and SYN508272 were extracted from milk by shaking with acetonitrile. An aliquot of the extract was diluted with water/acetonitrile prior to analysis by LC-MS/MS, using matrix matched calibration.

A method was provided for the determination of free and conjugated SYN547897 and SYN548263 in kidney and liver. The LOQ for the method was 0.01 mg/kg. Samples of liver or kidney were extracted by homogenisation with acetonitrile/water. The extracts were centrifuged and an aliquot filtered and evaporated to the aqueous remainder. The mixture was buffered with aqueous sodium acetate containing β-glucuronidase and diluted with water. Conjugates of SYN547897 and SYN548263 were hydrolysed by incubation. Samples were diluted and cleaned up by Solid Phase Extraction (SPE) prior to analysis by LC-MS/MS.

4.4 Stability of residues in stored analytical samples

Plant commodities

The stability of pydiflumetofen in seven different plant matrices (lettuce, orange, oilseed rape seed, potato, beans without pods, wheat grain and straw) when stored frozen at ≤ -18ºC was investigated. Residues of pydiflumetofen were confirmed to be stable in these plant matrices when stored deep frozen at ≤-18°C for at least 23 months.

The stability of pydiflumetofen in plant processed commodities from corn (flour, meal and oil), soya bean (flour, milk and oil), grape (raisin) and apple fractions (dried fruit and juice) under freezer storage conditions was also investigated. No apparent degradation of pydiflumetofen was observed over the first 12 months of freezer storage in any of the matrices.

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

Animal commodities

Residues of pydiflumetofen have been shown to be stable in bovine muscle, liver, fat, milk and eggs when stored frozen for at least 12 months at -20ºC.

A study investigated the storage stability of conjugated 2,4,6-trichlorophenol in animal matrices (bovine muscle, liver, kidney, fat, whole milk and egg) stored frozen for up to 12 months at -18ºC. There was no significant decrease (>30%) in the observed residue levels of conjugated 2,4,6-TCP in any of the animal matrices studied after deep frozen storage for 12 months.

Residues of SYN548264 and SYN508272 have been shown to be stable in milk when stored deep frozen at <-18ºC for up to twelve months.

Residues of SYN547897 declined over time when stored deep frozen. Loses of *ca* 30% in liver and *ca* 20% in kidney were observed up to 11 months of storage. Loses of >30% where measured after 12 months storage.

Residues of SYN548263 have been shown to be stable in kidney when stored deep frozen at <-18ºC for up to twelve months.

In the cow and hen animal transfer studies provided by the applicant, the maximum storage period for samples prior to analysis was 326 days. This is acceptable for the purposes of the current application.

4.5 Residue definition

Plants

Given that parent was the major component of the residue in plants, with all other metabolites forming < 10% of the TRR in primary crops and ≤ 13% of the TRR in confined rotational crops, the recommended residue definition for commodities of plant origin is parent compound only. This definition is suitable both for enforcement of MRLs and for dietary risk assessment.

Animals

The metabolism of pydiflumetofen in livestock was more complex than that observed in plants. In the goat and hen metabolism studies parent compound was detected in all tissues and milk/eggs.

In goats, parent pydiflumetofen was identified in milk and all tissues. The proportion of TRR as parent was greatest in fat (≤ 74% TRR), muscle (≤ 24% TRR), milk (≤ 16% TRR) and liver (≤ 8.2% TRR) with much smaller %TRRs being found in kidney (≤ 0.8% TRR). Absolute residues of parent were greatest in liver (≤ 0.570 mg/kg) and fat (≤ 0.206 mg/kg) with lower residues (0.011 to 0.025 mg/kg) present in muscle, milk and kidney.

In hens, the proportion of TRR as parent was greatest in egg white (≤ 47% TRR) and fat (≤ 31% TRR) with much smaller %TRRs being found in muscle (≤ 8.7% TRR), egg yolk (≤ 11% TRR) and liver (≤ 5.3% TRR). Absolute residues of parent were greatest in egg white (≤ 0.025mg/kg), liver (≤ 0.021 mg/kg) and fat (0.017 mg/kg) with lower residues present in egg yolk (0.011 to 0.012 mg/kg) and muscle (0.001 to 0.002 mg/kg).

A major metabolite in both goats and hens was 2,4,6-TCP sulphate conjugate (milk: 42% TRR; 0.051 mg/kg, egg yolk: 68% TRR; 0.242 mg/kg, hen muscle: 48% TRR; 0.013 mg/kg, hen fat: 26% TRR; 0.027 mg/kg, egg white: 14% TRR; 0.008 mg/kg). As this was the highest absolute residue in milk and was also significant in poultry commodities it will be included in the residue definition for risk assessment. This metabolite will not be included in the enforcement definition as parent is a suitable marker for misuse for more matrices, noting also that a separate analytical method is required for 2,4,6-TCP and that it is not expected to occur in animal matrices based on the estimated livestock dietary burden.

A metabolite that occurred in both goats and hens was SYN508272 (goat muscle: 18% TRR; 0.024 mg/kg, milk: 11.0%TRR; 0.014 mg/kg, hen muscle: 46.3% TRR; 0.010 mg/kg, egg white: 34% TRR; 0.018 mg/kg). As this metabolite occurred at relatively low absolute levels it will not be included in the residue definition.

A major metabolite in goat only was SYN548263 (kidney: 16.6% TRR; 0.389 mg/kg, milk: 14.2% TRR; 0.019 mg/kg). This was the highest absolute residue in goat kidney. However, it was not a significant residue in the dairy cattle transfer study (<0.01 mg/kg after dosing at 15 ppm) and therefore will not be included in the residue definition for animal commodities.

A metabolite found in liver and kidney in the goat metabolism study was SYN547897 (up to 3% TRR, 0.268 mg/kg). As this was the major residue in liver and kidney in the dairy cattle transfer study it will be included in the residue definition for risk assessment. This metabolite will not be included in the enforcement definition as parent is a suitable marker for misuse for more matrices, noting also that a separate analytical method is required for SYN547897 and that it is not expected to occur in animal matrices based on the estimated livestock dietary burden.

NOA449410 was found in both goats and hens (goat kidney: 12% TRR, 0.275 mg/kg; egg white: 15% TRR; 0.008 mg/kg). This was a significant residue in goat kidney, but was not the highest absolute residue. It will not be included in the enforcement definition as parent is a suitable marker for misuse. NOA449410 will also not be included in the definition for dietary risk assessment for pydiflumetofen for commodities of animal origin as it is considered to be of low toxicological concern.

Based on the goat and hen metabolism studies and the dietary burden expected as a result of the uses considered here, the recommended residue definition of commodities of animal origin for enforcement is pydiflumetofen. The recommended residue definition for commodities of animal origin for risk assessment is the sum of pydiflumetofen, 2,4,6-trichlorophenyl (free and conjugated) and 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid methoxy-[1-methyl-2-(2,4,6-trichloro-3-hydroxy-phenyl)-ethyl]-amide (SYN547897), expressed as pydiflumetofen.

