Australian Government

Australian Pesticides and Veterinary Medicines Authority

Public Release Summary

on the evaluation of the new active constituent fenpropidin in the product SEEKER Duo Fungicide

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This publication is available from the APVMA website.

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Preface

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator responsible for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia. Before approving an active constituent and/or registering a product, the APVMA must be satisfied that the statutory criteria, including the safety, efficacy, trade, and labelling criteria, have been met. The information and technical data required by the APVMA to assess the statutory criteria of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined on the APVMA website.

The APVMA has a policy of encouraging transparency in its activities and seeking community involvement in decision making. Part of that process is the publication of Public Release Summaries for products containing new active constituents. 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 advisory agencies, including other Australian Government agencies and State departments of primary industries. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience to encourage public comment.

About this document

This Public Release Summary indicates that the APVMA is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

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

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

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of SEEKER Duo 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 11 July 2023 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:

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

Please note: submissions will be published on the APVMA website unless you have asked for the submission to remain confidential, or if the APVMA chooses at its discretion not to publish any submissions received (refer to the public consultation coversheet).

Please lodge your submission using the public consultation coversheet, which provides options for how your submission will be published.

Note that all APVMA documents are subject to the access provisions of the *Freedom of Information Act 1982* and may be required to be released under that Act should a request for access be made.

Unless you request for your submission to remain confidential, the APVMA may release your submission to the applicant for comment.

Written submissions should be addressed to:

Case Management Team – Pesticides
Australian Pesticides and Veterinary Medicines Authority
GPO Box 3262
Sydney NSW 2001

Phone: +61 2 6770 2300
Email: casemanagement@apvma.gov.au.

Further information

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

Copies of technical evaluation reports covering chemistry, efficacy and safety, 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.

Introduction

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of SEEKER Duo Fungicide, and approval of the new active constituent fenpropidin.

Applicant

Syngenta Australia Pty Ltd. is the applicant for the product SEEKER Duo Fungicide and the active constituent, fenpropidin.

Purpose of application

Syngenta Australia Pty Ltd has applied to the APVMA for the registration of the new product SEEKER Duo Fungicide, containing 375 g/L fenpropidin and 100 g/L difenoconazole in an emulsifiable concentrate (EC) formulation, in conjunction with approval of the new active constituent fenpropidin.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of the product SEEKER Duo Fungicide, and approval of the new active constituent fenpropidin.

Proposed claims and use pattern

SEEKER Duo Fungicide is intended for the control of powdery mildew (*Uncinula necator*) in wine grapes. One application of the product at 40 mL/100 L is proposed using ground application equipment only. At the specified maximum spray volume of 1,500 L/ha, the application rate is equivalent to 600 mL/ha (225 g/ha fenpropidin + 60 g/ha difenoconazole). SEEKER Duo Fungicide is to be applied within a protectant fungicide program aimed at controlling powdery mildew no later than 80% capfall (E-L 25). The product is not to be applied more than one application per season.

Mode of action

Fenpropidin is a preventative and curative fungicide which belongs to the Fungicide Resistance Action Committee (FRAC) Group 5 amines (morpholines) group of fungicides. It acts by inhibiting ergosterol synthesis in membranes (Activity Group G2). It blocks the ergosterol synthesis pathway at a different enzymatic site than the triazole group of fungicides.

Difenoconazole is a systemic triazole with broad spectrum inhibition activity against Deuteromycetes, Basidiomycetes and Ascomycetes fungal organisms. Difenoconazole inhibits the C14-demethylase enzyme which affects the production of sterols which are required for membrane stability and function. Inhibition of sterol production typically leads to the inhibition of growth of fungi. Triazoles have curative activity, although due to resistance management are only recommended to be used preventatively. Triazole tolerance, through multiple mutations within the nuclear CYP51 gene has been identified. Difenoconazole is classified in the FRAC group 3 of fungicides, known as demethylation inhibitors.

Overseas registrations

Fenpropidin is approved in the EU for the control of a range of foliar fungal diseases in cereals. It is also approved in other jurisdictions for the control of foliar fungal diseases in bananas, beets and grapes.

Chemistry and manufacture

Active constituent

The active constituent fenpropidin is manufactured overseas. Details of the chemical name, structure, and physicochemical properties of fenpropidin are listed below in Tables 1 to 2.

Table 1: Nomenclature and structural formula of the active constituent fenpropidin

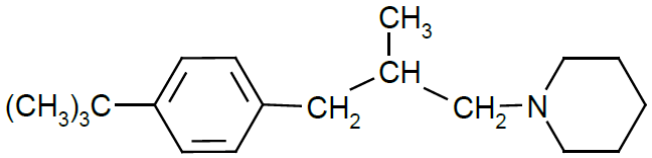
Common name (ISO):	Fenpropidin
IUPAC name:	1-[(*RS*)-3-(4-tert-butylphenyl)-2-methylpropyl]piperidine
CAS registry number:	67306-00-7
Molecular formula:	$C_{19}H_{31}N$
Molecular weight:	273.5 $g.mol^{-1}$
Structural formula:	

Table 2: Key physicochemical properties of the active constituent fenpropidin

Physical form:	Liquid
Colour:	Pale yellow
Boiling point:	Thermal decomposition starts before the boiling point is reached, >250°C, and oxidative decomposition starts at about 93°C
Relative density:	0.913 g/cm^3 @ 20°C
Stability:	In an accelerated model at temperature, the change in concentration of the active was within the error margin of the analytical method after 2 weeks storage at 54°C. Technical fenpropidin is expected to be stable during storage under normal conditions for at least 2 years.
Safety properties:	Not flammable, explosive, corrosive, or an oxidising substance.
Solubility in water:	130 g/L at pH 6.0 at 25°C 530 mg/L at pH 7.0 at 25°C 6.2 mg/L at pH 9.0 at 25°C
Organic solvent solubility:	Completely miscible in • acetone • dichloromethane

<table>
<tr><td></td><td>• ethyl acetate
• hexane
• methanol
• octanol
• toluene</td></tr>
<tr><td>Dissociation constant (PK_a):</td><td>10.1</td></tr>
<tr><td>pH:</td><td>8.57 (1% w/v, 25 °C)</td></tr>
<tr><td>Octanol/water partition coefficient (Log K_{ow}/K_{OW}):</td><td>log P_{ow} = 0.83 at pH 4.2
log P_{ow} = 2.9 at pH 7.0
log P_{ow} = 4.5 at pH 9.0</td></tr>
<tr><td>Vapour pressure:</td><td>0.017 Pa (25 °C)</td></tr>
<tr><td>Henry's law constant:</td><td>3.39 Pa m^3/mol (25 °C)</td></tr>
<tr><td>UV/VIS absorption spectra:</td><td>List of characteristic bands:
<table>
<tr><th></th><th>Wavelength [nm]</th><th>Molar extinction Coefficient [$L \cdot mol^{-1} \cdot cm^{-1}$]</th></tr>
<tr><td>Neutral solution</td><td>218.2</td><td>10,760</td></tr>
<tr><td></td><td>263.7</td><td>410</td></tr>
<tr><td>Acidic solution</td><td>217.9</td><td>9,670</td></tr>
<tr><td></td><td>262.9</td><td>310</td></tr>
<tr><td>Basic solution</td><td>219.2</td><td>9,440</td></tr>
<tr><td></td><td>263.9</td><td>250</td></tr>
</table></td></tr>
</table>

Fenpropidin is a pale-yellow liquid. Its solubility in water is highly dependent on the pH (130 g/L at pH 6.0, 530 mg/L at pH 7.0, and 6.2 mg/L at pH 9.0). There are no explosive, self-ignition, or corrosive properties of safety concern for fenpropidin.

Based on the toxicological assessment and Declaration of Composition provided, the following APVMA Active Constituent Standard is proposed for fenpropidin in Table 3.

Table 3: Proposed APVMA active constituent standard for fenpropidin

Constituent	Parameter	Level
Fenpropidin	Purity	980 g/kg minimum

Formulated product

The product SEEKER Duo Fungicide will be manufactured in Australia and overseas. Tables 4 and 5 below outline some key aspects of the formulation and physicochemical properties of the product.

SEEKER Duo Fungicide will be available in 1 L to 20 L fluorinated high density polyethylene, high density polyethylene/polyamide and co-extruded high-density polyethylene/ethylene vinyl alcohol containers.

Table 4: Key aspects of the formulation of the product SEEKER Duo Fungicide

Distinguishing name:	SEEKER Duo Fungicide
Formulation type:	Emulsifiable concentrate (EC)
Active constituent concentrations:	375 g/L fenpropidin 100 g/L difenoconazole

Table 5: Physicochemical properties of the product SEEKER Duo Fungicide

Physical form:	Brownish liquid
pH:	10.0 (1% in deionised water)
Specific gravity/density:	0.978 to 0.995 g/cm3 at 20°C
Viscosity:	Newtonian liquid
Emulsifiability, emulsion stability, re-emulsifiability:	0.075% and 1% in CIPAC water A at 30°C 0.075%, and 1% in CIPAC water D at 30°C Emulsifiability: spontaneous Emulsion stability: After 0.5 h: no cream, no oil After 2 h: no cream, no oil After 24 h: no cream, no oil Re-emulsifiability: complete Emulsion stability: After 0.5 h re-emulsifiability: no cream, no oil
Persistent Foaming:	1% in CIPAC water D: after 1 minute: 56 mL after 12 minutes: 24 mL 0.075% in CIPAC water D: after 1 minute: 26 mL after 12 minutes: 22 mL
Safety properties:	Not classified as an explosive, or a corrosive substance. Classified as a flammable liquid, category 4 under the Australian Dangerous Goods Code
Storage stability:	There were sufficient data to conclude that the product is expected to remain within specifications for at least 2 years when stored under normal conditions

Recommendations

The APVMA has evaluated the chemistry and manufacture of the active constituent fenpropidin and associated product SEEKER Duo Fungicide, including the manufacturing process, quality control procedures, stability, batch analysis results and analytical methods, and found them to be acceptable. The available storage stability data indicate that the formulated product is expected to remain stable for at least 2 years when stored under normal conditions.

Based on a review of the chemistry and manufacturing details, the registration of SEEKER Duo Fungicide, and approval of the active constituent fenpropidin, are supported from a chemistry perspective.

Toxicological assessment

The submitted data package was sufficient to assess the toxicity of fenpropidin.

Evaluation of toxicology

Chemical class

Fenpropidin is a piperidine derivative. Its fungicidal mode of action is through inhibition of the enzymes Δ^{14}-reductase and $\Delta^{8}\rightarrow\Delta^{7}$ isomerase, resulting in sterols synthesis disruption.

Structurally related chemical classes of fungicides include the morpholines (e.g. fenpropimorph, dimethomorph and amorolfine) and the “amine fungicides”/spiroketalamines (e.g., spiroxamine). Spiroxamine and dimethomorph are approved in Australia.

Pharmacokinetics

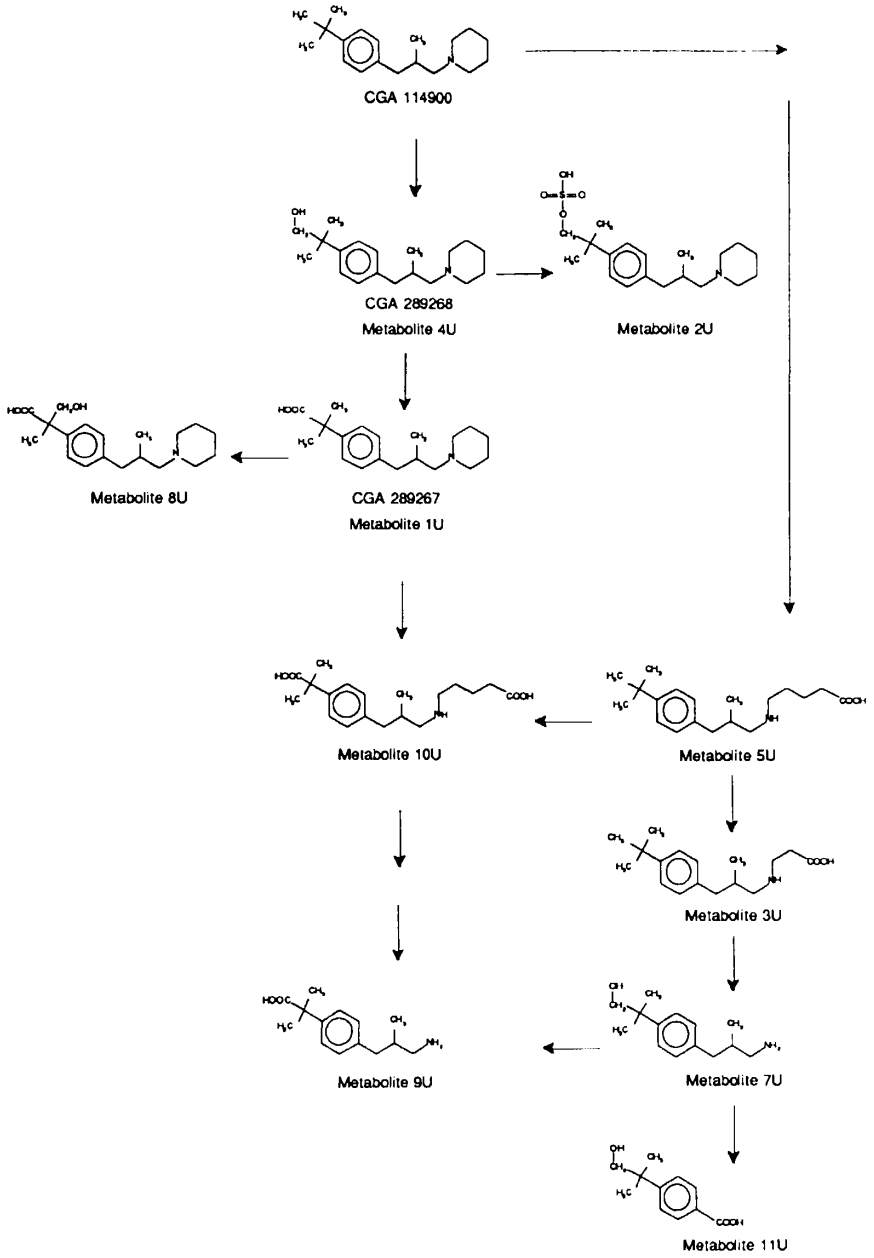
In rats, lactating goats and laying hens, fenpropidin was rapidly and extensively absorbed, metabolised, and excreted. Metabolism primarily consisted in successive oxidations.

Following single oral administration of radiolabelled fenpropidin to rats by gavage, fenpropidin was nearly completely absorbed in males. Oral absorption after a single dose was lower in females at 0.5 mg/kg bw (about 82%) and was reduced to about 59% following dosing at 100 mg/kg bw. Repeated administration resulted in a reduced absorption (about 79% in males and 74% in females).

Based on increased T_{max}, the rate of systemic absorption, particularly in females, decreased with oral dosing over the 0.5 to 100 mg/kg bw dose range. Based on a limited range of tissues, distribution of radioactivity derived from fenpropidin was extensive but sub-dose proportional over the 0.5 to 100 mg/kg bw dose range. Based on tissue T_{max}, peak tissue distribution *cf*. blood was substantially delayed in the liver and kidney (consistent with longer tissue elimination $t_{½}$ in these tissues *cf*. blood and plasma and the routes of elimination). The plasma:blood ratio was approximately 1.