4.6 Residue trials

Canola

The proposed maximum GAP for canola is for a single application at the 4–6 leaf stage (BBCH14-16) at up to 120 g ai/ha. The proposed harvest withholding period is “Not required when used as directed”, the proposed grazing withholding period is 6 weeks.

In Australian trials which are most representative of the proposed GAP, residues in the seed at harvest 110–189 days after application at 99–116 g ai/ha at the 4–6 leaf growth stage were <0.01 (n = 4) mg/kg. (actual estimated values ranged from 0.003–0.006 mg/kg, all between the LOD and LOQ). In EU trials involving a single treatment at 200 g ai/ha at BBCH 65–71 (46–85 days before harvest) residues in the seed were <0.01 (6), 0.01 (2), 0.02, 0.03, 0.04 and 0.05 mg/kg. Scaled for the proposed application rate of 120 g ai/ha residues in the EU trials were <0.01 (8), 0.01, 0.02 (2) and 0.03 mg/kg.

Based on the Australian and EU data for canola seed, the OECD calculator recommends an MRL of 0.04 mg/kg. This MRL will likely be conservative as the EU data involves application at a later growth stage than proposed. An MRL of 0.05 mg/kg is proposed for pydiflumetofen on SO 0495 Rape seed [canola] in conjunction with a harvest withholding period of “Not required when used as directed” and a latest growth stage for application of 4–6 leaf.

Residues did not concentrate on processing to refined canola oil (average processing factor 0.37×). It is therefore not necessary to establish a separate MRL for this commodity.

In Australian trials which are most representative of the proposed GAP, residues in the hay at harvest 110–189 days after application at 99–116 g ai/ha at the 4–6 leaf growth stage were 0.02, 0.02, 0.03 and 0.03 mg/kg (dry weight). Residues in canola forage in these trials at 42 days after application were 0.83, 0.83, 1.09 and 1.38 mg/kg dry weight. In EU trials involving treatment at 200 g ai/ha at BBCH 65–71 residues in plant material at 42 DAT were 0.07, 0.11, 0.17, 0.18, 0.18, 0.23, 0.25 and 0.48 mg/kg fresh weight. Correcting for an assumed dry matter content of 30%, the HR in the EU trials is 1.6 mg/kg.

Based on the Australian and EU forage data the OECD MRL calculator recommends an MRL of 3 mg/kg. Based on the data for hay/straw at harvest in the Australian trials the OECD MRL calculator recommends an MRL of 0.08 mg/kg, noting the data set is small. An MRL of 3 mg/kg is proposed for pydiflumetofen on canola forage in conjunction with a 6 week grazing withholding period. An MRL of 0.1 mg/kg is proposed for Canola straw and fodder (dry).

The highest transfer factor for canola meal (which is a feed for livestock) was 0.09×. Applying this to the HR of canola seed of 0.03 mg/kg gives an HR-P of 0.003 mg/kg. A Table 4 entry of 0.01 mg/kg is recommended for pydiflumetofen on canola meal. The STMR-P for canola meal is 0.01 × 0.09 = 0.001 mg/kg.

Potatoes

The proposed use on potatoes is for application of pydiflumetofen at up to 75 g ai/ha with a minimum 7 day re-treatment interval and a 7 day harvest withholding period.

In Australian trials, residues of pydiflumetofen in potato tubers at 7 days after the last of 3 applications at the nominal rate of 75 g ai/ha (1×) were <0.01 (n = 6) mg/kg. In European trials, residues of pydiflumetofen in potato tubers at 7 days after the last of 3 application at the nominal rate of 70 g ai/ha (~1×) were <0.01 (n = 7) mg/kg.

An MRL of *0.01 mg/kg is recommended for pydiflumetofen on VR 0589 Potato in conjunction with a 7 day withholding period.

Grapes

The proposed use of pydiflumetofen on grapes is for 2 applications at 4 g ai/100L with a minimum 14 days between applications, with application up until pre-flowering EL-19 (BBCH 49). The proposed harvest withholding period is “Not required when used as directed”.

In Australian table grape trials, residues of pydiflumetofen in grapes at 35 days after the last of 3 applications at 4 g ai/100 L were 0.04 (3) and 0.05 mg/kg. In Australian wine grape trials, residues of pydiflumetofen in grapes at harvest after 3 applications at 4 g ai/100 L with the last application at EL-31 were 0.03 (3), 0.04 (2) and 0.05 mg/kg.

Based on the Australian data involving application at 4 g ai/100 L the OECD MRL calculator recommends an unrounded MRL of 0.12 mg/kg, noting that the HR was 0.05 mg/kg. It is proposed that an MRL of 0.1 mg/kg be established for pydiflumetofen on FB 0269 Grapes in conjunction with a harvest withholding period of ‘Not required when used as directed’ and a latest growth stage for application of EL19.

It is noted that residues in wine after 3 applications to grapes at 4 g ai/100 L up to growth stage EL-31 were all <0.003 (n = 6) mg/kg. Processing studies from the US and EU also showed that residues of pydiflumetofen do not concentrate in wine or juice (Processing factors ranged from 0.02–0.57×).

Transfer factors for processing to raisins were 1.96, 2.40, 2.81 and 3.14×. Based on a HR in grapes of 0.05 mg/kg and a highest processing factor of 3.14×, the HR-P for raisins is 0.16 mg/kg. An MRL of 0.3 mg/kg is proposed for pydiflumetofen on DF 0269 Dried grapes (=Currants, Raisins and Sultanas).

Transfer factors for dry pomace were 9.91, 10.57, 19.26 and 28.94×. Based on a HR in grapes of 0.05 mg/kg and a highest processing factor of 28.94× the HR-P for dry pomace is 1.45 mg/kg. An MRL of 2 mg/kg is recommended for pydiflumetofen on AB 0269 Grape pomace, dry. The STMR-P for grape pomace dry is 0.04 × 14.92 = 0.060 mg/kg.

Rotational crops

Considering the available rotational crop data, low residues of pydiflumetofen may be expected to occur in cereal straw in following crops that have not been directly treated (estimated HR 0.06 mg/kg). To cover this possibility, an MRL of 0.1 mg/kg is proposed for pydiflumetofen on Primary feed commodities [except Canola forage; and Canola straw and fodder (dry)].

Residues of pydiflumetofen in other food commodities from rotational crops are expected to be below the LOQ of 0.01 mg/kg. An MRL of *0.01 mg/kg is proposed for pydiflumetofen on “All other foods” for rotational crop purposes.

4.7 Animal commodity MRLs

Ruminants

Animal transfer studies were considered for lactating cattle where animals were dosed with pydiflumetofen for 28 days at 15, 45 or 150 ppm in the feed. It is noted that this study did not include a depuration phase. The results of this study and the estimated livestock burdens are considered here.