Fenpropidin was extensively metabolised in rats with over 20 identified metabolites. Two concomitant metabolic pathways were proposed. The dominant pathway in females involves oxidation followed by sulphate conjugation of the resultant alcohol group. Sulphate conjugation was more limited in males where further oxidations rather than phase II conjugation were the predominant reactions. The second, quantitatively smaller pathway, involved oxidative cleavage of the piperidine ring followed by downstream oxidative reactions. Two major metabolites, CGA289267 (urine) and 2u (bile/faeces) were identified in rat excreta, but the major blood/plasma metabolites were not identified. Major food/feed metabolites of human dietary exposure concern were not identified in plants. However, 6 major food metabolites were identified in animal food commodities. Of these there were 4 major food animal metabolites (including the conjugates) that were either not identified in rats or were identified as minor metabolites in this species.

Figure 1: Proposed metabolic pathways of fenpropidin in the rat



On an AUC and C_{max} basis, systemic exposure to radioactivity derived from fenpropidin was sub-dose proportional (particularly in females) over the 0.5 to 100 mg/kg bw oral dose range and blood radioactivity elimination $t_{½}$ increased substantially (≥ 670 minutes), and sub-dose proportionately (by a factor of 15 in males and 13.4 in females over the 0.5 to 100 mg/kg bw dose range), with dose. There were no biologically meaningful sex differences in blood radioactivity elimination $t_{½}$. The major route of elimination of radioactivity was in the urine (about 80% of the dose in males and females at 0.5 mg/kg bw, and about 90% of the dose in males and 50% of the dose in females at 100 mg/kg bw). Faecobiliary excretion was a secondary route of excretion. Irrespective of dose level, most of the administered radioactivity (> 70%) was eliminated within 24 hours following dosing with elimination following a single oral dose being essentially complete at 7 days

post-dose. Repeated oral dosing did not result in biologically meaningful changes in the extent or routes of excretion.

Fenpropidin's dermal absorption was ≤ 1% when tested with the neat EC formulation and ~10% with the EC formulation diluted 100 to 400 times.

Acute toxicity (active constituent)

Fenpropidin has a very low acute oral toxicity, low acute dermal toxicity and moderate acute inhalation toxicity. It is a pulmonary irritant in rats, a moderate skin irritant and a severe eye irritant. Fenpropidin was a skin sensitiser (GPMT).

Acute toxicity (product)

SEEKER Duo Fungicide has low acute oral and dermal toxicity, and low to moderate acute toxicity by the inhalation route. It has moderate to severe skin irritation potential and severe eye irritation potential. The product is a respiratory irritant and a skin sensitiser (GPMT). Furthermore, due to its designated solvent content, the formulated product is considered an aspiration hazard.

Repeat-dose toxicity

In repeated daily oral, dermal and inhalation studies in the species evaluated (mice, rats, rabbits and dogs), many of the adverse effects associated with fenpropidin were due to local site of first contact irritancy (skin irritation, gastrointestinal irritation and metaplasia, secondary loss of body weight due to reduced feed consumption, occurrence of pulmonary alveolar foam cells, respiratory tract irritation). In dietary exposure studies where skin irritation and pulmonary foam cells (lipid laden alveolar macrophages) were observed it was considered that these effects were mostly likely to have occurred due to local effects rather than systemic toxicological effects. Fenpropidin is volatile (vapour pressure at 20 °C = 17.0 mPa). Accordingly, exposure to the skin and via inhalation could occur via direct contact or degassing from the prepared diets. The appearance of pulmonary alveolar foam cells was not associated with dyslipidemia (i.e. not caused by hyper beta-lipoproteinaemia or any other evidence of altered systemic lipid handling in any species) or inhalation exposure to other known causes (air pollution, e-cigarettes) or consistent evidence of chronic systemic inflammation. Given the level of local damage to the oesophagus and gastric mucosa, exposure of the lung due to micro-aspiration/eructation and inhalation of irritant materials (an established cause of induction of pulmonary alveolar foam cells as well as the type of lung injuries seen in dogs following repeated oral dosing) is a potential other concurrent cause. Notably there was no progression to pulmonary fibrosis associated with fenpropidin induction of pulmonary alveolar foam cells and other pulmonary injuries.

Adverse systemic effects attributable to fenpropidin following repeated daily dosing of rats (including up to near life-time exposure) included some cases of reduced body weight that were not correlated with reduced feed intake, bladder epithelial hyperplasia (likely associated with the irritancy of urinary metabolites), demyelination injury (in the ventral columns of the lumbar spinal cord, dorsal and ventral spinal and cranial nerve roots and in the peripheral nerves) associated with hindlimbs paresis, bilateral eye lenses cataract, and hepatotoxicity. Systemic adverse effects resulting from repeated daily inhalation exposure of rats to fenpropidin included increased mortality, adrenal hyperaemia/haemorrhage, brain hyperaemia, hepatotoxicity and lymphoid degeneration in thymus and spleen.

In a 28-day dietary toxicity study in rats, the NOAEL was established at 5.4 mg/kg bw/d based on increased incidence of oesophagus epithelium hyperkeratosis.

In a 28-day inhalation toxicity study, rats were exposed to atomised fenpropidin. The LOAEC for local effects in the respiratory tract was 20 mg/m^3 due to respiratory and skin irritancy at all concentrations tested. The NOAEC for systemic effects was 20 mg/m^3 based on severely decreased bodyweight and feed consumption, adverse effects in the lungs, liver, kidneys, thymus and spleen, and severely increased mortality.

In a 13-week dietary study in mice, the NOAEL was 58 mg/kg bw/d based on increased incidence of excitability/irritability and skin irritation.

In a 3-month dietary study in rats, the LOAEL was 1.1 mg/kg bw/d based on increased incidence of foam cells in the lungs. No NOAEL was established.

In a 90-week dietary study in mice, the NOAEL was 4 mg/kg bw/d based on increased incidence of oesophagus hyperkeratosis.

In a 94 to 97-week dietary study in rats, the NOAEL for toxicity was 0.34 mg/kg bw/d based on increased incidence of skin irritation and for systemic toxicity 2.27 mg/kg bw/d based on increased incidence of liver lesions (centrilobular fat) and decreased body weight gain in females.

Chronic toxicity and carcinogenicity

Fenpropidin was not carcinogenic in mice or rats following near lifetime daily oral exposure. There were no treatment-related neoplastic lesions in mice or rats fed fenpropidin in the diet for 80 to 90 or 94 to 97 weeks, respectively, up to the highest dose tested. The NOAEL for carcinogenicity was 144 mg/kg bw/d in mice and 8.53 mg/kg bw/d in rats.

In 12-month dietary study in dogs, increased electrocardiographic QT and corrected QT interval, spinal cord demyelination associated with hindlimbs paresis, bilateral cataract, minimal hepatotoxicity, and urinary bladder epithelial hyperplasia was observed at 20 mg/kg bw/d and the NOAEL was established at 5 mg/kg bw/d.

Considering the available carcinogenicity and genotoxicity studies conducted with fenpropidin, no potential for carcinogenicity in humans was demonstrated. Therefore, fenpropidin is unlikely to pose a carcinogenic risk to humans.

Reproductive and developmental toxicity

Across all fenpropidin reproductive and developmental toxicity studies available, reproductive toxicity and/or treatment related effects on foetal development, were never seen in the absence of maternal toxicity. On this basis, fenpropidin was not a reproductive toxin and was not teratogen.

In a multigenerational study in rats the key effects of dietary fenpropidin exposure in parental and developing animals were reduction in body weight and delayed development. Reproductive toxicity manifested as reduction in the number of implantations and, consequently, reduced litter size. Oral dosing with fenpropidin was associated with an increased incidence of hydrocephalus and non-adverse skeletal developmental

delay in the presence of substantial maternotoxicity manifesting as reduced body weight in a prenatal developmental toxicity study in rats. In a rabbit prenatal developmental toxicity study, oral dosing with fenpropidin was associated with an increased incidence of decreased male body weight, visceral (persistent truncus arteriosus) and skeletal (severely malaligned sternebrae) malformations in the presence of substantial maternotoxicity manifesting as reduced body weight.

Reduction in female pups' brain weight on post-natal day 72 (PND72) was noted in a rat developmental neurotoxicity study.

In the 2-generation reproduction toxicity study in rats, the NOAEL for parental and reproductive toxicity was 42 mg/kg bw/d while for developmental/offspring toxicity, the NOAEL was 8 mg/kg bw/d.

In the developmental toxicity study in rats, the NOAEL for maternal toxicity was gestational day (GD) 7–16 was ~20 mg/kg bw/d and for foetal developmental toxicity during GD 7–16 ~44-50 mg/kg bw/d.

In rat teratogenicity study, the NOAEL for maternotoxicity was 60 mg/kg bw/d and for foetal development 9 mg/kg bw/d.

In rabbit embryotoxicity study, the NOAEL for maternotoxicity was 12 mg/kg bw/d and for foetal developmental toxicity 30 mg/kg bw/d.

In the prenatal developmental toxicity study in rabbits, the NOAEL for maternotoxicity was 5 mg/kg bw/d and for foetal developmental toxicity 10 mg/kg bw/d.

Genotoxicity

Fenpropidin was not genotoxic either *in vitro* or *in vivo* in an appropriately validated test battery.

Neurotoxicity

Acute neurotoxicity

The NOAEL for acute neurotoxicity was established in a developmental neurotoxicity study in rats at 7 mg/kg bw/d based on decreased female brain weight on PND72.

Subchronic neurotoxicity

The NOAELs for peripheral nerves (spinal cord) demyelination were 5 mg/kg bw/d in dogs and 27 mg/kg bw/d in rats.

Demyelination of peripheral nerves, particularly the spinal cord, was observed in a single female rat fed 1,500 ppm fenpropidin in the diet (equal to a mean group intake of ~97 mg/kg bw/d), with associated paresis first diagnosed after 76 days of treatment. Functional observational battery (FOB) and motor activity (MA) tests conducted in the same study revealed no other treatment related signs of neurotoxicity.

In dogs, demyelination was observed in 3 out of 4 high dose males capsule fed fenpropidin at 20 mg/kg bw/d for 12 months, with hindlimbs paresis diagnosed in one of them after 30 weeks treatment. Limited

neurological examinations (sensorimotor reflexes) conducted in control and high dose animals of the same study revealed no additional signs of neurotoxicity.

Health-based guidance values for fenpropidin are protective of all known neurotoxicological effects.

Immunotoxicity

Based on the weight of evidence, fenpropidin was not immunotoxic.

No immunotoxicity studies conducted with fenpropidin were available. Observed effects on the immune system were considered secondary to other effects (stress and/or reduced bodyweight). In the repeat rat inhalation study, mid-dose and high dose animals were highly stressed and died early. They had reduced spleens, atrophic thymus with lymphocyte cells degeneration, reduced white blood cells, especially lymphocytes and neutrophils. In the two generations rat study, high dose second generation female parents had reduced thymus weight, while high dose pups had decreased absolute thymus weight, thymus atrophy and increased phagocytic cells. These effects observed in the two generations study were considered secondary to decreased bodyweight.

Mode of action (toxicology)

No mode of action studies were submitted. Nevertheless, a plausible mammalian toxicity mode of action based on fenpropidin's fungicidal mode of action was proposed, which may explain eye lens cataract and peripheral nerves demyelination observed in laboratory animals exposed to fenpropidin.

In rats, cataract and demyelination were observed in a single female (~97 mg/kg bw/d), with bilateral cataract and bilateral paresis of the hindlimbs first diagnosed after 56 and 76 days of treatment, respectively. In dogs, demyelination was observed in 3 out of 4 males capsule fed fenpropidin at 20 mg/kg bw/d for 12 months, with hindlimbs paresis diagnosed in one of them after 30 weeks treatment. Bilateral clouding of the eye lenses was observed in one female capsule fed fenpropidin at 12 mg/kg bw/d for 26 weeks, while bilateral cataract was observed in all dogs (four males and four females) capsule fed fenpropidin at 20 mg/kg bw/d for 12 months.

Fenpropidin's fungicidal mode of action is based on disruption of sterols metabolism. Fenpropidin may similarly disrupt sterols metabolism in eye lenses and in Schwann cells. Such disruptions are known causes of cataract and peripheral nerves demyelination in mammals. Furthermore, cataractous effects have also been reported following prolonged high dose exposure to other compounds (e.g. difenoconazole, spiroxamine) which fungicidal mode of action also consists in disruption of sterols metabolism.

Health-based guidance values for fenpropidin are protective of peripheral nerves demyelination and eye lenses effects (clouding and cataract).

Toxicity of metabolites and/or impurities

Impurities

The technical grade active constituent proposed for use in Australia is ≥ 98% pure and contains no impurities of toxicological concern.

Metabolites

Absorption, distribution, metabolism, and elimination of fenpropidin radiolabels, and therefore of fenpropidin metabolites, were documented in rats, lactating goats, and poultry, following single or repeated oral administration. An adequate package of fenpropidin toxicity studies conducted on laboratory animals has been assessed where the effects associated with treatment are attributable to fenpropidin and/or its metabolites. Besides, a limited range of *in vitro* genotoxicity studies conducted with CGA289267, the main fenpropidin metabolite identified in rats, goats and hens, indicated no potential for genotoxicity. Overall, the toxicity of fenpropidin metabolites and/or its degradates raised no additional concerns to the toxicological evaluation of fenpropidin.

Reports related to human toxicity

The applicant indicated that fenpropidin has "registered uses worldwide (including in grapes in Switzerland) for foliar use in broadacre and horticultural crops". No reports of poisoning or adverse human health effects related to handling of fenpropidin or SEEKER Duo Fungicide; or consumption of crops treated with fenpropidin/ SEEKER Duo Fungicide were provided. Literature searches conducted by APVMA returned no references relevant to potential allergy, hypersensitivity, or asthma effects in humans.

Health-based guidance values and poisons scheduling

Poisons Standard

Fenpropidin is included in Schedule 6 of the Standard for the Poisons Standard with no exemptions.

Health-based guidance values

Australian Acceptable Daily Intake (ADI) and Acute Reference Dose (ARfD) for fenpropidin were established based on systemic toxicological effects assessed in APVMA's human health risk assessment technical report conducted following Syngenta Australia Pty Ltd.'s application for approval of the new technical grade active constituent fenpropidin, and registration of the associated product SEEKER Duo Fungicide.

Acceptable daily intake

An ADI for fenpropidin was established at 0.023 mg/kg bw/d, based on the NOAEL of 2.3 mg/kg bw/d due to decreased body weight parameters and hepatotoxicity in females at the next highest dose of 11.8 mg/kg bw/d (LOAEL) in a chronic, near lifetime repeat daily oral dosing study in rats.

Acute reference dose

An ARfD for fenpropidin was established at 0.07 mg/kg bw, based on a NOAEL of 7 mg/kg bw/d due to decreased female brain weight on PND72 at the next highest dose of 27 mg/kg bw/d (LOAEL) in the rat developmental neurotoxicity study. This is supported by a NOAEL of 10 mg/kg bw/d in a rabbit prenatal developmental toxicity study due to the occurrence of decreased male body weight and increased foetal (litter) incidence of malformations (persistent truncus arteriosus, severely malaligned sternebrae) in the presence of substantial maternotoxicity at the next highest dose (LOAEL) of 20 mg/kg bw/d).

Recommendations

There are no objections on human health grounds to the approval of the new TGAC, fenpropidin.

There are no objections on human health grounds to the registration of the product SEEKER Duo Fungicide, containing 375 g/L fenpropidin and 100 g/L difenoconazole when used in accordance with the directions for use (DFU) and adhering to the recommended label statements.

Residues assessment

The proposed use of difenoconazole in grapes in this application represents a lower dilute or concentrate spraying concentration with less applications at an earlier application timing compared to the currently approved use patterns in grapes.

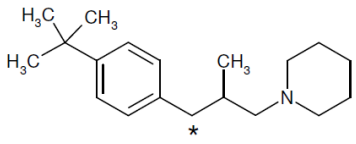
As part of the residues assessment of the new active constituent fenpropidin, plant and target animal metabolism studies, supervised residue trial data for grapes, analytical methodology, fate in storage and processing data, and residues in trade information were considered.