For beef cattle the estimated maximum livestock dietary burden is 1.6 ppm based on a diet of 100% canola forage. For dairy cattle the estimated maximum livestock dietary burden is 0.7 ppm based on a diet of 40% canola forage, 20% grape pomace, 10% potato culls and 15% canola meal. Based on the animal transfer study residues of parent pydiflumetofen or its metabolites above the LOQ are not expected to occur in tissues or milk as a result of these feeding levels as summarised in the following table:

Cattle

FEEDING LEVEL (ppm)	MILK	MUSCLE	LIVER	KIDNEY	FAT
	SYN545974 + 2,4,6-TCP + SYN547897 (mg/kg)				
15 (actual)	<0.01 + <0.01	<0.01 + <0.01	0.02 + <0.01 + 0.06	<0.01 + 0.01 + 0.06	0.02 + <0.01
1.6–beef, estimated burden	<0.01 + <0.01	<0.01 + <0.01	<0.01 + <0.01 <0.01	<0.01 + <0.01 <0.01	<0.01 + <0.01
0.7–dairy, estimated burden	<0.01 + <0.01	<0.01 + <0.01	<0.01 + <0.01 <0.01	<0.01 + <0.01 <0.01	<0.01 + <0.01
Established MRLs	-	-	-		-
Recommended MRLs	*0.01	*0.01	*0.01		-

Poultry

The estimated maximum livestock dietary burden for poultry is low (0.001 ppm) and is based on a diet of 5% canola meal. Considering a laying hen transfer study involving dosing at 3, 9 or 30 ppm in the feed, the proposed use is not expected to lead to residues in tissues or eggs as summarised in the following table:

Poultry

FEEDING LEVEL (ppm)	EGGS	MUSCLE	LIVER	KIDNEY	FAT
	SYN545974 + 2,4,6-TCP RESIDUE (mg/kg)				
3 (actual)	<0.01 + <0.01	<0.01 + <0.01	<0.01 + <0.01	<0.01 + <0.01	<0.01 + <0.01
0.001–estimated burden	<0.01 + <0.01	<0.01 + <0.01	<0.01 + <0.01	<0.01 + <0.01	<0.01 + <0.01
Established MRLs	-	-	-		-
Recommended MRLs	*0.01	*0.01	*0.01		-

4.8 Estimated dietary intake

The chronic dietary exposures to pydiflumetofen 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 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines[2] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for pydiflumetofen is equivalent to <1% of the ADI. It is concluded that the chronic dietary exposures to pydiflumetofen 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 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. An acute reference dose is not required for pydiflumetofen and a NESTI calculation will not be undertaken.

4.9 Bioaccumulation potential

The Log P_{ow} of pydiflumetofen has been determined to be 3.8 at 25 ^{o}C suggesting some fat solubility. The metabolites recommended for inclusion in the residue definition for risk assessment for animal commodities are likely to be less fat soluble than parent. As residues are not expected to occur in animal commodities as a result of the proposed use pattern, the meat MRLs (at the LOQ for parent) will not be established “in the fat” at this time.

2 WHO (2008). Consultations and workshops: Dietary Exposure Assessment of Chemicals in Food: Report of a joint FAO/WHO Consultation, Annapolis, Maryland, USA, 2–6 May 2005.

4.10 Spray drift

The product will be applied by ground application only with medium spray droplets.

In an animal transfer study, the maximum residue in tissues after dosing at 15 ppm was 0.06 mg/kg of metabolite SYN547897 in liver and kidney. The feeding level for residues of SYN547897 to be at the LOQ of 0.01 mg/kg is 2.5 ppm. Assuming pasture consists of 1500 kg DM/ha this corresponds to an allowable drift of 3.75 g ai/ha. As a fraction of the field rate for canola this is 0.031×.

The APVMA's standard scenario for ground application with a high boom and medium droplets indicates drift will drop to below 0.031× the field rate by 6 metres downwind of the application area. Mandatory no-spray zones for protection of international trade are not required for application to canola (or potatoes which have a lower application rate).

The application concentration for grapes is 4 g ai/100 L. For a spray volume of 1000 L/ha this corresponds to a rate of 40 g ai/ha. The allowable drift of 3.75 g ai/ha corresponds to 0.094× the field rate. The APVMA's standard scenario for airblast application to vineyards indicates drift will drop to below 0.094× the field rate by 0.5 metres downwind of the application area. Mandatory no-spray zones for protection of international trade are not required for airblast application to grapevines.

4.11 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 1

COMPOUND		FOOD	MRL (mg/kg)
ADD:			
Pydiflumetofen			
		All other foods	*0.01
DF	0269	Dried grapes (= Currants, Raisins and Sultanas)	0.3
MO	0105	Edible offal (Mammalian)	*0.01
PE	0112	Eggs	*0.01
FB	0269	Grapes	0.1
MM	0095	Meat [mammalian]	*0.01
ML	0106	Milks	*0.01
VR	0589	Potato	*0.01
PO	0111	Poultry, Edible offal of	*0.01
PM	0110	Poultry meat	*0.01
SO	0495	Rape seed [canola]	0.05

TABLE 3

COMPOUND	RESIDUE
ADD:	
Pydiflumetofen	Commodities of plant origin: Pydiflumetofen
	Commodities of animal origin for enforcement: Pydiflumetofen
	Commodities of animal origin for dietary exposure assessment: sum of pydiflumetofen, 2,4,6-trichlorophenyl (free and conjugated) and 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid methoxy-[1-methyl-2-(2,4,6-trichloro-3-hydroxy-phenyl)-ethyl]-amide (SYN547897), expressed as pydiflumetofen

TABLE 4

COMPOUND		ANIMAL FEED COMMODITY	MRL (mg/kg)
ADD:			
Pydiflumetofen			
		Canola forage	3
		Canola meal	0.01
		Canola straw and fodder (dry)	0.1
AB	0269	Grape pomace, dry	2
		Primary feed commodities [except Canola forage; and Canola straw and fodder (dry)]	0.1

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

Canola (including derived oils and meals) and grapes (including dried grapes and wine) are considered to be major export commodities[3], as are commodities of animal origin, such as meat, offal and dairy products, which may be derived from livestock fed feeds produced from treated canola and grapes. Residues in these commodities resulting from the use of *Miravis Fungicide* may have the potential to unduly prejudice trade.

5.2 Destination and value of exports

Canola

Australian exports of canola grain, oil and meal totalled 1945.6 kt (value $1097 million), 154.1 kt and 22.86 kt respectively in 2015–16.[4]

The major export markets for canola grain in 2015–16 included Belgium, France, Germany, Japan, and The Netherlands. Destinations for canola oil included China, Japan, the Republic of Korea, Malaysia and New Zealand in 2014–15 (2015–2016 figures not available). The major market for Canola meal in 2015–16 was New Zealand.