Metabolism

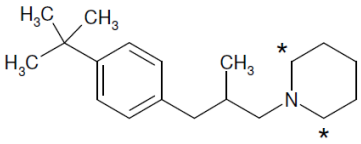
The metabolism of fenpropidin was investigated in fruits (bananas and grapes), root and tuber vegetables (sugar beets) and cereals (spring and summer wheat). No confined rotational studies were provided which is considered acceptable for the current application given that grapes are not considered a rotational crop. For target animals, metabolism studies were conducted with lactating goats and laying hens.

Plants

The plant metabolism studies involved foliar applications of [N-2- methylpropyl-3-^{14}C] labelled fenpropidin or [2, 6-^{14}C-piperidine] labelled fenpropidin.



[N-2-methyl-3-^{14}C]-fenpropidin



[2-6-^{14}C-piperidine]-fenpropidin

Banana

Three foliar applications of [N-2- methylpropyl-3-^{14}C] labelled fenpropidin, formulated as an emulsifiable concentrate (EC), were applied to a greenhouse grown banana tree at a rate equivalent to 1,800 g ai/ha with the first application applied at the blooming stage, the second application 35 days later at the fruiting stage and the final application 55 days later at maturity. Fruit and leaves were sampled just prior to the second application (35 days after application one, 35 DAA1), and at maturity, just prior to the third application (55 days after the second application, 55 DAA2) and 1 day following the third application (1 DAA3). All fruits harvested were separated into peel and pulp.

At maturity, total residues were 3.39 mg eq./kg in peel and 5.10 mg eq./kg in pulp (corresponding to 3.63 mg eq./kg in banana (whole fruit)). In banana fruit, parent fenpropidin was the major component of the radioactivity at 44.2% Total Radioactive Residues (TRR) in peel and 76.5% TRR in pulp. The metabolite CGA 289263 was also observed at 16.1% TRR in peel and 3.3% TRR in pulp. The metabolite CGA 289268 was only observed in peel at 2.1%.

Grape

Three foliar applications of [N-2- methylpropyl-3-^{14}C] labelled fenpropidin, formulated as a water dispersible granule (WG), were applied to grapevines grown outdoors in containers at a rate equivalent to 300 g ai/ha. The first application occurring at BBCH 61, the second application 16 days later and the final application 14 days after the second application. Whole leaves and fruits were harvested 81 days after the third application. The mature grapes were crushed and divided into juice and cake by filtration through filter cloth under vacuum.

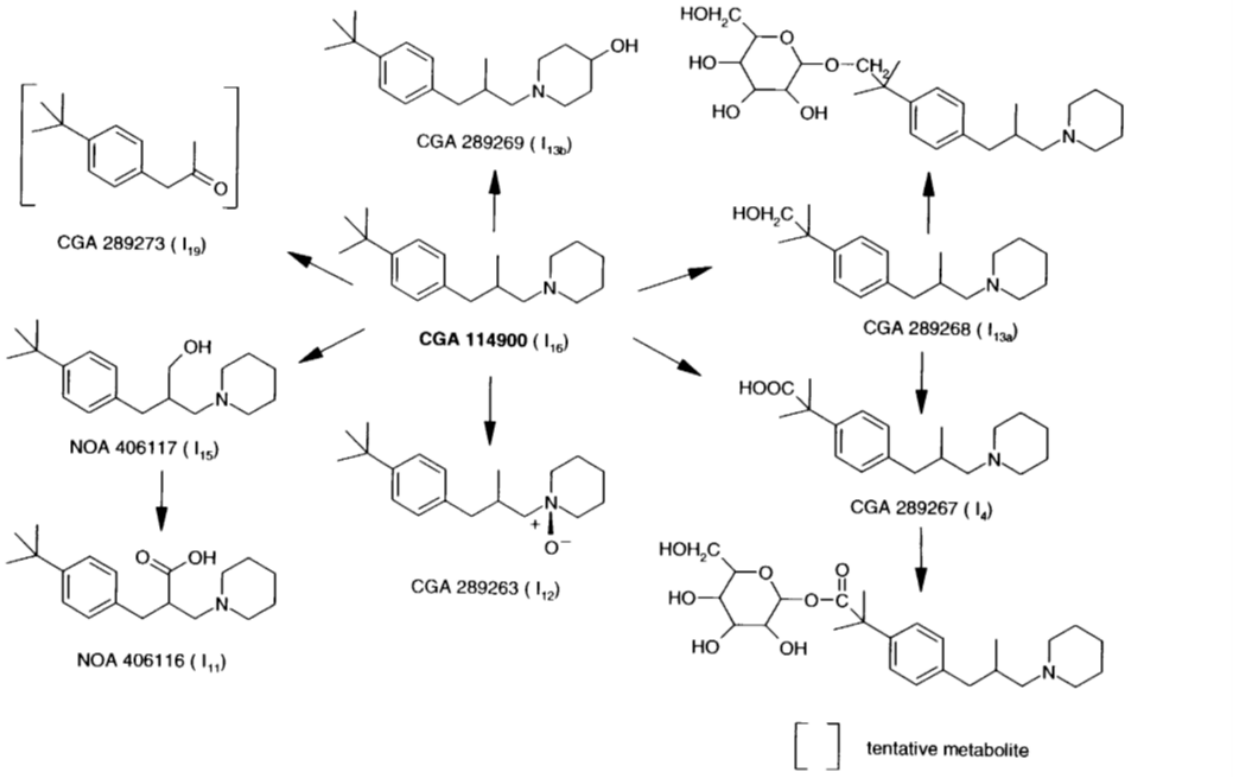
At maturity, total residues in juice and cake of grapes reached levels of 0.098 mg eq./kg and 1.580 mg eq./kg, respectively (corresponding to 0.355 mg eq./kg in grapes (whole fruit)). In mature grapes, parent fenpropidin was the largest component of the residue at 62.8% TRR in whole fruit. Fenpropidin was extensively metabolized in grapevines resulting in the formation of about 20 minor metabolites, all present in the juice and whole fruit were individually <0.01 mg/kg, with the exception of CGA 289263 that was calculated at 0.012 mg/kg fenpropidin equivalents in the whole fruit.

Based on the structures identified, the metabolism of fenpropidin in grapevines occurred primarily via:

- oxidation of the piperidine ring to form CGA 289263 and metabolite CGA 289269
- oxidation of the tertiary butyl side chain to form metabolite CGA 289268 and metabolite 289267. Both metabolites were also found and identified by GC/MS as glucose conjugates
- oxidation of the 2-methylpropyl chain to form metabolite NOA 406117 and NOA 406116
- tentative loss of the piperidine ring to form CGA 289273.

The proposed metabolic pathway of fenpropidin in grapevines is summarised in Figure 2.

Figure 2: Proposed metabolic pathway of fenpropidin in grapevines



Sugar beet

Two foliar applications of [N-2- methylpropyl-3-^{14}C] labelled fenpropidin, formulated as an emulsifiable concentrate (EC), were applied to field grown sugar beets at a rate equivalent to 375 g ai/ha. The first application occurred 69 days after sowing (at the beginning of crop cover, BBCH 31) and the second application was 30 days later. Three plants were collected randomly from the treated plot about one hour after each application and six plants 60 days after application two (60 DAA2). At maturity, 92 days after application two (92 DAA2), the whole plot of the remaining 60 plants was harvested. All plants were divided into tops and roots.

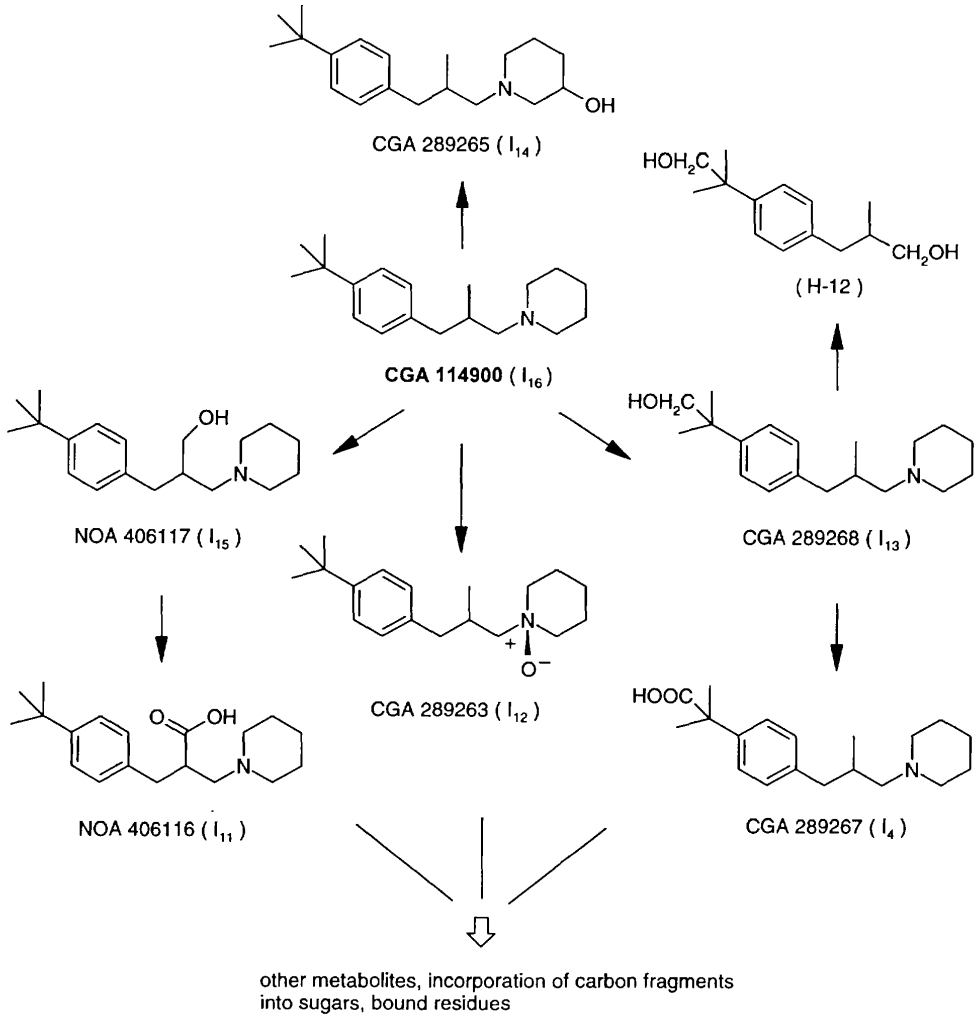
At maturity, total residues were 11.7 mg eq./kg at 0 DAA1 declining to 1.74 mg eq./kg in sugar beet tops and were 0.24 mg eq./kg at 0 DAA1 declining to 0.02 mg eq./kg in roots. In sugar beet tops, parent fenpropidin was the major component of the extracted residue at up to 85.8% TRR directly after application declining to 48.5% TRR in the mature tops. Numerous minor metabolites were identified in sugar beet tops with none individually above 2.9% TRR. Minor metabolites at levels greater than 0.01 mg eq./kg were CGA 289268 (2.9% TRR), CGA 289263 (2.8% TRR), CGA 289273 (1.2% TRR), NOA 406117 (0.8% TRR) and CGA 289267 (0.7% TRR) in mature tops. In sugar beet roots, parent fenpropidin accounted for 73.0% of the TRR in the roots at the first sampling but declined rapidly to only 2.3% of the TRR in the mature root. Numerous metabolites, including CGA 289263, CGA 289268, CGA 289267, NOA 406116 and CGA 289265 were observed but all were <5% TRR (<0.01 mg eq./kg).

Based on the structures identified, the metabolism of CGA 114900 in sugar beets occurred primarily via:

- oxidation of the piperidine ring to form CGA 289263 and CGA 289265
- oxidation of the tertiary butyl side chain to form CGA 289268 and CGA 289267
- oxidation of the 2-methylpropyl chain to form NOA 406117and NOA 406116
- loss of the piperidine ring to form H-12 (2-[4-(2-hydroxypropyl)-phenyl]-2-methylpropan-l-ol)
- incorporation of carbon from CGA 114900 and its metabolites into the molecules of sugar.

The proposed metabolic pathway of fenpropidin in sugar beets is summarised in Figure 3.

Figure 3: Proposed metabolic pathway of fenpropidin in sugar beets



Wheat

Two foliar applications of [N-2- methylpropyl-3-^{14}C] labelled fenpropidin or [2, 6-^{14}C-piperidine] labelled fenpropidin, formulated as an emulsifiable concentrate (EC), were applied indoor grown spring wheat at a rate equivalent to 500 g ai/ha. The first application occurred when the plants had five leaves with the flag leaf just visible (GS 37) and the second application twenty days later at anthesis of plants (GS 67). For the first sampling time 20 stalks were collected randomly from the treated plants one day after the second application. At maturity, 59 days after the second treatment (for the [N-2- methylpropyl-3-^{14}C] labelled fenpropidin experiment) and 71 days after the second treatment (for the [2, 6-^{14}C-piperidine] labelled fenpropidin experiment), all plants were harvested and separated in grains, husks, and straw.

For the [N-2- methylpropyl-3-^{14}C] labelled fenpropidin experiment total residues were 6.74 mg eq./kg in forage (shoots), at 1 DAA2 and 14.5, 9.64 and 0.19 mg eq./kg in straw, husks, and grain, respectively, at maturity. In wheat forage (shoots), wheat straw and wheat husks parent fenpropidin was the major component of the extracted residue at up to 73.7, 52.2 and 58.8% TRR, respectively. Two minor metabolites were identified: CGA 289263 and CGA 289268 in wheat forage (shoots), wheat straw, wheat husks (up to 7.2% TRR for CGA 289263 in wheat husks). Numerous unidentified metabolite fractions were observed at <5% TRR. In wheat grain, parent fenpropidin was the major component of the residue at up to 55.7% TRR with CGA 289263 the only one other metabolite or metabolite fraction observed at 2.4% TRR. Up to 38.5% TRR remained unextracted with a significant proportion (16.8% TRR) incorporated into the starch of the grains.

For the [2, 6-^{14}C-piperidine] labelled fenpropidin experiment the pattern was similar to the other radiolabeled experiment with total residues at 8.86 mg eq./kg in forage (shoots), at 1 DAA2 and 19.1, 10.9 and 0.20 mg eq./kg in straw, husks, and grain, respectively, at maturity. In wheat forage (shoots), wheat straw and wheat husks parent fenpropidin was the major component of the extracted residue at up to 79.2, 54.0 and 65.1% TRR, respectively. CGA 289263 and CGA 289268 were observed as minor metabolites (up to 6.9% TRR for CGA 289263 in wheat straw). Again, numerous unidentified metabolite fractions were observed at <5% TRR. In wheat grain, parent fenpropidin was the major component of the residue at up to 37.5% TRR with CGA 289263 the only one other metabolite or metabolite fraction observed at 2.0% TRR. Up to 50.6% TRR remained unextracted with a significant proportion (20.2% TRR) incorporated into the starch of the grains.

In summary, parent compound was the largest component of the residue in forage, straw, husks and grain. N-oxidation of the piperidine ring resulted in the formation of CGA 289263. Oxidation of the propyl group of the phenyl ring resulted in the formation of CGA 289268. The metabolite pattern was similar for both radiolabelled experiments.

Another metabolism study was conducted in summer wheat following a foliar application of [N-2-methyl-3-^{14}C] labelled fenpropidin.

A single foliar application of [N-2-methyl-3-^{14}C] labelled fenpropidin, formulated as an emulsifiable concentrate (EC), was applied to greenhouse grown summer wheat at BBCH 51 at a rate equivalent to 910 g ai/ha. At 23 days after application, green plants were collected and analysed. At 72 days after application (BBCH 71-75) straw, chaff and grain were harvested.

In green plants, 66.9% (5.82 mg/kg; fresh weight) of the radioactivity applied to the plants was recovered. An amount of 50% of the initially applied dose was identified as parent fenpropidin in the various fractions. This corresponds to a concentration of 4.35 mg/kg fenpropidin in green plants at 23 days after application. In straw, 55.2% (19.66 mg/kg) of the radioactivity applied to the plants was recovered. A total of 21.3% (7.59 mg/kg) of the initially applied radioactivity was identified as parent fenpropidin at 72 days after application. In chaff, 1.1% (2.35 mg/kg) of the radioactivity applied to the plants was recovered. A total of 0.44% of the initially applied radioactivity were present as parent fenpropidin. In grain, 0.038% of the radioactivity applied to the plants was recovered. A total of 0.005% of the applied dose was identified as parent fenpropidin and 0.001% as metabolites.

No metabolic pathways were presented in the spring or summer wheat metabolism studies.

Summary of plant metabolism

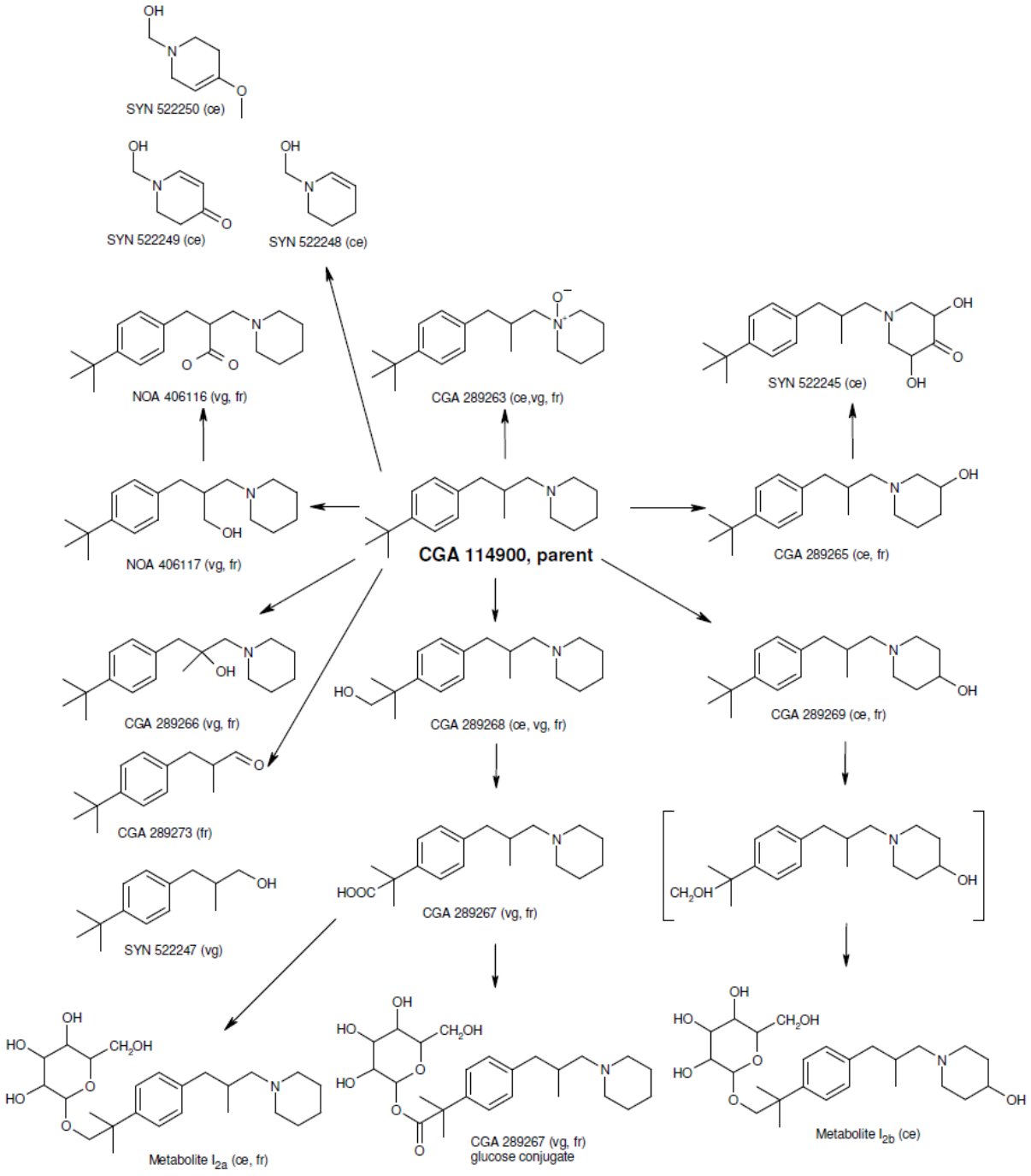
Metabolism was observed to be similar in all crop types investigated, namely bananas and grapes (fruits), sugar beets (root vegetables), and wheat (cereals). Parent fenpropidin was the major component of the radioactivity in all mature plant matrices at 77% TRR in banana pulp, 63% TRR in grape (whole fruit), 56% TRR in wheat grain, 59% TRR in wheat husk, 52% in wheat straw, 74% in wheat forage and 48% TRR in sugar beet tops but was observed to rapidly decline in sugar beet root at 2.3% in the mature root. Numerous minor metabolites were observed generally <10% TRR and <0.01 mg eq./kg except for CGA 289263 which was observed in banana pulp and whole grapes at 3.3-3.5% TRR (0.012 mg eq./kg in whole grapes and 0.17 mg eq./kg in banana pulp).

The primary metabolic process in all three crop types involved:

- oxidation of the piperidine ring to CGA 289263, CGA 289269, CGA 289265 and wheat metabolite I9
- oxidation of the tertiary-butyl side chain to CGA 289268 and CGA 289267
- oxidation of the 2-methylpropyl chain to CGA 289266, NOA 406117 and NOA 406116
- other primary metabolism processes included cleavage of the piperidine bond to form CGA 289273 and H-12
- glucose conjugation of the tertiary-butyl side chain metabolites was observed as a secondary metabolism process.

A proposed metabolic pathway of fenpropidin in plants is presented in Figure 4 (as extracted from the European Commission *Draft Assessment report (DAR) on fenpropidin*).

Figure 4: Proposed metabolic pathway of fenpropidin in plants



ce = cereals, vg = root vegetables, fr = fruit, [ ] = proposed intermediate

Target animals

Lactating goat

A lactating goat was administered 4 consecutive daily doses of [N-2-methylpropyl -3-^{14}C]-fenpropidin orally at a dose level of 121 ppm/day in the feed. The study determined that fenpropidin is extensively metabolized in the goat with most of the radioactivity rapidly excreted in urine (49.3%) and faeces (14.3%) or associated with bile and the gastrointestinal tract (17.2%) within 24 hours of the final dose. Only a small amount of the applied dose was observed in edible tissues (1.2%) and milk (<0.1%). Total radioactive residues were 7.649 mg eq./kg in liver, 4.373 mg eq./kg in kidney, 0.164 mg eq./kg in muscle, 0.042 mg eq./kg in fat and 0.196 mg eq./kg in milk. Total recovery accounted for 83.6% of the applied dose.

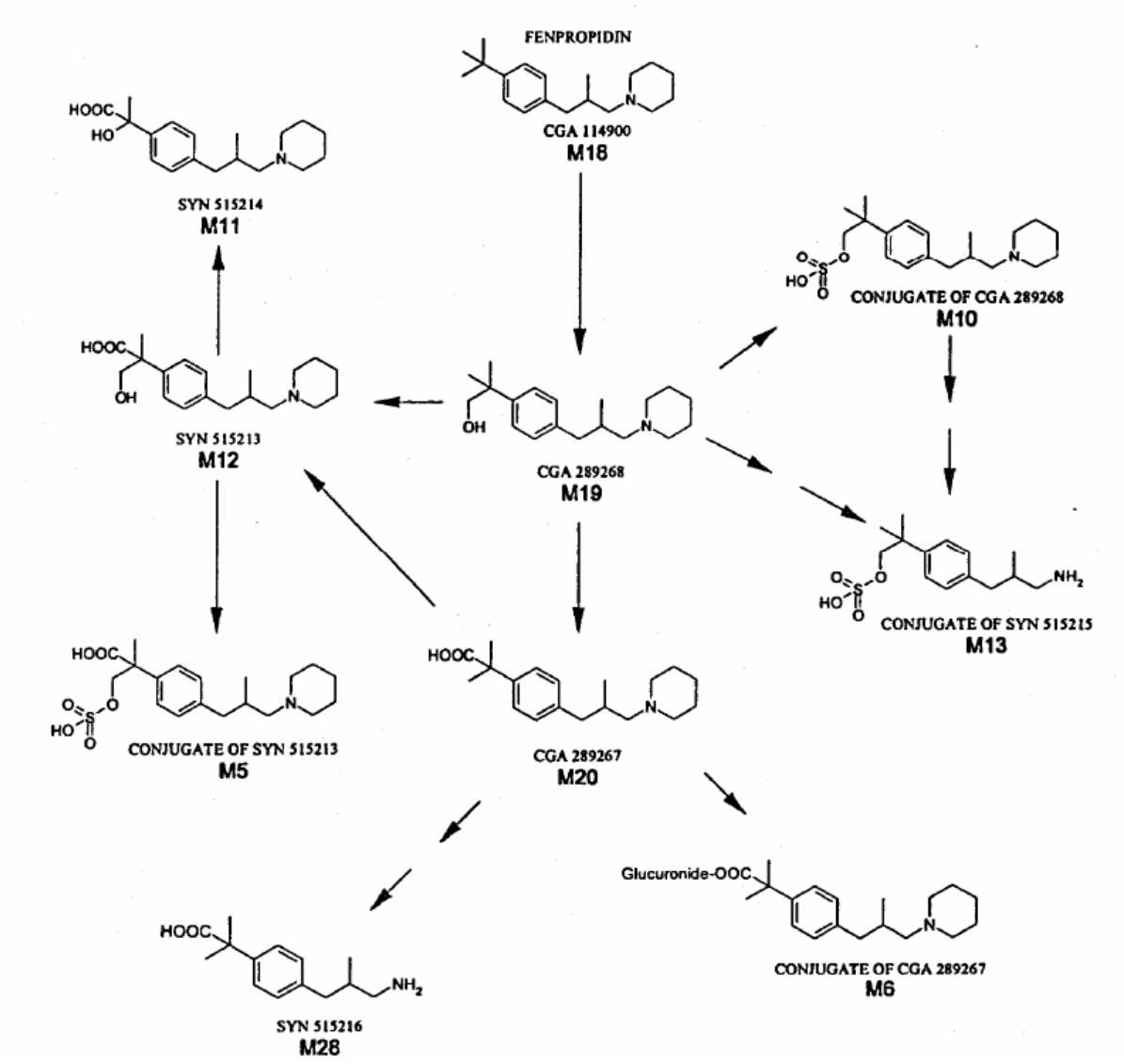
Parent fenpropidin was only detected in liver at 1.1% TRR and fat at 6.6% TRR. CGA 289267 was the major metabolite and was observed in all tissues and milk at 38.4, 15.2, 12.6, 8.4 and 23.5% TRR in muscle, fat, kidney, liver and milk, respectively. SYN 515213 was a significant metabolite at 30.0, 15.3, 16.3, 6.5 and 21.3% TRR in muscle, fat, kidney, liver and milk, respectively. The sulphate ester conjugate of SYN 515213 was also significant in all tissues at 10.7, 12.3, 13.0 and 12.6% TRR in muscle, fat, kidney and liver, respectively. The sulphate ester conjugate of CGA 289268 was observed at 13.3, 6.4 and 33.4% TRR in liver, kidney and milk, respectively but at low levels 2.7-3.3% TRR (0.001-0.004 mg eq./kg) in muscle and fat. The sulphate ester conjugate of SYN 515215 was observed at 5.2 and 12.7% TRR in kidney and liver, respectively but was not observed in muscle, fat and milk. All other metabolites were considered minor at <10% TRR (<0.01 mg eq./kg) in all tissues and milk.

The metabolism in the lactating goat proceeds via:

- oxidation of the tertiary-butyl group to CGA 289268
- further oxidation leading to the formation of metabolites CGA 289267, SYN 515213 and SYN 515214
- oxidation of the piperidine ring also occurs, leading to the formation of SYN 515215 and SYN 515216
- sulphate ester conjugation of SYN 515213, CGA 289268 and SYN 515215
- glucuronide conjugation of CGA 289268 are also major metabolic processes.

The proposed metabolic pathway of fenpropidin in the lactating goat is summarised in Figure 5.

Figure 5: Proposed metabolic pathway of fenpropidin in the lactating goat



Laying hen

Two metabolism studies involving [3-^{14}C-propylpiperidine] radiolabelled fenpropidin or [2,6-^{14}C-piperidine] radiolabelled fenpropidin were conducted. The laying hens received 4 consecutive daily doses orally at a nominal dose level of 10.3 ppm/day [3-^{14}C-propylpiperidine] fenpropidin in the feed or 4 consecutive daily oral doses of at a nominal dose level of 11.6 ppm/day [2,6-^{14}C-piperidine] fenpropidin in the feed.

In both studies, most of the radioactivity was rapidly excreted with 88.0-91.8% found in excreta, a further 0.06-0.08% found in cage wash, and up to 2.8%, 0.10% and 0.14% was found in gizzard, blood and eggs, respectively. Only low levels of the administered radioactivity were recovered in muscle, liver, kidney, skin + fat and peritoneal fat at up to 0.50, 0.42, 0.14, 0.10 and 0.03%, respectively. The highest total residue levels were found in kidney at up to 0.62 mg eq./kg and liver up to 0.52 mg eq./kg. Levels in the other edible tissues were lower at up to 0.073 mg eq./kg in muscle, 0.047 mg eq./kg in skin plus attached fat, 0.030 mg eq./kg in peritoneal fat and 0.043 mg eq./kg in whole eggs.