Grapes

Grapes are a significant export, particularly as wine, although table grapes and dried fruit are also exported. In 2015–16 Australia exported 727.08 ML of wine worth $2183.9 million. Australia exports wine to the USA, EU, China, Canada, New Zealand, Singapore, Japan and Malaysia.[4]

The much smaller table grape exports are predominantly Asia bound. Dried grapes are exported worldwide. In 2015–16 Australia exported 5 kt of dried vine fruit worth $19.4 million.[4]

Beef, sheep and pig meat and offals

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). However, quantifiable residues are not expected to occur in animal commodities as a result of the proposed use. The risk to Australia's trade in animal commodities is low and will not be considered further.

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

[4] Australian Commodity Statistics 2016

5.3 Overseas registrations

The applicant indicated that Miravis Fungicide is registered for use in potatoes and grapes in New Zealand, and products containing pydiflumetofen in combination with difenoconazole have been approved for use in soybean, peanuts, tomatoes, peppers and grapes in Argentina. Submissions for registration of products containing pydiflumetofen have also been made in a number of other overseas countries.

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. Pydiflumetofen has not been considered by Codex and overseas MRLs have yet to be established.

5.5 Potential risk to trade

Export of treated produce containing finite (measurable) residues of pydiflumetofen 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.

The applicant is proposing to manage the risk to trade through the following statement on the label:

EXPORT OF TREATED PRODUCE – Crops treated with Miravis Fungicide may contain finite (measurable) residues of pydiflumetofen and may pose a risk to trade in situations where no residue tolerance (import tolerance) is established in the importing country or where residues in Australian commodities are likely to exceed a residue tolerance (import tolerance) established in the importing country. Before you use this product, you are advised to contact Syngenta and/or your industry body about any potential trade issues and their management.

Canola

A finite MRL is proposed for canola. However, in 4 residue trials which are most representative of the proposed GAP, residues in the seed at harvest were <0.01 mg/kg (n = 4) indicating that it is unlikely that quantifiable residues will be routinely observed. In addition, processing studies showed residues did not concentrate in oil or meal. Comment is sought on the potential risk to trade caused by the proposed use of pydiflumetofen on canola.

Grapes and wine

Residues in wine after 3 applications to grapes at 4 g.a.i./100 L up to growth stage EL-31 were all <0.003 (n = 6) mg/kg, suggesting the risk to trade in wine is low. Finite residues are expected to occur in grapes (HR = 0.05 mg/kg) and dried grapes (HR-P = 0.16 mg/kg) as a result of the proposed use. Comment is sought on the potential risk to trade caused by the proposed use of pydiflumetofen on grapes.

Animal Commodities

Residues of pydiflumetofen are not expected to occur in animal commodities as a result of the proposed use and the risk to trade is considered to be low.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Use pattern

Miravis Fungicide will be applied to canola, grapes and potatoes via boom spray or air-blast or handheld equipment. It will be applied at the maximum recommended application rate of 200 g.a.i./ha (active - pydiflumetofen) when applied to canola (300 ha/d).

6.2 Exposure during use

The product is 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) with some possibility of ocular exposure.

In repeat dose toxicity studies the primary target organ of toxicity was the liver with increased liver weight, associated with hepatocyte hypertrophy, generally defining the LOAEL in conjunction with reduced bodyweight gains.

A 28-day dermal study in rats identified no treatment-related effects at the highest dose of 1000 mg/kg bw/d, reflecting both the poor dermal absorption of pydiflumetofen, its rapid clearance and relatively benign toxicological profile. Pydiflumetofen also has very low aqueous solubility, consequently material applied to the skin, moistened with only a small amount of water, will deliver a quite limited effective dose in contact with the skin, further contributing to the absence of observed effects in this study. Although this study was fully OECD TG compliant, given the limitations in determining the effective dose applied, the NOAEL obtained is not considered suitable for OH&S risk assessment. The lowest relevant NOAELs in oral short term and sub-chronic studies with pydiflumetofen are 612 and 81.6 mg/kg bw/d respectively in the mouse and 322 and 18.6 mg/kg bw/d respectively in the rat. In the rat reproduction study (which included liver microscopy), a NOAEL of 46 mg/kg bw/d for systemic toxicity, manifest as a reduction in bodyweight gain, was observed in males. This dose is between the NOAEL and LOAEL observed in the sub-chronic rat study, and is therefore selected as the most suitable NOAEL for OH&S risk assessment.

An exposure assessment was conducted, and in conjunction with the hazard profile, used to determine whether the proposed use of the product would be an undue health hazard to humans. In the absence of exposure data for the proposed modes of application, the US Environmental Protection Agency (US EPA) Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used to estimate exposure. The toxic endpoint of concern and identified NOAEL for risk assessment was derived from a repeat dose study in animals, and in this instance a margin of exposure (MOE) of 100 or above was considered acceptable. The MOE takes into account both potential inter-species extrapolation and intra-species variability. Based on the risk assessment, the proposed uses of the product for fungal growth control was considered acceptable without the use of PPE.

Application of Miravis Fungicide by air-blast and groundboom may lead to unintended bystander exposure via chemical spray drift. In the event that members of the public are exposed intermittently to spray drift, the risk is less than that for worker mixing, loading and applying the spray, which has been assessed as low, and is therefore also low.

6.3 Exposure during 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. The margin of exposure (MOE) determined for re-entry activities associated with the use of the product were considered acceptable on day zero after application. Hence, a re-entry statement is not required for Miravis Fungicide.

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; New Zealand 0800 764 766.

Safety directions

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

6.5 Conclusion

The registration of Miravis Fungicide, containing 200 g/L of pydiflumetofen in a suspension concentrate formulation for control of fungal growth in canola, grapes and potatoes, is supported from a human health perspective.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

Miravis Fungicide is a 200 g/L pydiflumetofen suspension concentrate (SC) formulation proposed for use for the control of black leg (*Leptosphaeria maculans*) and white leaf spot (*Mycosphaerella capsellae*) of canola, powdery mildew (*Uncinular necator*) of grapevines and target spot/early blight (*Alternaria solani*) of potatoes.

7.2 Environmental fate and behaviour

Fate and behaviour in soil

Pydiflumetofen biodegrades slowly in soil under both aerobic and anaerobic conditions in the laboratory ($DegT_{50}$ ranged from 398 to 1,690 d and 313 to 1,970 d, respectively). Degradation on soil is faster by photolysis ($DegT_{50}$ = 197 and 77 d on moist and dry soil, respectively). There was no clear relationship between soil type and conditions (pH, cation exchange capacity, etc.) and degradation half-lives for pydiflumetofen under either aerobic or anaerobic conditions.