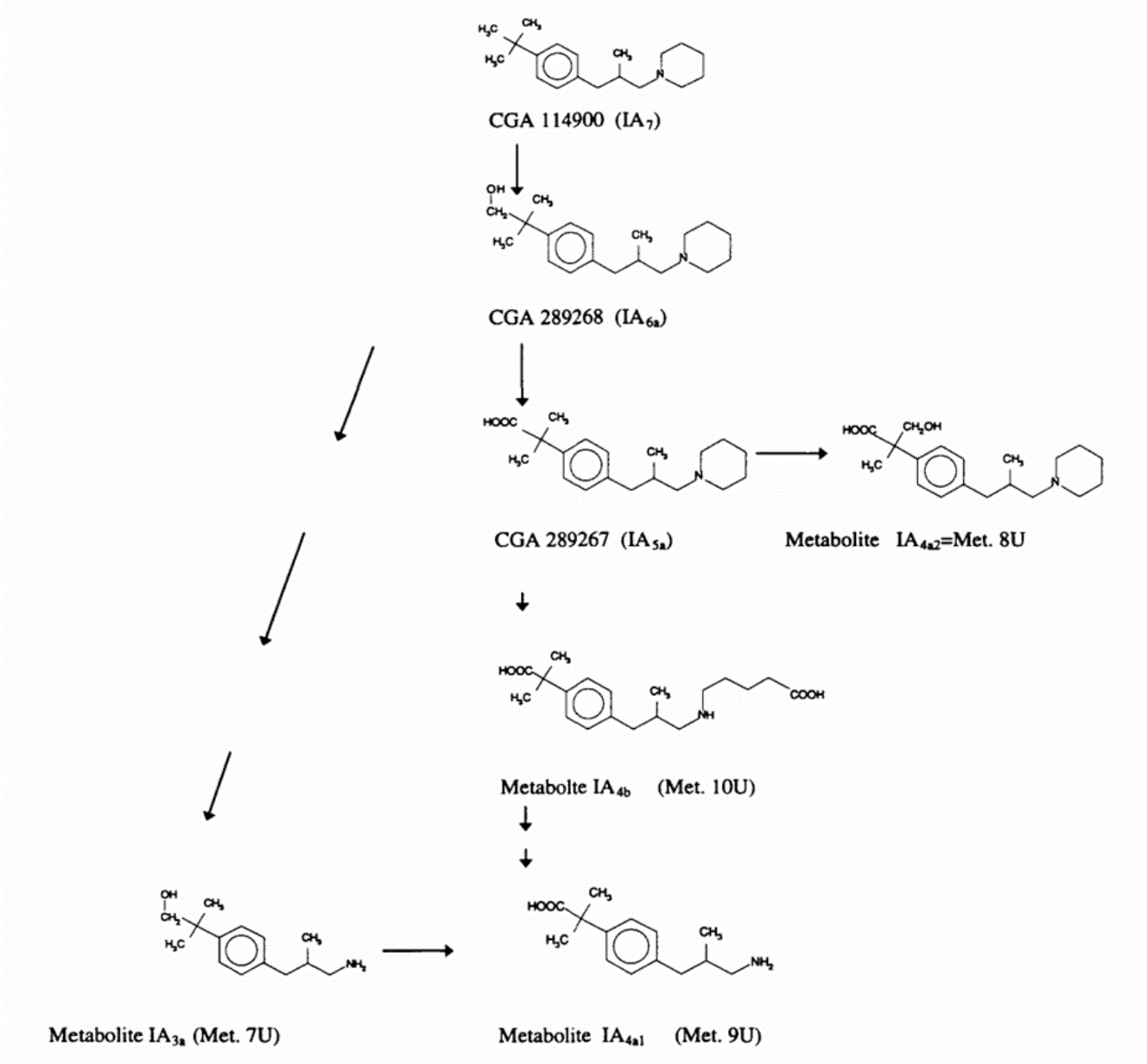
For both radiolabelled experiments, parent fenpropidin was detected in eggs and all tissues. The highest levels of fenpropidin occurred in the liver at up to 9.8% TRR with the remaining tissues and eggs containing <10% TRR (<0.01 mg/kg). The major metabolite in all samples analysed was CGA 289267. The amount of CGA 289267 was up to 91.7, 52.9, 86.6, 59.7 and 46.5% TRR in lean meat, whole fat+ skin, white egg, egg yolk and liver, respectively. Metabolite IA_{5b} was also significant at 22.9% TRR in liver in the [3-^{14}C-propylpiperidine] radiolabelled experiment, but <5% TRR in other tissues and eggs. Other metabolites, including CGA 289268 were <10% TRR (up to 0.014 mg/kg in liver).

The proposed metabolic pathway from the [3-^{14}C-propylpiperidine]-fenpropidin experiment involves:

- oxidation of the tertiary-butyl moiety to CGA 289268
- further oxidation to CGA 289267, which is by far the dominating metabolite (36-92% of the tissue residues)
- stepwise oxidations and cleavage of the piperidine ring yields metabolites IA_{4b}, IA_{3a} and IA_{4a1}
- conjugation of metabolite IA_{4a1} led to a presumably fatty acid conjugate or IA_{5b} also found in the rat experiment as metabolite 6U.

The proposed metabolic pathway from the [3-^{14}C-propylpiperidine]-fenpropidin experiment in the laying hen is summarised in Figure 6.

Figure 6: Proposed metabolic pathway from the [3-^{14}C-propylpiperidine]-fenpropidin experiment in the laying hen

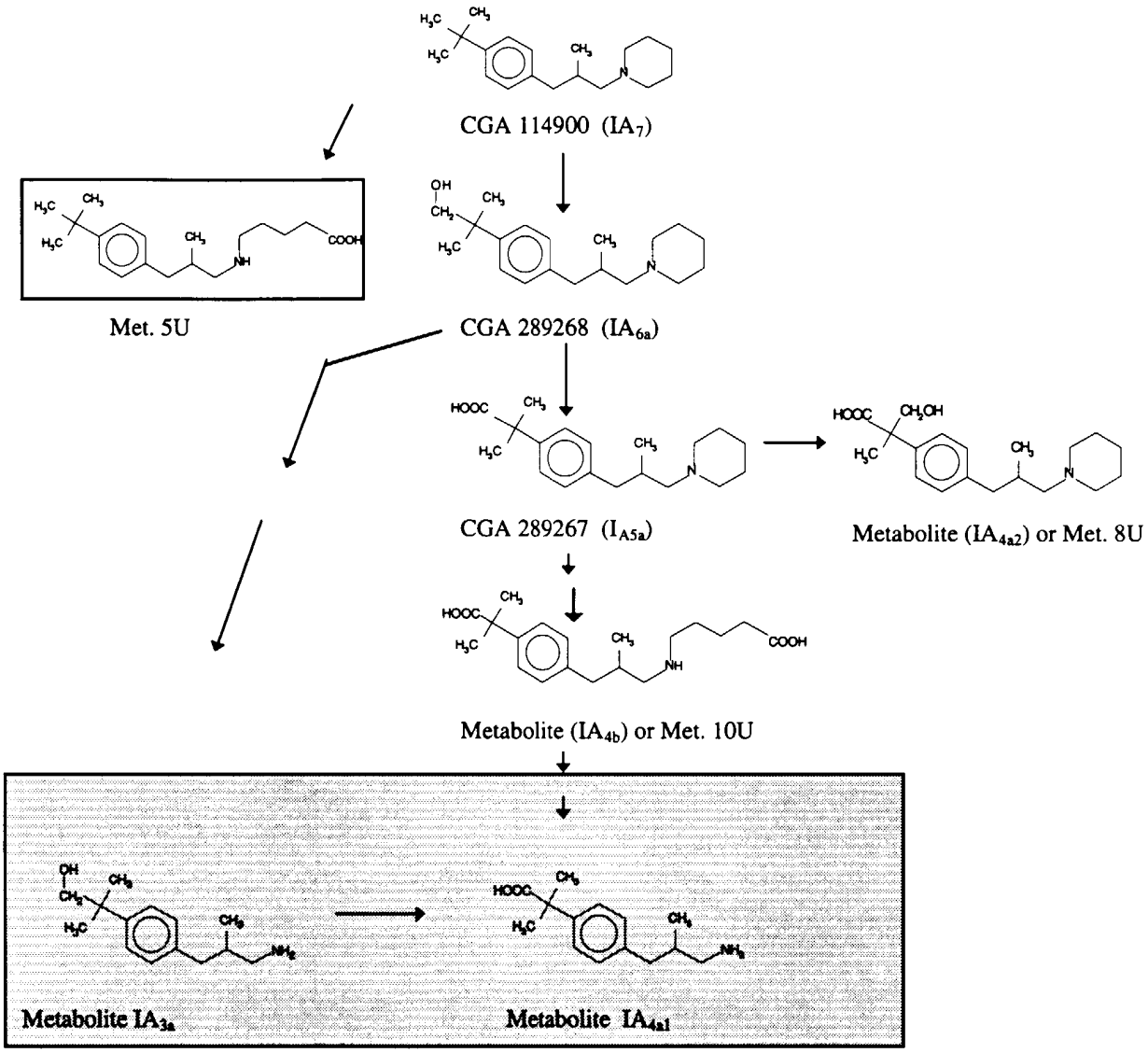


The proposed metabolic pathway of [2,6-^{14}C-piperidine]-fenpropidin was similar to the other radiolabelled experiment and involves:

- oxidation of the tertiary-butyl moiety to CGA 289268
- further oxidation leads to CGA 289267 (47-87% of the tissue residues)
- oxidation of CGA 289267 to metabolite IA_{4a2}
- stepwise oxidation of the piperidine ring and cleavage of the piperidine ring yield metabolite IA_{4b}.

The proposed metabolic pathway from the [2,6-^{14}C-piperidine]-fenpropidin experiment in the laying hen is summarised in Figure 7.

Figure 7: Proposed metabolic pathway from the [2,6-^{14}C-piperidine]-fenpropidin experiment in the laying hen



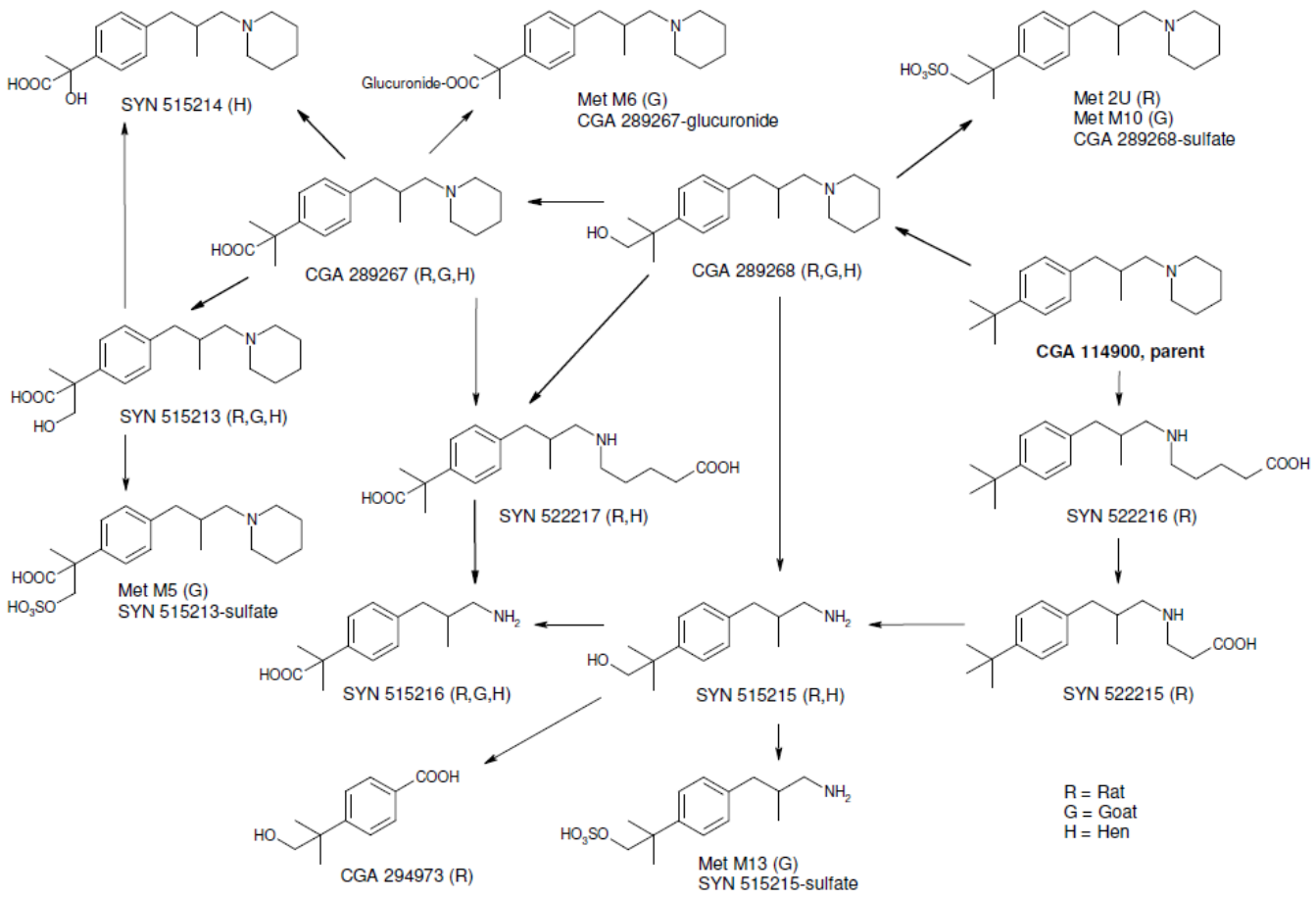
Summary of animal metabolism

The metabolism in the lactating goat, laying hen and rat was observed to be similar. Fenpropidin was rapidly and extensively metabolized, with most of the administered radioactivity excreted in the urine and faeces (88% to 92% in the hen and 64% to 94% in the goat).

Parent fenpropidin was only detected at significant levels (>0.01 mg/kg) in goat and hen liver and goat kidney. CGA 289267 was the major metabolite and was observed in all tissues, milk and eggs at 8% to 38 TRR in the goat and 36% to 92% TRR in the hen. In the goat, SYN 515213 and its sulphate ester conjugate were also significant metabolites in all tissues and milk at between 7% to 30% TRR. The sulphate ester conjugate of CGA 289268 was also observed in goat liver, kidney and milk between 6% to 33% TRR. Free CGA 289268 was observed at <10% TRR in most tissues, eggs and milk but was observed in hen liver at >0.01 mg eq./kg (up to 0.014 mg eq./kg). Metabolite IA_{5b} was also significant at 22.9% TRR in hen liver in the [3-^{14}C-propylpiperidine] radiolabelled experiment, but <5% TRR in other tissues and eggs.

A proposed metabolic pathway of fenpropidin in the lactating goat, laying hen and rat is presented in Figure 8 (as extracted from the European Commission *Draft Assessment report (DAR) on fenpropidin*).

Figure 8: Proposed metabolic pathway of fenpropidin in the lactating goat, laying hen and rat



Analytical methods and storage stability

For plant commodities, an analytical method, *REM 164.09 Residue Method for the Determination of Residues of Fenpropidin (CGA114900) in Crop Samples. Final Determination by LC-MS/MS,* for the determination of residues of fenpropidin in crop samples using an external standardisation procedure has been provided along with its validation study. The method was successfully validated in apple (whole fruit), grape (whole fruit), oilseed rape (seed), sugar beet (root) and wheat (grain and straw) with LOQs at 0.01 mg/kg for fenpropidin in all crops.

In the Australian grape trials, samples were analysed in accordance with AWRI methods GM119 (for grapes, juice, pomace and leaves) and GM121 (for wine). Summary validation data was provided within the report demonstrating that the QuEChERS multi residue methods were suitably valid for the grape matrices. The LOQs for the method were 0.005 mg/kg in grapes (whole fruit), wine and juice and 0.10 mg/kg for pomace.

Storage stability studies for grapes (fruit) and wine were provided demonstrating that fenpropidin remains stable for at least 24 months when stored frozen at –18°C. In the supervised residue trials, all samples were stored frozen prior to analysis with the maximum storage duration from the supervised residues trial samples approximately 12 months.

For animal commodities, an analytical method, *REM 164.10 Residue method for the determination of residues of fenpropidin (CGA114900) and its metabolites CGA289267 and CGA289268 in animal tissue samples. Final determination by LCMS/MS,* for the determination of residues of fenpropidin and its metabolites CGA 289267 and CGA 289268, in bovine muscle, liver, kidney, fat, milk and hen eggs using an external standardisation procedure has been provided along with its validation study. The method was successfully validated for fenpropidin, CGA 289267 and CGA 289268 in all representative matrices and LOQs established at 0.01 mg/kg for bovine muscle, liver, kidney, fat & hen eggs and for bovine milk 0.005 mg/kg.

In the feeding studies provided, animal commodities (Bovine milk and tissue samples) were analysed for fenpropidin, CGA 289267 and CGA 289268 in accordance with the verified methods REM 164.02 (for fenpropidin), REM 164.05 (for CGA 289267) and REM 164.06 (for CGA 289268), which are previous iterations of REM 164.10.

Storage stability for fenpropidin, CGA 289267 and CGA 289268 were shown to be stable in all matrices when stored frozen at -20°C for 2, 24 and 30 months, respectively, in-line with the study samples.

Residue definition

For plants, based on parent fenpropidin being the major component of the radioactivity identified in all plant matrices accounting for 44% to 77% TRR (except sugar beet root where many metabolites were observed all at <10% TRR) and the capability of the analytical methods (which was analysed for parent fenpropidin only), the residue definition for enforcement and risk assessment is recommended to be fenpropidin.

For animals, based on the significant metabolites identified from the available animal metabolism data at >10% TRR in muscle, fat, liver, kidney, milk or hen eggs, the results of the animal transfer study which found CGA 289267 followed by parent to have the highest residues, the capability of the analytical methods and

toxicological advice on predominant residues of toxicological significance (see Toxicology assessment), the residue definition for enforcement purposes is recommended to be the sum of fenpropidin and CGA 289267, expressed as fenpropidin and for risk assessment is recommended to be sum of fenpropidin, CGA 289267, SYN 515213, CGA 289268 and their conjugates, expressed as fenpropidin.

It is noted that the analytical method for animal commodities does not include analysis of SYN 515213 and its conjugates or conjugates of CGA 289267 or CGA 289268. In accordance the OECD Guidance document D*efinition of Residue - Series on Pesticides, No. 31; Series on Testing and Assessment, No. 63; revision, published 28 July 2009*[1] *ENV/JM/MONO(2009)30*, the principles for derivation and application of M:M_R ratios from the goat metabolism study (the ratio of the metabolite of interest (M) to another main component/representative metabolite (M_R)) will be employed for dietary exposure estimations of these metabolites in animal commodities.

Also, for metabolite IA_{5b}, observed at significant levels (22.9% TRR in the [3-^{14}C-propylpiperidine] radiolabelled experiment) in hen liver only, the expected poultry burden from the proposed use on grapes is not significant and therefore this metabolite is not expected in poultry livers as a result of the proposed use. However, if the poultry burden increases in the future, further consideration of this metabolite may be necessary.

Residues in food and animal feeds

Difenoconazole and fenpropidin residue trials on grapes were provided from Australia, Europe and South Africa. The treatment regime used differed between trials. The 6 Australian trials addressed the proposed critical GAP (Good Agricultural Practice) i.e. a single foliar application applied at 80% capfall (E-L 25, BBCH 68), as a concentrated spray at a concentration of 45 g fenpropidin/100 L + 12 g difenoconazole/100 L; however, the international trials involved 3 to 5 foliar applications generally at higher concentrations and later application timings and are therefore considered as supportive only.

Difenoconazole

Residues of difenoconazole were below the LOQ (n=6) in all matrices (grapes (whole fruit), wine, juice and pomace) following treatment at the proposed critical GAP. It is concluded that the existing difenoconazole MRLs for Grapes at 2 mg/kg and Grape pomace, dry at 10 mg/kg will cover the expected residues for the proposed use.

Fenpropidin

Following a single foliar application at pre-flowering (E-L 18, BBCH 60), at the proposed dilute spraying concentration or as a concentrated spray (3× concentration), no detectable residues of fenpropidin were observed in grapes (whole fruit), juice or wine.

[1] OECD Publications on pesticide residues

Following a single foliar application at 80% capfall (E-L 25, BBCH 68), as a concentrated spray (1× proposed critical GAP), residues of fenpropidin were 0.006, 0.008, 0.010, 0.011 (2) and 0.012 mg/kg (n=6) in grapes (whole fruit). A fenpropidin MRL for FB 1236 Wine-grapes at 0.03 mg/kg is recommended to cover the expected residues in the Raw Agricultural Commodity (RAC).

Residues of fenpropidin were not observed to concentrate in juice or wine. At the critical GAP, low level finite residues of fenpropidin were observed in juice at <0.003 (4), <0.005 and 0.006 mg/kg (n=6, Supervised Trials Median Residue (STMR) = <0.003 mg/kg), and in wine at <0.003 (2), <0.005, 0.006 and 0.007 (2) mg/kg (n=6, STMR = 0.006 mg/kg). It is concluded that the potential residues in wine will be covered by the MRL established in the RAC.

Residues of fenpropidin were observed to concentrate on grape pomace. At the critical GAP, measured residues of fenpropidin were <0.005, 0.056, 0.065, 0.099, 0.128 and 0.142 mg/kg in dry pomace (n=6, STMR = 0.083 mg/kg). Based on the HR in grapes from the proposed use at 0.012 mg/kg and the highest processing factor of 18×, the HR-P for dry pomace is 0.216 mg/kg. A fenpropidin MRL for AB 0269 Grape pomace, dry at 0.3 mg/kg is recommended to cover the expected residues in dry pomace. The Supervised Trials Median Residues – Processed (STMR-P) for Grape pomace, dry is 0.011 × 7.44 = 0.082 mg/kg.

Crop rotation

No rotational crop studies (confined or field) were provided. This is acceptable for the current application noting that grapes are not considered a rotational crop. Should future uses be proposed on commodities which are grown in rotation, rotational crop studies will be necessary.

Residues in animal commodities

The OECD calculator indicates grape pomace is considered a significant animal feed in beef and dairy cattle. Grape pomace can constitute up to 20% of the diet. In vineyard situations, animals may also graze inter-rows and forage on grape vine leaves.

Difenoconazole

The livestock dietary burden of difenoconazole is not expected to increase as a result of the proposed use, therefore animal commodity MRLs remain appropriate.

Fenpropidin

The livestock dietary burden of fenpropidin is calculated to be 0.05 ppm based on the fenpropidin STMR-P in grape pomace, dry at 0.082 mg/kg and the expected residues in interrow forage at 0.01 mg/kg and 0.005 mg/kg in grape leaves at the proposed grazing WHP of 12 weeks.

Based on the animal transfer studies, residues of fenpropidin + CGA 289267 (expressed as fenpropidin) would be expected at <0.01 mg eq./kg in milk, <0.02 mg eq./kg in meat, fat, liver and kidney. Fenpropidin animal commodity MRLs are recommended at *0.01 for ML 0106 Milks, *0.02 for MM 0095 Meat

(mammalian) and *0.02 for MO Edible offal (mammalian) in conjunction with the proposed grazing withholding period of 12 weeks.

No poultry feeding study was provided and is not considered necessary for the proposed use on grapes noting that grapes and grape pomace are not a significant poultry feed. Hence, the expected poultry burden from the proposed use on grapes is not significant. Fenpropidin poultry commodity MRLs are recommended for PE 0112 Eggs, PM 0110 Poultry meat and PO 0111 Poultry, edible offal of at *0.02 mg/kg.

Dietary risk assessment

The chronic dietary exposures to difenoconazole and fenpropidin are estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived primarily from the 2011–12 National Nutritional and Physical Activity Survey. The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for difenoconazole is equivalent to <95% of the ADI. The NEDI for fenpropidin is equivalent to <1% of the ADI. It is concluded that the chronic dietary exposures to difenoconazole and fenpropidin are acceptable.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived primarily from the 2011–12 National Nutritional and Physical Activity Survey. NESTI calculations are conservative estimates of short-term exposure (24-hour period) to chemical residues in food. The highest acute dietary intake of difenoconazole was estimated at <1% of the JMPR ARfD. The highest acute dietary intake of fenpropidin was estimated at <1% of the recommended ARfD. It is concluded that the acute dietary exposure of difenoconazole and fenpropidin is acceptable.

Recommendations

The following amendments in Table 6 are required to be made to the APVMA MRL Standard (Table 5).

Table 6: Amendments to the APVMA MRL Standard

Amendments to Table 1			
Compound		**Food**	**MRL (mg/kg)**
Add:			
Fenpropidin			
MO	0105	Edible offal (mammalian)	*0.02
PE	0112	Eggs	*0.02
MM	0095	Meat (mammalian)	*0.02
ML	0106	Milks	*0.01

Amendments to Table 1			
Compound		**Food**	**MRL (mg/kg)**
PM	0110	Poultry meat	*0.02
PO	0111	Poultry, edible offal of	*0.02
FB	1236	Wine-grapes	0.03

Amendments to Table 3	
Compound	**Residue**
Add:	
Fenpropidin	Commodities of plant origin: Fenpropidin Commodities of animal origin for enforcement: Sum of fenpropidin and 2-methyl-2- [4-(2-methyl-3- piperidin-1-ylpropyl)-phenyl]-propanoic acid (CGA 289267), expressed as fenpropidin Commodities of animal origin for dietary risk assessment: Sum of fenpropidin, 2-methyl-2- [4-(2-methyl-3- piperidin-1-ylpropyl)-phenyl]-propanoic acid (CGA 289267), 3-Hydroxy-2-methyl-2-[4-(2-methyl-3-piperidin-1-ylpropyl)-phenyl]-propionic acid (SYN 515213), 2-methyl-2- [4-(2-methyl-3- piperidin-1-ylpropyl)-phenyl]-propan-1-ol (CGA 289268) and their conjugates, expressed as fenpropidin

Amendments to Table 4			
Compound		**Animal feed commodity**	**MRL (mg/kg)**
Add:			
Fenpropidin			
AB	0269	Grape pomace, dry	0.3

Assessment of overseas trade aspects of residues in food

Grapes and wine are considered to be major export commodities[2], as are commodities of animal origin, such as meat, offal and dairy products, which may be derived from livestock fed grape pomace produced from treated fruit or grazed in treated vineyards. Residues in these commodities resulting from the use of SEEKER Duo Fungicide may have the potential to unduly prejudice trade.

The applicant has proposed the following risk mitigation statement which is considered appropriate and acceptable:

EXPORT OF TREATED PRODUCE

Growers should not that appropriate MRLs or import tolerances may not be established in all markets for fruit harvested from SEEKER™ Duo treated grapes. If you are growing grapes for export, please check with the Australian Wine Research Institute (in regard to wine) or Syngenta Australia for the latest information on MRLs and import tolerances before using SEEKER™ Duo Fungicide.

Commodities exported and main destinations

Australian exports of wine totalled 744 ML and 707 ML ($2,900 million and $2,619 million) in 2019–20 and 2020–21 respectively. The major export markets for wine in the year ending June 2021 included China, United Kingdom, United States, Hong Kong, Canada, Singapore, New Zealand, Netherlands, Japan and Denmark[3].

Overseas registrations and approved label instructions

The applicant indicated that fenpropidin products are registered for use worldwide (including in grapes in Switzerland) for foliar use in broadacre and horticultural crops for control of powdery mildews, rusts, and leaf spots.

Comparison of Australian MRLs with Codex and international MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. 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. Fenpropidin has not been considered by Codex. The following relevant international MRLs have been established for fenpropidin (Table 7).

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

[3] Australian Government Department of Agriculture, Fisheries and Forestry, ABARES, *Agricultural commodities and trade data*, cited 8 March 2023.

Table 7: Proposed Australian and current international MRLs for fenpropidin

Country	Residue definition	Commodity	MRL (mg/kg)
Australia (proposed)	Commodities of plant origin: Fenpropidin. Commodities of animal origin for enforcement: Sum of fenpropidin and 2-methyl-2- [4-(2-methyl-3- piperidin-1-ylpropyl)-phenyl]-propanoic acid (CGA 289267), expressed as fenpropidin.	Edible offal (mammalian)	*0.02
		Eggs	*0.02
		Meat (mammalian)	*0.02
		Milks	*0.01
		Poultry meat	*0.02
		Poultry, edible offal of	*0.02
		Wine-grapes	0.03
Codex	–	–	–
European Union[4]	Commodities of plant origin: Sum of fenpropidin and its salts, expressed as fenpropidin. Commodities of animal origin: Sum of fenpropidin, CGA 289267, and their salts, expressed as fenpropidin.	Edible offal (mammalian)	0.2 (liver)
			0.05 (kidney)
		Eggs	0.02*
		Meat (mammalian)	0.02* (muscle)
			0.02* (fat)
		Milks	0.02
		Poultry meat	0.02* (muscle)
			0.02* (fat)
		Poultry, edible offal of	0.02* (liver)
			0.02* (kidney)
		Wine-grapes	0.01*
United States of America[5] #	Tolerances are established for the residues of fenpropidin, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only fenpropidin (1-[3-[4-(1,1-dimethylethyl)phenyl]-2-methylpropyl]piperidine).	–	–

There are no U.S. registrations as of 13 December 2013. The residue definition is established due to an import tolerance established for banana.

[4] European Commission, Pesticide residue(s) and maximum residue levels (mg/kg), cited 8 March 2023.

[5] United States of America, Code of Federal Regulations, *Part 180 – Tolerances and exemptions for pesticide chemical residues in food*, cited 8 March 2023.

Potential risk to trade

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

As shown in Table 7, international MRL coverage for wine-grapes is limited to the European Union (EU) only and the fenpropidin MRL for Wine grapes is established at the LOQ (<0.01 mg/kg).

When a single foliar application, applied pre-flowering (E-L 18, BBCH 60), residues of fenpropidin are expected at <0.003 mg/kg (LOD) (n=6) in grapes (whole fruit) and wine.

When a single foliar application applied at 80% capfall (E-L 25, BBCH 68), at the proposed critical GAP, low level finite residues of fenpropidin may occur in wine (High Residue (HR) = 0.007 mg/kg, STMR = 0.006 mg/kg, LOQ = 0.005 mg/kg).

Comment is sought from industry on the potential for industry to manage this potential trade risk associated with the proposed establishment of a finite fenpropidin MRL for Wine grapes and the potential for low level residues in wine.

Work health and safety assessment

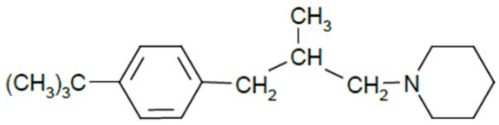
Occupational risk assessment is based on both acute exposure to the product formulation and repeat exposure to the active constituents. Workers may be exposed repeatedly to the product through the dermal and/or inhalation routes during mixing, loading and application (M/L/A) and dermal exposure during post-application activities. Minor or accidental ocular exposure may also occur.

Health hazards

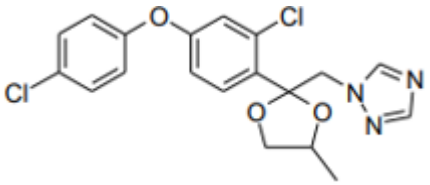
SEEKER Duo Fungicide has low acute toxicity by the oral and dermal routes, moderate to severe skin irritation potential, severe eye irritation potential, is a respiratory irritant and a skin sensitiser in Guinea pig (GPMT). SEEKER Duo acute toxicity by the inhalation route was estimated to be low to moderate; due to its designated solvent content, the formulated product is considered an aspiration hazard.

SEEKER Duo Fungicide contains 2 active constituents which, in Australia, form a novel combination. Therefore, the possibility that these active constituents enhance each other's toxicity was considered.

Fenpropidin



Difenoconazole



Fenpropidin and difenoconazole have markedly different chemical structures; although their pesticidal action is based on the disruption of ergosterol synthesis, their pesticidal molecular targets are different. Difenoconazole is a demethylation inhibitor (fungicides FRAC group 3), while fenpropidin inhibits the Δ^{14}-reductase and $\Delta^{8}\rightarrow\Delta^{7}$ isomerase in sterol biosynthesis (fungicides FRAC group 5). The acute toxicity of the product is largely predictable, based on the toxicity profile of its constituents. Although acute toxicity studies have limited sensitivity to assess potential toxicity enhancements that may result from a combination of chemicals, taking these results together with above considerations indicates that considerable toxicity enhancement (e.g., through synergism or potentiation) is unlikely to result from the combination of fenpropidin and difenoconazole in SEEKER Duo Fungicide. Furthermore, in laboratory animals repeat dose studies, fenpropidin and difenoconazole main targets are different. Liver toxicity, which was essentially negligible in most fenpropidin studies, was generally the most significant finding in difenoconazole studies. On the other hand, irritation/inflammation was the most prominent effect of fenpropidin, while difenoconazole potential for irritation was limited. Therefore, it appears unlikely that fenpropidin and difenoconazole present in SEEKER Duo Fungicide may enhance each other's effects on these endpoints.