There was a large range of dissipation half-lives of pydiflumetofen in soils ($DissT_{50}$ = 84 to 697 d). Dissipation was faster in the field than in the laboratory studies conducted in the dark. Photolysis on the soil surface is likely to have contributed to field dissipation in the bare soil plots. Soil type did not appear to influence the dissipation of pydiflumetofen from soil. In field dissipation studies, metabolites and degradation products were not significant (<10% AR). Pydiflumetofen was primarily in the top 10 to 15 cm of the treated soil and was below the limit of detection at greater depths.

Pydiflumetofen is not readily mobile (low to slight mobility) in soil, and hence is unlikely to leach into groundwater. The K_{OC} for pydiflumetofen in soils ranged from 1,949 mL/g to 3,808 mL/g. There was no clear relationship between organic matter content, organic carbon content or pH and K_{OC} for pydiflumetofen. This is supported from the in-field observations that pydiflumetofen remained in the top 10 to 15 cm of soil.

SYN545547 (as identified in the Proposed Metabolic Pathways in the residues section*)* was a minor pydiflumetofen metabolite and degradation product in soil (<10% AR). SYN545547 has a low to medium mobility in soils (K_{OC} = 490.7–1,300 mL/g). There was no correlation between organic matter content, organic carbon content or pH and K_{OC} for SYN545547.

SYN545547 was also a metabolite and degradation product from the anaerobic soil metabolism or soil photolysis of pydiflumetofen.

Fate and behaviour in water

Pydiflumetofen was resistant to hydrolysis—hydrolytically stable under a range of environmentally relevant pH values (pH 4, pH 7 and pH 9).

Pydiflumetofen is expected to degrade slowly in water with half-lives due to direct and indirect photolysis of 89 and 33 d, respectively. Microbial degradation by aerobic mineralisation in water was slower than via photolysis, with degradation half-lives ranging from 402 to >1,000 d.

Only minor metabolites and degradation products (SYN545547, SYN548262, NOA449410, Unk AP2) were observed in photolysis and aerobic mineralisation studies.

Fate and behaviour in water-sediment systems

Pydiflumetofen will partition favourably to sediment and persist in water-sediment systems. A metabolite and degradation product – SYN545547 was identified in the aerobic and anaerobic biodegradation of pydiflumetofen. Degradation half-lives ($DegT_{50}$) for pydiflumetofen in water-sediment systems, determined from laboratory-based studies ranged from 221 to 252 d and 152 to 163 d under aerobic and anaerobic conditions, respectively.

Pydiflumetofen dissipates relatively quickly from the water column in water-sediment systems compared to total degradation time from the whole system. Time taken for half the amount of pydiflumetofen to dissipate from the water column ($DissT_{50}$) ranged from 6.4 to 34 d and 33 to 42 d in aerobic and anaerobic conditions, respectively. This indicates that the dissipation of pydiflumetofen primarily involves its transfer from water to sediment; and most of the pydiflumetofen degradation is expected to occur in the sediment compartment of water-sediment systems.

SYN545547 was a major metabolite and degradation product (>10% AR) in both aerobic and anaerobic systems. SYN545547 was also found prior to experiment initiation. SYN545547 was typically in sediment extracts. SYN545547 may also be persistent in the sediment of some water-sediment systems. Yet, the $DegT_{50}$ under aerobic conditions varied by an order of magnitude (460 d and 19 d for the two systems tested, the former being a silt-loam sediment and the latter a sand sediment).

Bioaccumulation

Pydiflumetofen is not expected to bioaccumulate because the bioconcentration factors were <100, ie, slightly bioconcentrating (EPHC 2009) (steady state and lipid normalised steady state BCFs were 28 and 31, respectively).

Fate and behaviour in air

Pydiflumetofen is not considered volatile (1.8×10^{-7} Pa @ 20°C and 5.3×10^{-7} Pa @ 25°C (99.5% purity)), and hence it is unlikely to reach significant concentrations in the air as a result of volatilisation from dry soil or vegetation. The dimensionless Henry's Law Constant of 3.7 x 10, indicates that pydiflumetofen is highly volatile from a water surface. However, pydiflumetofen is only slightly soluble in water (1.5 mg/L @ 25°C (99.5% chemical purity) so volatilisation from spray droplets or moist soil surfaces is unlikely to occur to a significant extent. Pydiflumetofen is also likely to degrade quickly in air with an estimated atmospheric half-life of approximately 6 hours due to hydroxyl radical reactions.

7.3 Environmental Effects

Terrestrial organisms

Pydiflumetofen is slightly toxic to birds and practically non-toxic to mammals. The chronic toxicity to birds was 90 (21-w NOEC for *Colinus virginianus*) and 141 mg ac/kg bw/d (20-w NOEC for *Anas platyrhynchos*).

Pydiflumetofen was not toxic to adult bees following oral or contact exposure (LD_{50} >100 µg ac/bee). However, reproductive effects on bee brood were observed after chronic exposure at low levels (8-d cumulative mean larval mortality at 0.14 µg ac/larva/d) of this compound. Although pydiflumetofen is a systemic fungicide, it moves within the plant via the xylem and therefore it is not expected to be translocated to pollen and nectar if applied outside of the blooming period.

There were no significant effects on other beneficial arthropods after exposure to MIRAVIS FUNGICIDE under laboratory or field simulated exposure conditions.

Pydiflumetofen had no adverse effects on soil macro- and micro-organisms. Pydiflumetofen was slightly acutely toxic to earthworms and chronic effects were seen to reproduction at relatively low levels (4-w NOEC (reproduction) of 32 mg ac/kg soil dw).

Pydiflumetofen has demonstrated no phytotoxic effects at the levels tested.

Aquatic organisms

Pydiflumetofen is moderately to very toxic to aquatic organisms due to acute exposure. The most sensitive species to pydiflumetofen toxicity were aquatic invertebrates and fish.

In regards to the acute toxicity of pydiflumetofen the 96-h LC_{50} for fish and the 48-h LC_{50} for *Daphnia* were <1 mg ac/L for most of the studies. Therefore pydiflumetofen was considered very acutely toxic to fish and aquatic invertebrates (Mensink et al. 1995). The most sensitive aquatic species for acute toxicity of pydiflumetofen was the sediment dwelling *Hyalella azteca* (48-h LC_{50} was 0.12 mg ac/L). *Oncorhynchus mykiss* was the most sensitive fish species to the acute toxicity of pydiflumetofen (96-h LC_{50} = 0.18 mg ac/L). The toxicity of the pydiflumetofen formulation tested was similar to that of the active constituent. SYN545547 was a major metabolite and degradation product (>10% AR) in water-sediment systems under aerobic and anaerobic conditions. However, the lowest SYN545547 acute toxicity endpoint for water column species was at least an order of magnitude higher (96-h LC_{50} = 1,400 µg as/L; rainbow trout (*Oncorhynchus mykiss*)) than that for pydiflumetofen. The geomean (range) of the acute toxicity data for fish (96-h LC_{50}; 5 species) was 0.37 (0.18–0.66) mg ac/L, and was the lowest for all aquatic taxonomic groups. The geomean (range) of the acute toxicity data for invertebrate species (48-h EC_{50} (immobility); 7 species) was an order of magnitude higher at 1.8 (0.42–4.7) mg ac/L.

Pydiflumetofen is slightly to moderately toxic (between 0.01 and 1 mg ac/L) in terms of chronic toxicity to the aquatic organisms tested that dwell in the water column (Mensink, Montforts et al. 1995). The most sensitive chronic endpoint for species exposed to pydiflumetofen in the water column was live, normal fathead minnow (*Pimephales promelas*) at hatch (32-d NOEC – 0.025 mg ac/L). For sediment dwelling invertebrates the lowest NOEC was 15 mg ac/kg sediment dw. The toxicity of pydiflumetofen and SYN545547 was similar for sediment dwelling organisms.

Pydiflumetofen is not expected to significantly inhibit the respiration rate of the activated sludge.

7.4 Risk assessment

The focus for the risk assessment was aquatic organisms, which are the most sensitive to pydiflumetofen. The risk to aquatic organisms from exposure to pydiflumetofen through direct overspray and spray drift, as well as the risk to aquatic organisms exposed to pydiflumetofen via surface water and sediment runoff was assessed. Exposure of aquatic organisms to pydiflumetofen in groundwater is unlikely as the compound has a low mobility and is expected to remain in the surface layers of soil.

Non-target terrestrial organisms are likely to be exposed to pydiflumetofen under the proposed application scenario for Miravis Fungicide. However, terrestrial vertebrate and invertebrate species were less sensitive to pydiflumetofen than aquatic species. Potential chronic effects were assessed for birds, honey bees and earthworms. Acute effects were determined to be acceptable due to low toxicity. The risks to mammals, leaf and soil dwelling arthropods, as well as soil macro- and micro-organisms are considered to be acceptable due to low acute and/or chronic toxicity of pydiflumetofen to these organisms.

Risk was acceptable to aquatic organisms from spray drift resulting from the proposed use without a mandatory no-spray zone. Risk was acceptable to aquatic organisms from runoff resulting from the proposed use provided label restraints limiting application within 3 days of irrigation or heavy rainfall are followed. Although Miravis Fungicide showed chronic effects on bee larvae, their exposure is expected to be negligible as residues are not expected to be present in pollen or nectar provided the product is not applied during blooming periods. Additional protection measures on the label limit spray drift exposure to flowering weeds or flowering crops in the vicinity. Risk was acceptable for all other test species for short and long-term exposure from the proposed use pattern. Therefore the proposed use of this product is considered to be unlikely to have an unintended effect that is harmful to animals, plants or things or the environment.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed product use pattern

The proposed product use pattern is for:

1. **Canola** - control of black leg (*Leptosphaeria maculans*) and white leaf spot (*Mycosphaerella capsellae*) at an application rate of 300 to 450 mL/ha, applied at the 4–6 leaf crop stage when combined with use of a seed treatment or in-furrow treatment, or at a rate of 450 to 600 mL/ha without prior use of seed treatment or in-furrow treatment.

2. **Grapes** - control of powdery mildew (*Uncinular necator*) at an application rate of 20 mL/100 L by either dilute or concentrate methods as part of a regular spray program for powdery mildew control until pre-flowering (EL19; BBCH49)). No more than two applications are to be applied per growing season and no more than three applications of a Group 7 containing fungicide.

3. **Potatoes** - control of target spot/early blight (*Alternaria solani*) at an application rate of 250 to 375 mL/ha when used in a protectant program. No more than three applications are to be made to a single crop.

8.2 Assessment of study/trial data

Efficacy and Crop safety

Data from 52 replicated Australian field trials on efficacy and crop safety in canola, grapevines and potatoes from 2012–2016 were assessed. Miravis Fungicide was applied either as a sole fungicide or in conjunction with other fungicides and compared against the efficacy of standard commercial fungicides in all trials.

Canola

Data from 20 Australian field trials with application rates up to 2 L/ha (400 g.a.i./ha) were submitted to demonstrate efficacy and crop safety against blackleg disease in several varieties of canola of different resistance ratings. Application at the 4–6 leaf stage at the proposed label rates of 300–600 mL/ha (ie 60–120 g.a.i./ha) demonstrated that the proposed product was effective in significantly reducing blackleg disease including stem cankers, leaf disease and improving yield compared to the untreated controls and was as effective as industry standards. A lower rate was effective when used in conjunction with an industry standard seed treatment. The higher rate of 90–120 g.a.i./ha was more effective if disease pressure was high, or if less resistant varieties were used, or in the absence of a seed treatment.

Two Australian trials were undertaken to demonstrate effectiveness on white leaf spot in canola. Application at the rates of 45 and 90 g.a.i./ha at 4–6 leaf stage were effective in reducing white leaf spot in canola (as were higher rates up to 200 and 400 g.a.i./ha), and application at the proposed label rates was as effective as an industry standard.

Trial data on common canola varieties at the proposed label rates and above (up to X2 label rate) demonstrated satisfactory crop safety.

Grapevines

Data from 13 Australian field trials were submitted to demonstrate efficacy and crop safety against powdery mildew in several varieties of grapes (wine and table) at application rates of up to 300 mL/100 L (60 g.a.i./100L). At the proposed label rate of 20 mL/100 L (4 g.a.i./100 L) the product significantly reduced powdery mildew disease in leaves and bunches compared to the untreated controls and was as effective as the industry standard fungicides. There was no evidence of phytotoxicity on grapes at any of the application rates trialled at up to X3 label rate.

Potatoes

Data from 17 Australian field trials were submitted to demonstrate efficacy and crop safety against early blight in several varieties of potato when the product is applied at rates of up to 1 L/ha (200 g.a.i./ha) . The proposed label rate of 250 to 375 mL/ha (50–75 g.a.i./ha) in potato applied at 7–14 day intervals was effective in reducing early blight disease incidence and severity on leaves compared to the untreated controls and was as effective as the industry standard fungicides. The higher rate of 75 g.a.i./ha was effective if spray intervals were increased to 21–day intervals. There was no evidence of phytotoxicity on potatoes at any of the application rates trialled at up to X2 label rate and five spray applications.

Resistance management

Pydiflumetofen is a new broad-spectrum fungicide of the chemical group of N-methoxy-(phenyl-ethyl)-pyrazole-carboxamide). The mode of action of the active substance is respiration inhibition at complex II (Succinate-Dehydrogenase) in mitochondria of phytopathogenic fungi, thus pydiflumetofen belongs to the SDHI fungicide group. For the purpose of fungicide resistance management, Miravis Fungicide is a Group 7 fungicide.