Conversely, eye lens cataract was observed following repeat dose studies with fenpropidin and/or difenoconazole, and these effects may be related to both fungicides' general mode of action, i.e. disruption of sterols metabolism. Therefore, toxicity enhancement that may result from the combination of fenpropidin and difenoconazole in SEEKER Duo Fungicide cannot be excluded for this endpoint. Nevertheless, based on the different chemical structures and fungal molecular targets of fenpropidin and difenoconazole, it is

likely that their mammalian molecular targets relevant to the development of cataract are also different. On this basis, APVMA consider plausible that some toxicological effects, especially eye lens cataract, resulting from repeated exposure to the active constituents fenpropidin and difenoconazole in SEEKER Duo Fungicide may be 'additive' in nature. However, as cataractous effects were only seen following repeat exposure to fenpropidin and/or difenoconazole in high doses, the human health risk assessment is based on other, more sensitive endpoints.

Occupational exposure

SEEKER Duo Fungicide, containing 375 g/L fenpropidin and 100 g/L difenoconazole in an emulsifiable concentrate (EC) formulation, is intended for the control of powdery mildew (*Erysiphe necator*) in wine grapes. SEEKER Duo Fungicide will primarily be applied by professionals using airblast spray equipment, although mechanically pressured handgun/wand and backpack spraying equipment may also be employed. Based on the product use instructions, the pattern of exposure was considered to be of short-term duration.

Selection of parameters for occupational health risk assessment.

The APVMA considered unlikely that fenpropidin and difenoconazole present in SEEKER Duo Fungicide may enhance each other's effects on the endpoints selected for systemic and/or local exposure risk assessment. Therefore, health risks resulting from exposure to each active constituent were evaluated separately. Furthermore, assuming the same level of concern for both ingredients, fenpropidin was considered to drive repeat exposure effects (i.e., conditions resulting in acceptable risks from fenpropidin repeat exposure also result in acceptable risks from difenoconazole repeat exposure) and the corresponding risk assessment is only presented for fenpropidin.

Considering fenpropidin potential for irritation/inflammation, points of departure (PODs) for fenpropidin occupational health risk assessment were selected for local and systemic effects as follows.

- The LOAEL of 0.02 mg/kg bw/d resulting from a 23-day rabbit repeat dermal exposure study was selected for local skin effects.
- The Lowest Observed Adverse Effect Concentration (LOAEC) of 20 mg/m^3 resulting from a 28-day rat repeat inhalational study was selected for local respiratory tract effects.
- The No Observed Adverse Effect Concentration (NOAEC) of 20 mg/m^3 resulting from a 28-day rat repeat inhalational study was selected for systemic effects resulting from inhalational exposure.
- The NOAEL of 5 mg/kg bw/d resulting from a 28-day dog repeat oral exposure (capsule) study was selected for systemic effects resulting from dermal and/or inhalational exposure.

Above PODs are relevant for the human health risk assessment and collectively, they are protective of all potential effects in humans.

When route-to-route extrapolation was conducted (i.e. to assess the risks of systemic effects from dermal and/or inhalational exposure based on an oral POD), dermal absorption values of 1% and 10% were used for fenpropidin during SEEKER Duo Fungicide mixing/loading and application, respectively, while a default inhalation absorption value of 100% was used for M/L/A.

Exposure during use

The US EPA Occupational Pesticide Handler Exposure Calculator (OPHEC) was used to estimate workers exposure during M/L/A (US EPA 2021a). Margins of Exposure (MOEs) were calculated by dividing PODs by the corresponding exposure estimates.

For local skin effects, APVMA concluded that the rabbit LOAEL constitutes an acceptable NOAEL for occupational health risk assessment, based on the excessively stringent conditions of the study (daily exposure of 6 hours under occlusive dressing, test sites left unwashed after undressing) which do not match occupational exposure scenarios, and the mildness of skin effects with no cumulative skin irritation observed at this dose in rabbits. Based on similar sensitivity between rabbit and human for local skin irritation effects (Ishii et al 2013), an interspecies uncertainty factor of 1 was considered acceptable, in agreement with ECETOC (2003). Based on statistical analyses of dose response curves obtained across human populations including both sexes, a variety of disease states and ages, an intraspecies uncertainty factor of 5 for local effects was considered protective of 95% of the population (ECETOC 2003). In conclusion, APVMA considers an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 5 (total uncertainty factor of 1 x 5) to be acceptable regarding local effects in the skin, in agreement with ECETOC (2003) recommendations. MOEs ≥ 5 were considered acceptable for this endpoint.

For the three other endpoints selected, MOEs ≥ 100 were considered acceptable. This value is based on a 10-fold uncertainty factor (UF) for intra-species and 10-fold UF for inter-species differences in susceptibility to effects.

Acceptable MOEs were found with all endpoints selected for users complying with the recommended safety directions while handling SEEKER Duo Fungicide according to the proposed directions for use.

Exposure during re-entry

Dermal exposure of workers undertaking activities associated with wine grapes maintenance in vineyards treated with SEEKER Duo Fungicide was estimated using the US EPA Occupational Pesticide Re-entry Exposure Calculator (US EPA 2021b), and MOEs were calculated as detailed above. Acceptable MOEs were found with the endpoints selected for workers conducting all post-application activities once spray has dried, with no requirement to wear specific protective equipment.

Public health risk assessment

Bystander risk from spray drift

Application of SEEKER Duo Fungicide by airblast may lead to unintended bystander exposure via chemical spray drift. This may be in the form of a single random exposure or repeat exposure of residents who reside adjacent to areas being treated with the product. Risks from spraying activities were estimated, based on potential risks to toddlers (considered the most sensitive sub population), using the APVMA Spray Drift Risk Assessment Tool (SDRAT).

Assessment was conducted against the POD selected for local skin effects, as detailed above. Resulting RALs (regulatory acceptable levels) were 3.54 x 10^{-4} and 6.60 x 10^{-4} mg/cm^2 or 65 and 66 g/ha for 1 to 2 year old and 2 to 3 year old toddlers, respectively.

Assessment was also conducted against the oral NOAEL of 5 mg/kg bw/d for systemic effects that may result from fenpropidin absorption through toddlers' skin (using a dermal absorption value of 10%), and toddlers' oral exposure that may result from hand-to-mouth and object-to mouth exposure. Resulting RALs were 1.94 x 10^{-3} and 2.46 x 10^{-3} mg/cm^2 or 194 and 246 g/ha for 1 to 2 year old and 2 to 3 year old toddlers, respectively.

Results from the APVMA Spray Drift Risk Assessment Tool indicate that no buffer zones are required for airblast application on wine grapes.

Recommendations

The following first aid instructions, safety directions, restraints and re-entry statement are recommended for the product label.

First aid instructions

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 0800 764 766. If swallowed, do NOT induce vomiting. If skin contact occurs, remove contaminated clothing and wash skin thoroughly. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

Safety directions

Warning – aspiration hazard. This product contains ingredients that may be fatal if swallowed. Harmful if inhaled. Will damage eyes. Will irritate the nose and throat and skin. Repeated exposure may cause allergic disorders. Do not inhale vapour or spray mist. Avoid contact with eyes and skin. When opening the container, preparing spray and using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and a washable hat, elbow-length chemical resistant gloves and face shield. Wash hands after use. After each day's use, wash gloves, face shield and contaminated clothing.

Restraints

DO NOT use on broken skin, cover any skin wounds with an impermeable dressing before using.

DO NOT continue using if skin, eye or respiratory irritation occurs.

DO NOT apply by aircraft.

DO NOT apply more than one (1) application per season.

DO NOT apply later than 80% capfall (E-L 25).

DO NOT allow bystanders to come into contact with the spray cloud.

Re-entry statement

DO NOT enter treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

Environmental assessment

Fate and behaviour in the environment

Soil

Fenpropidin is resistant to photolysis on soil, and to anaerobic soil metabolism. The aerobic soil metabolism half-lives ranged 9.5 to 155 days (4 soils). Degradation was indicative of a single first order (SFO) decline in all soils. With the exception of CO_2, no metabolite exceeded 5% AR. Mineralisation was extensive with CO_2 reaching 16% to 32% AR after 3 months and 60% to 63% AR after 12 months. Bound residues were 8.9% to 19% after 3 months and <17% after 12 months.

The minor soil metabolite CGA289267 (max 4.6%) was applied as test substance to 3 laboratory soils. Single first-order DT_{50} values from these studies were calculated to be 9.5 to 63 days.

The sorption of fenpropidin was tested in 11 soils. Tests were variable in terms of soil:solution ratios and tested concentrations. There was no correlation between sorption and organic carbon. Sorption was dependent on concentration (average 1/n 0.76). Based on the variability, the median K_F of 44 mL/g was determined to be appropriate for risk assessment, regardless of soil organic carbon.

Sorption of the minor soil metabolite CGA289267 was tested in 5 soils. This metabolite was mobile with K_F values ranging 0.6 to 4.1 L/kg with an average 1/n of 0.93. The low mobility of fenpropidin and potential mobility of CGA289267 were confirmed by the results of laboratory unaged (7 soils) and aged (3 soils) column leaching studies.

Field soil dissipation studies (bare soil) were provided from 6 sites located in Switzerland and Germany. Dissipation was generally described by single first order kinetics (4 sites) but was biphasic at 2 sites. Model DT_{50} values ranged 7.0 to 116 days at 5 sites. At one site, the overall DT_{50} was 38 days, but due to the biphasic nature of degradation, the slow rate DT_{50} was calculated to be 1,180 days. Residues of fenpropidin were <0.05 mg/kg in soil layers deeper than 5 cm or <0.02 mg/kg in soil layers deeper than 10 cm when this was the shallowest upper depth segment analysed in a trial.

Water and sediment

Fenpropidin was stable under sterile aqueous hydrolysis conditions at 50°C at pH 3, 7 and 9. Measurement of the UV/visible absorption spectrum of aqueous solutions of fenpropidin indicated that direct aqueous photolysis of fenpropidin would not be expected due to the absence of any significant absorption over the relevant wavelengths for sunlight (>290 nm). A ready biodegradability test (OECD 301B) indicated that fenpropidin is ‘not readily biodegradable’.

In water/sediment studies (four systems) fenpropidin dissipated rapidly from the water partitioning to sediment with DT_{50} values ranging 1.0 to 5.9 days (geomean 2.1 days). Degradation in sediment subsequently occurred with single first order whole system DT_{50} being calculated as 77 to 183 days (geomean 41 days). The metabolite CGA289267 was identified and present at maxima of 27% AR at

30 days after treatment accounting for 19% AR in water and 7.8% AR in sediment. The terminal metabolite CO_2 accounted for up to 60% of the benzylic bridge-^{14}C-radiolabel by 84 days.

Air

Fenpropidin is highly volatile (0.017 Pa) and may exhibit volatility from soil and foliage following application. Based on a range of testing conditions in wind tunnels (different crops, application rates, wind speeds, humidity, etc.), deposition downwind resulting from volatility ranged from 0.19 to 1.9% at 1 metre to 0.04% to 0.25% at 20 metres. Based on a global annual average 24-hour concentration of 1.5×10^6 OH-radicals/cm³, reaction with hydroxyl radicals and a 12-hour day, the atmospheric DT_{50} was calculated to be 0.042 days.

Difenoconazole

Difenoconazole is persistent in the environment because it is resistant to biodegradation and hydrolysis. It is poorly mobile in soils, and hence is not likely to leach into groundwater. In water-sediment systems, difenoconazole moves rapidly from the water to sediments where it may be persistent. The low vapour pressure and modelled atmospheric half-life of <2 days for difenoconazole indicate it is not a potential candidate for long range atmospheric transport.

Effects and associated risks to non-target species

Terrestrial vertebrates

Fenpropidin has moderate toxicity to mammals (geomean LD_{50} 1,708 mg a.c./kg bw, *Rattus norvegicus*) and birds (lowest LD_{50} 431 mg a.c./kg bw, *Colinus virginianus*). Following short-term dietary exposure, some toxicity was observed in the mallard duck with a LC_{50} of 3762 mg a.c./kg diet (NOEL 103 mg a.c./kg bw/d, *Anas platyrhynchos*). In reproductive toxicity tests, a delay in sexual maturation of mammals was observed at doses as low as 60 mg a.c./kg bw/d (NOEL 11 mg a.c./kg bw/d, *Rattus norvegicus*), reduced number of eggs laid, egg weights, viable embryos, hatched eggs, and 14d survivors was observed at doses as low as 82 mg a.c./kg bw/d (NOEL 15 mg a.c./kg bw/d, *Colinus virginianus*).

The combination product SEEKER Duo Fungicide was moderately toxic to birds (LD_{50} 593 mg acs/kg bw, *Colinus virginianus*).

Risks of SEEKER Duo Herbicide to terrestrial vertebrates were determined to be acceptable assuming direct dietary exposure within the treatment area at the maximum seasonal rate. No protection statements are therefore required for terrestrial vertebrates.

The octanol-water partition coefficient for fenpropidin indicates a potential for bioaccumulation. A food chain assessment indicates that any accumulated residues in earthworms or fish will not reach levels harmful to predators under the proposed conditions of use. Based on low potential for accumulation in mammalian tissues, biomagnification is not expected up the food chain.

Aquatic species

Fenpropidin has moderately toxicity to fish (lowest LC_{50} 1.9 mg a.c./L, *Lepomis macrochirus*) and aquatic invertebrates (EC_{50} 0.54 mg a.c./L, *Daphnia magna*), and high toxicity to algae (lowest E_rC_{50} 0.0011 mg a.c./L, *Desmodsemus subspicatus*) and aquatic plants (lowest E_rC_{50} 0.079 mg a.c./L, *Lemna gibba*). The major metabolite CGA289267 was less toxic to fish, aquatic invertebrates and algae than the parent substance.

Following chronic exposure to fenpropidin, reduced growth of fish in the early life stages was observed at concentrations as low as 0.010 mg a.c./L (NOEC 0.0038 mg a.c./L, *Pimephales promelas*), increased mortality of aquatic invertebrates was observed at concentrations as low as 1.0 mg a.c./L (NOEC 0.32 mg ac/L, *Daphnia magna*), and reduced development rate of sediment dwellers was observed at concentrations as low as 2.0 mg a.c./L or 80 mg a.c./kg dry sediment (NOEC 1.0 mg a.c./or 40 mg a.c./kg dry sediment, *Chironomus riparius*).

In a higher tier outdoor mesocosm study examining the effects of fenpropidin on aquatic communities containing phytoplankton, zooplankton, periphyton, macroinvertebrates, macrophytes and fish, the most sensitive effect was depression of green algae *Crucigeniella rectangularis* populations (NOEC 0.13 µg a.c./L). The mesocosm study is the basis of the overall RAL for fenpropidin in natural aquatic areas.

The combination product SEEKER Duo Fungicide was very toxic to algae (E_rC_{50} 0.00027 mg acs/L, *Desmodesmus subspicatus*), and moderately toxic to fish (LC_{50} 1.5 mg acs/L, *Oncorhynchus mykiss*) and daphnids (EC_{50} 0.67 mg acs/L, *Daphnia magna*). In the absence of formulation toxicity data, SEEKER Duo Fungicide was predicted to be moderately toxic to mysid shrimp (LC_{50} 0.35 mg acs/L, *Americamysis bahia*) and aquatic plants (EC_{50} 0.10 mg acs/L, *Lemna gibba*).