8.3 Conclusions

The product MIRAVIS FUNGICIDE acts as a broad-spectrum fungicide and is expected to provide safe and efficacious control of the nominated diseases of canola, grapevines and potatoes when used as directed on the proposed label.

9 LABELLING REQUIREMENTS

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

MIRAVIS™ Fungicide

syngenta®

ACTIVE CONSTITUENT: 200 g/L PYDIFLUMETOFEN

GROUP	7	FUNGICIDE

For the control of various diseases in Canola, Grapes and Potatoes as per the Directions for Use

1–20 Litres

Syngenta Australia Pty Ltd
Level 1, 2-4 Lyonpark Road, Macquarie Park NSW 2113

In a transport emergency dial 000, Police or Fire Brigade
For specialist advice in an emergency only, call 1800 033 111 (24 hours)

APVMA Approval no. 82484/105866

™

DIRECTIONS FOR USE

Restraints
DO NOT apply with aircraft
DO NOT apply if heavy rains or storms that are likely to cause runoff are forecast within 3 days
DO NOT irrigate to the point of runoff for at least 3 days after application

Spray Drift Restraints:
Except when applying with vineyard airblast equipment, DO NOT apply with spray droplets smaller than a MEDIUM spray droplet size category according to nozzle manufacturer specifications that refer to the ASAE S572 Standard or the BCPC Guideline.
DO NOT apply when the 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 vines 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.)

Crop	Disease	Rate	Critical Comments
Canola	Black leg (*Leptosphaeria maculans*) White leaf spot (*Mycosphaerella capsellae*)	300 to 450 mL/ha when combined with use of a seed treatment or in-furrow treatment 450 to 600 mL/ha without prior use of seed treatment or in-furrow treatment	Apply at the 4–6 leaf crop stage. Use lower rate range when used in combination with an effective seed treatment/in-furrow product. When planting highly susceptible varieties combine with effective seed or in-furrow treatment. Application of MIRAVIS™ will reduce lodging, improve adult plant survival and stem canker from blackleg. Use higher rate in crops with a higher disease risk (see Disease control in canola)
Grapes, wine, table and dried fruit production	Powdery Mildew (*Uncinular necator*)	20 mL/100 L	Apply as part of a regular spray program for powdery mildew until pre-flowering (EL19; BBCH49). Apply by dilute or concentrate spraying equipment applying the same total amount of product to the crop. Refer to Application Section for calculations. Do not apply at more than 3x concentration. Apply MIRAVIS™ as part of a protectant fungicide program at 14 to 21 day intervals. Apply an alternative mode of action fungicide at no more than 21 days after the application of MIRAVIS™ during periods conducive to powdery mildew infection or periods of rapid vine growth. Do not apply more than two applications of MIRAVIS™ per growing season and no more than three applications of a group 7 containing fungicide. Do not apply consecutive applications of a group 7 fungicide.

Crop	Disease	Rate	Critical Comments
Potatoes	Target spot/early blight (*Alternaria solani*)	250 to 375 mL/ha	Use in a protectant program before disease occurs. Use the 375 ml/ha when conditions favour high disease pressure at 7–14 day intervals, when extending the application interval to 14–21 days or later in the season when using the higher recommended water rates. Solo applications of MIRAVIS™ should be applied in strict alternation with fungicides from a different mode of action group. MIRAVIS™ applied in a mixture with a non-cross resistant fungicide can only be applied in 2 consecutive sprays before rotation to a different fungicide group. Refer to manufacturers' recommendations for rates of partner fungicides. DO NOT apply more than 3 applications per crop. Group 7 containing fungicides should compose up to 33% of the fungicide program. Apply in sufficient water volume to achieve thorough coverage of the canopy.

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

WITHHOLDING PERIODS:
Harvest
Canola, Grapes: NOT REQUIRED WHEN USED AS DIRECTED
Potatoes: DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION

Grazing
Canola: DO NOT GRAZE TREATED CROPS OR CUT FOR STOCKFOOD FOR 6 WEEKS AFTER APPLICATION

EXPORT OF TREATED PRODUCE – Crops treated with MIRAVIS™ may contain finite (measurable) residues of pydiflumetofen and may pose a risk to trade in situations where no residue tolerance (import tolerance) is established in the importing country or where residues in Australian commodities are likely to exceed a residue tolerance (import tolerance) established in the importing country. Before you use this product, you are advised to contact Syngenta and/or your industry body about any potential trade issues and their management.

GENERAL INSTRUCTIONS
MIRAVIS™ is a broad spectrum fungicide, recommended for control of foliar and soil borne plant diseases, it has preventative activity with limited curative activity.

Disease control in canola
Blackleg is a disease which is highly dependent on distance planted from canola stubble, rainfall and canola variety. Higher blackleg risk can be expected in districts which receive higher rainfall (above 500 mm annual rainfall). Canola grown within 500 m of a previous two year's standing stubble and in later sown crops (May to August) are also at higher risk. Other factors will also increase the risk of blackleg infection, including the intensity of canola cropping in a district, rainfall before sowing and the frequency of growing the same canola cultivar. Consult industry guidelines for more detailed assessment of blackleg risk in specific situations.

Mixing
MIRAVIS™ is a Suspension Concentrate (SC) formulation that mixes readily with water and is applied as a spray.

Measure the required amount of MIRAVIS™, add to the partly filled spray tank, and then add the remainder of the water. If oil is recommended add this after the MIRAVIS™ is well mixed. Wetting agent is not required.

Application
Ground Application only
Ensure thorough coverage of foliage and/or fruit (or bunches) using equipment delivering a MEDIUM spray quality. Ensure that the correct amount of MIRAVIS™ is applied per hectare irrespective of water application rate per hectare. Apply to grapes by high volume (dilute) sprayer or by concentrate sprayer. Apply the same total amount of product to the target crop whether applying via dilute or concentrate spraying equipment.

Dilute Spraying
Use a sprayer designed to apply high volumes of water up to the point of runoff and matched to the crop being sprayed. 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 runoff. Avoid excessive runoff. 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 Direction for Use table for each 100 L of water. Spray to the point of runoff. 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
Use a sprayer designed and set up for concentrate spraying (that is a sprayer which applies water volumes less than those required to reach the point of runoff) and matched to the crop being sprayed. Set up and operate the sprayer to achieve even coverage throughout the crop canopy using your chosen water volume. Determine an appropriate dilute spray volume (see Dilute Spraying) for the crop canopy. This is needed to calculate the concentrate mixing rate. The mixing rate for concentrate spraying can then be calculated in the following way:
Example only
1. Dilute spray volume as determined above: for example 1000 L/ha
2. Your chosen concentrate spray volume: for example 500 L/ha
3. The concentration factor in this example is: 2 x (ie, 1000 L ÷ 500 L = 2)
4. If the dilute label rate is 20 mL/100 L, then the concentrate rate becomes 2 x 20, that is 40 mL/ 100 L of concentrate spray.

The chosen spray volume, amount of product per 100 L of water, and the sprayer set up and operation may need to be changed as the crop grows. For further information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow industry Best Practices.

Compatibility
MIRAVIS™ is compatible with a range of commonly used fungicides, insecticides, herbicides and fertilizers. Always consult your Syngenta representative before mixing MIRAVIS™ with other products. As formulations of other manufacturer's products are beyond the control of Syngenta, and the quality of water may vary with location, all mixtures should be tested prior to mixing commercial quantities.

Fungicide Resistance Warning | **GROUP** | **7** | **FUNGICIDE**

MIRAVIS™ contains a Group 7, SDHI fungicide. Some naturally occurring individual fungi resistant to MIRAVIS™ and other Group 7 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungi population if these fungicides are used repeatedly. These resistant fungi will not be controlled by MIRAVIS™ and other Group 7 fungicides, thus resulting in a reduction in efficacy. Since the occurrence of resistant fungi is difficult to detect prior to use, Syngenta Australia Pty Ltd accepts no liability for any losses that may result from the failure of MIRAVIS™ to control resistant fungi.

MIRAVIS™ may be subject to specific resistance management strategies. To help prevent the development of resistance to MIRAVIS™, use MIRAVIS™ fungicide in accordance with the current CropLife resistance

management strategy. For further information contact your local Syngenta representative, CropLife Australia, farm chemical supplier, local Department of Agriculture or Primary Industries or consultant.

PROTECTION OF HONEY BEES AND OTHER INSECT POLLINATORS
Bee brood development may be harmed by exposure to residues transported into the hive by foraging bees, overspray or drift. DO NOT spray while bees are actively foraging on or around the treatment area. DO NOT allow spray drift to flowering weeds or flowering crops in the vicinity of the treatment area. Before spraying, notify beekeepers to move hives to a safe location with an untreated source of nectar and pollen, if there is potential for managed hives to be affected by the spray or spray drift.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product or used containers. DO NOT apply under weather conditions, or from spraying equipment, that may cause spray to drift onto adjacent areas, particularly wetlands, waterbodies, or watercourses. DO NOT apply if heavy rains are imminent.

STORAGE AND DISPOSAL
Store in the closed original container in a cool, well ventilated area. DO NOT store for prolonged periods in direct sunlight.
Triple or preferably pressure rinse containers before disposal. Add rinsings to treatment 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 for appropriate disposal 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. Do not inhale spray mist. May irritate the eyes. Avoid contact with the eyes. When opening the container, and preparing the spray, wear:
- cotton overalls buttoned to the neck and wrist (or equivalent clothing)
- a washable hat.
Wash hands after use.

FIRST AID
If poisoning occurs contact a doctor or Poisons Information Centre. Phone 131 126.

SAFETY DATA SHEET
If additional hazard information is required refer to the Safety Data Sheet. For a copy phone 1800 067 108 or visit our website at www.greencast.com.au or www.syngenta.com.au

DISCLAIMER
This product complies with the specifications in its statutory registration. Implied terms and warranties are excluded. Syngenta's liability for breach of the express or any non-excludable implied warranty is limited to product replacement or purchase price refund. The purchaser must determine suitability for intended purpose and take all proper precautions in the handling, storage and use of the product including those on the label and/or safety data sheet failing which Syngenta shall have no liability.

Batch No	
Date of Manufacture	

ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
AR	Applied residue
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
BBCH	Scale for identification of phenological development of plants
bw	bodyweight
C_{max}	maximum plasma concentrations
CAR	Constitutive Androstane Receptor
CXL	Codex Maximum Residue Limit
d	day
DAT	Days After Treatment
$DegT_{50}$	Time taken for 50 percent of substance to disappear from a compartment due to degradation processes alone
$DissT_{50}$	Dissipation half-life of a substance (eg in soils)
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
EC_{10}/EC_{50}	concentration at which 10%/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

EL	System for measurement of grapevine growth stages
ER_{25}/ER_{50}	Effective rate of a substance that causes 10%/50% of the maximum response
ESI	Export Slaughter Interval
EU	European Union
EUP	End Use Product
FAO	Food and Agriculture Organisation
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GI	Gastro-intestinal
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Heamatocrit
HDPE	high density polyethylene
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HR	Highest Residue Value
HR-P	Highest Predicted Residue Value
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
IV/iv	intravenous
in vitro	outside the living body and in an artificial environment

in vivo	inside the living body of a plant or animal
JMPR	Joint Meeting on Pesticide Residues (CODEX)
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
K_{ow}	Concentration in octanol phase/Concentration in aqueous phase
kt	Kilo tonne
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LC-MS/MS	High performance liquid chromatography with triple quadrapole mass spectrometric detection
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LLNA	Local Lymph Node Assay
LOD	Limit of Detection – level at which residues can be detected
LOEL/LOAEL	Lowest Observed Effect Level/Lowest Observed Adverse Effect Level
LR_{25}/LR_{50}	Lethal rate of a substance that causes 25%/50% of the maximum response
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
ML	Megalitres
MoA	Mode of Action
MOE	Margin of Exposure
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
MTD	Maximum tolerated dose
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram

NHMRC	National Health and Medical Research Council
NOAEC/NOAEL	No Observable Adverse Effect Concentration/Level
NOEC/NOEL	No Observable Effect Concentration Level
NOER	No Observable Effect Rate
NZW	New Zealand White (rabbits)
OC	Organic Carbon
OECD	Organisation for Economic Cooperation and Development
OCS	Office of Chemical Safety
OM	Organic Matter
PBI	Plant Back Interval
PET	polyethylene terephthalate
PHED	Pesticide Handler Exposure Database
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RAC/RAL	Regulatory Acceptable Concentration/Level
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SPE	Solid Phase Extraction
STMR	Supervised Trial Median Residue
STMR-P	STMR for a processed commodity
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration

TGAC	Technical grade active constituent
TRR	Total Radioactive Residue
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
USEPA	United States Environmental Protection Agency
vmd	volume median diameter
WG	Water Dispersible Granule
WHO	World Health Organisation
WHP	Withholding Period
XME	Xenobiotic Metabolising Enzymes

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
Degradation	Decomposition of a chemical compound. Loss process by which a substance is physically transformed from one chemical entity to another. This can ultimately result in the formation of unextracted residues and CO2, but not necessarily in all cases
Desorption	Removal of a material from or through a surface
Dissipation	The result of one or more loss processes leading to the disappearance of a substance from an environmental matrix, eg soil. Loss processes contributing to dissipation include degradation within the soil matrix by biotic and/or abiotic processes, soil surface photolysis, volatilisation, plant uptake and leaching
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
Percutaneous	Through the skin
Phenology	Study of cyclical biological events such as flowering of plants
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

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