Following chronic exposure to SEEKER Duo Fungicide, growth of fish in the early life stages was reduced in a dose-dependent manner (EC_{10} 0.052 mg acs/L, *Oncorhynchus mykiss*), and reproduction of aquatic invertebrates was observed at concentrations as low as 0.15 mg acs/L (NOEC 0.048 mg acs/L, *Daphnia magna*).

SEEKER Duo Fungicide and its active constituents are very toxic to some aquatic species and a protection statement is required on the label to identify the hazard. Spray drift risks to aquatic species were determined to be acceptable provided a mandatory downwind buffer zone of 55 metres is observed for the protection of natural aquatic areas.

Runoff risks of difenoconazole to aquatic species are considered to be no greater than the reference product Nufarm Digger Herbicide (Product no. 65130), which is registered for the same use situation in grapevines at a higher rate. Runoff risks of fenpropidin were determined to be acceptable after considering spatial and temporal characteristics typical of grape growing regions of Australia. General runoff restraints are advised to mitigate the risk of a runoff event soon after application (i.e. due to heavy storms or irrigation).

Bees

Fenpropidin has moderate toxicity to adult bees by contact exposure (LD_{50} 63 µg a.c./bee, *Apis mellifera*) and oral exposure (LD_{50} 58 µg a.c./bee, *Apis mellifera*), and low toxicity to bee larvae (LD_{50} 100 µg a.c./bee,

Apis mellifera). Following long-term dietary exposure to fenpropidin, increased mortality of adult bees was observed at doses as low as 7.1 µg a.c./bee/d (NOEL 3.8 µg ac/bee/d, *Apis mellifera*), while emergence of bee larvae was negatively affected in a dose-dependent manner (EC_{10} 7.9 µg a.c./bee/d, *Apis mellifera*).

The combination product SEEKER Duo Fungicide has moderately toxic to bees by contact exposure (LD_{50} 84 µg acs/bee, *Apis mellifera*) and oral exposure (LD_{50} 94 µg acs/bee, *Apis mellifera*). Following long-term dietary exposure to SEEKER Duo Fungicide, increased mortality of adult bees was observed at doses as low as 0.92 µg acs/bee/d (NOEL 0.23 µg acs/bee/d, *Apis mellifera*).

Risks of SEEKER Duo Herbicide to bees were determined to be acceptable assuming dietary or contact exposure to blooming plants that have been directly over sprayed. No protection statements are therefore required for bees.

Other non-target arthropods

An EC formulation of fenpropidin had low toxicity to the indicator species of parasitic arthropods under extended laboratory conditions (ER_{50} >1500 g a.c./ha, *Aphidus rhopalosiphi*). Similarly, low toxicity was observed in ground dwelling parasitic arthropods under laboratory conditions (ER_{50} >1,500 g a.c./ha, *Aleochara bilineata*).

No data are available on the toxicity of fenpropidin to the indicator species of predatory arthropods (*Typhlodromus pyri*). Testing on other predatory species indicated mortality at relatively high rates in green lacewing (LR_{50} >30 g a.c./ha, *Chyrsoperla carnea*), but low toxicity at field relevant rates in ladybird beetles (LR_{50} >750 g a.c./ha, *Coccinella septempunctata*), carabid beetles (LR_{50} >750 g a.c./ha, *Bembidion tetracolum*), and other ground beetles (LR_{50} >1500 g a.c./ha, *Poecilus cupreus*). Following application of 750 g a.c./ha, toxicity of foliar residues to the predatory mite *Phytoseiulus persimilis* were acceptable after one day of ageing.

Low toxicity of the combination product SEEKER Duo Fungicide was observed in predatory mites (tier 1 LR_{50} >950 g acs/ha, *Typhlodromus pyri*), green lacewings (lab ER_{50} >950 g acs/ha, *Chrysoperla carnea*), ground beetles (lab ER_{50} >475 g acs/ha, *Poecilus cupreus*), parasitic wasps (extended lab LR_{50} 703 g acs/ha, *Aphidius rhopalosphi*), and rove beetles (ER_{50} >475 g acs/ha, *Aleochara bilineata*). Toxicity to ladybird beetles was low under semi-field conditions in broadbean (ER_{50} >475 g acs/ha, *Coccinella septempunctata*).

Based on a limited data set, acceptable risks of fenpropidin to green lacewings could not be concluded and fenpropidin residues were considered to be acceptable to predatory mites after 24 hours of ageing. However, available data on the combination product SEEKER Duo Herbicide enabled a conclusion of acceptable risk to these and other species of arthropods without mitigation. Therefore, the product is considered to be compatible with integrated pest management (IPM) programs utilising beneficial arthropods.

Soil organisms

Fenpropidin has low toxicity to soil macro-organsisms such as earthworms (LC_{50corr} >500 mg a.c./kg dry soil, *Eisenia andrei*). Following long-term exposure, reduced reproduction of collembola was observed at concentrations as low as 131 mg a.c./kg dry soil ($NOEC_{corr}$ 46 mg a.c./kg dry soil, *Folsomia candida*). No adverse effects were observed at the highest test concentrations on earthworms ($NOEC_{corr}$ 10 mg a.c./kg dry

soil, *Eisenia fetida*) or soil mites (NOEC 830 mg a.c./kg dry soil, *Hypoaspis aculeifer*). No adverse effects were observed on soil processes such as nitrogen transformation at exaggerated soil concentrations (NOEC 10 mg a.c./kg dry soil). The minor soil metabolite CGA289267 was less toxic to soil organisms than the parent substance.

The combination product SEEKER Duo Fungicide has moderately toxic to soil macro-organisms such as earthworms (LC_{50corr} 94 mg a.c./kg dry soil, *Eisenia fetida*). Low toxicity was observed in soil micro-organisms at exaggerated soil concentrations (NOEC 7.6 mg acs/kg dry soil). Following long-term exposure, reproduction of soil macro-organisms was inhibited at concentrations as low as 6.3 mg acs/kg dry soil ($NOEC_{corr}$ 1.6 mg acs/kg dry soil, *Eisenia fetida*).

Risks of SEEKER Duo Herbicide to soil organisms were determined to be acceptable following exposure to residues incorporated into the top 5 cm of soil assuming 40% crop interception. No protection statements are therefore required for soil organisms.

Non-target terrestrial plants

Following pre-emergent exposure in a seedling emergence test, an EC formulation of fenpropidin did not have any adverse effects on six species of non-target terrestrial plants at the highest tested rate (ER_{25} >750 g ac/ha). Two EC formulations of fenpropidin were tested in vegetative vigour tests, with phytotoxicity observed in 3 plant species in a non-GLP study (lowest ER_{25} 188 g a.c./ha, ER_{50} >375 g a.c./ha, *Glycine max*) and growth inhibition observed in 2 of these plant species in a GLP study (lowest ER_{25} 446 g a.c./ha, ER_{50} 1121 g a.c./ha, *Brassica napus*).

Some phytotoxicity of the combination product SEEKER Duo Fungicide was observed in non-target terrestrial plants (lowest ER_{25} >239 g acs/ha, ER_{50} >477 g acs/ha, *Brassica napus* following post-emergent exposure).

Although SEEKER Duo Fungicide and its active constituent fenpropidin are slightly phytotoxic to some species of non-target terrestrial plants, a spray drift assessment determined that buffer zones are not necessary for the protection of vegetation areas.

Recommendations

In considering the environmental safety of the proposed use of SEEKER Duo Fungicide, the APVMA had regard to the toxicity of the active constituent in relation to relevant organisms and ecosystems. Based on the available information, the APVMA can be satisfied that the proposed use of the product is unlikely to have an unintended effect that is harmful to animals, plants or things, or to the environment.

Efficacy and safety assessment

Syngenta Australia Pty Ltd has applied to the APVMA for registration of the new product SEEKER Duo Fungicide, containing 375 g/L fenpropidin and 100 g/L difenoconazole, as an emulsifiable concentrate (EC) formulation for use as a fungicide in wine grapes in grapes to control powdery mildew (*Uncinular necator*).

An application rate of 40 mL/100L is proposed with application restricted to one per season in a maximum spray volume of 1,500 L/ha to grapevine crops at up to 80% capfall (E-L 25). The product is to be applied by ground application only using dilute or concentrated spraying equipment applying the same total amount of product to the crop. The product is not to be applied at no more than 3x concentration.

The proposed label states SEEKER Duo Fungicide must be applied as part of a protectant fungicide program. SEEKER Duo Fungicide must not be applied later than 80% capfall (E-L 25), with only one application per season and in water volumes no greater than 1500 L/ha.

Efficacy

Twenty-one trials were conducted across all grape growing states (Vic, WA, Tas, SA, Qld, NSW) in Australia from 2017 through to 2022. Fourteen trials tested efficacy against powdery mildew in common wine grape varieties in comparison with industry standards. A further 7 trials evaluated crop safety only. All trials were conducted as randomised complete block design with 3 to 4 replicates. Plot sizes varied from 3 to 6 vines.

Across all trials, applications were made using handheld booms or airblast applicators delivering water volumes between 417 and 1,500 L/ha. Between one and 6 applications occurred in each trial, with the main disease assessment taking place after the second application, except for one trial. A minimum reapplication interval of 7 days was used. Sprays were applied at key stages, including prior to infection and over flowering. Disease pressure in the trials ranged from low to very high.

Efficacy of the product against powdery mildew was assessed as disease incidence – the percentage of plants infected within each plot, and disease severity – the percentage of leaf area and bunch area infected.

Crop safety

Crop safety was evaluated in all of the 21 trials at rates up to 3x the proposed dilute rate (ie. up to 120 mL/100 L). The trials included evaluations of phytotoxicity, ‘green’ index of grapevine leaves and harvest yield.

Organoleptic tests

Impacts on the fermentation or sensory characteristics of wine produced was assessed in one organoleptic trial. The results demonstrated SEEKER Duo Fungicide did not cause any significant impacts on the fermentation or sensory characteristics of the wine produced although SEEKER Duo Fungicide caused acceleration of fermentation, higher alcohol concentration and pH. However, the overall time to complete fermentation was not affected. There was a no significant difference in sensory detection when tested by an expert panel.

Resistance management

Fenpropidin belongs to the amines (morpholines) (SBI: Class III) group of chemicals with a mode of action classified by the Fungicide Resistance Action Committee (FRAC 2022) as Group 5 with a Δ^{14}-reductase and $\Delta^{8}\rightarrow\Delta^{7}$ isomerase in sterol biosynthesis target site.

Difenoconazole belongs to the DMI (SBI: Class I) group of chemicals with a mode of action classified by the Fungicide Resistance Action Committee (FRAC 2022) as Group 3 with a C14-demethylase in sterol biosynthesis target site.

Powdery mildew is a principal fungal disease of grapevine worldwide. Even though it usually does not cause plant death directly, heavy infections can lead to extensive yield losses, and even low levels of the disease can negatively affect the quality of the wine. Therefore, intensive spraying programs are commonly applied to control the disease, which often leads to the emergence and spread of powdery mildew strains resistant to different fungicides.

CropLife Australia recommends the following measures to manage powdery mildew resistance to difenoconazole and fenpropidin in grapevines: do not apply more than two consecutive sprays of Group 3 or 5 fungicides. The proposed label recommends using the product within a protectant fungicide program aimed at controlling powdery mildew and to not apply the product more than one application per season.

Recommendations

SEEKER Duo Fungicide is intended for use as part of a protectant fungicide program alternating with fungicides from different mode of action groups. The weight-of-evidence from evaluation of disease incidence and severity across the fourteen trials indicates that SEEKER Duo Fungicide will provide control of powdery mildew in grapevines commensurate with registered industry standards when used as part of a preventative spray program in accordance with CropLife resistance management guidelines.

Phytotoxicity at rates up to 120 mL/100 L (3X proposed label rate) was absent in all trials except for one that indicated minor leaf damage in grape variety Sauvignon blanc when applied at pre-flowering stage. However, no damage was noted at the second application (80% capfall) stage. No significant difference to untreated controls were reported in green index ratings on grapevine leaves or harvest yields in any of the trials. Thus, overall, the trials provided sufficient support for crop safety for the proposed use in grapevines at 40 mL/100 L for one application per season.

Spray drift assessment

Regulatory Acceptable Levels (RALs) were established using the APVMA Spray Drift Assessment Tool (SDRAT), or Spray Drift Management Tool (SDMT), by each risk area, in order to calculate the appropriate spray drift buffer zones for SEEKER Duo Fungicide.

Human health

RALs were 3.54 x 10^{-4} and 6.60 x 10^{-4} mg/cm^2 or 65 and 66 g/ha for 1 to 2 year olds and 2 to 3 year old toddlers, respectively. On this basis, no mandatory downwind buffer zones are required for bystanders' protection.

Residues and trade

For fenpropidin, MRLs/tolerances are not established in most significant markets therefore residues in animal commodities will need to be below the LOQ (<0.01 mg/kg for fenpropidin and its significant metabolites) to prevent residue related trade issues.

For fenpropidin, the target tissue is the liver. In the animal transfer study, a feeding level of 3.15 ppm in the feed resulted in highest residues of fenpropidin at 0.028 mg/kg and the metabolite CGA 289267 at 0.10 mg/kg in liver (0.13 mg/kg fenpropidin + CGA 289267). A RAL (feeding level) of 0.48 ppm ((0.02 mg/kg × 3.15 ppm) ÷ 0.13 mg/kg in the liver) would be required for residues of fenpropidin + CGA 289267 in liver to be at <0.02 mg/kg.

If this RAL (0.48 mg/kg) for fenpropidin and the proposed spray drift parameters are used in the APVMA Spray Drift Risk Assessment Tool (SDRAT) a livestock area mandatory downwind buffer zone of 5 metres for protection of international trade is required for the proposed use pattern.

Environment

The aquatic RAL of 0.16 µg acs/L is based on the *Desmodesmus subspicatus* E_rC_{10} of 0.16 µg acs/L for the combination product SEEKER Duo Fungicide and an assessment factor of 1. On this basis, a mandatory downwind buffer zone of 55 metres was determined for the protection of natural aquatic areas.

The pollinator RAL of 14000 µg acs/bee is based on the *Apis mellifera* contact LD_{50} 84 µg acs/bee for the combination product SEEKER Duo Fungicide and a conversion factor of LOC 0.4 / ExpE 2.4 * 1,000. On this basis, a mandatory downwind buffer zone is not required for the protection of pollinator areas.

The vegetation RAL of 120 g acs/ha is based on the *Brassica napus* post-emergent ER_{25} >239 g acs/ha for the combination product SEEKER Duo Fungicide and an assessment factor of 2. On this basis, a mandatory downwind buffer zone is not required for the protection of vegetation areas.

Table 8: Summary of RALs for SEEKER Duo Fungicide

Sensitive area	Regulatory Acceptable Level	
	Level of difenoconazole + fenpropidin	Units
Bystander	65	g/ha
Livestock	0.48	ppm
Aquatic	0.16	µg/L
Pollinator	0.014	g/ha
Vegetation	120	g/ha

Buffer zones calculated by the SDRAT or SDMT, using the above RALs, were incorporated into the SEEKER Duo Fungicide label spray drift instructions (see *Labelling Requirements* below).

Labelling requirements

POISON

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

Seeker® Duo

Fungicide

syngenta®

ACTIVE CONSTITUENTS: **375 g/L FENPROPIDIN**
100 g/L DIFENOCONAZOLE

SOLVENT: **318 g/L LIQUID HYDROCARBONS**

GROUP	5	3	FUNGICIDE

For the control of powdery mildew in wine grapes

1 - 20 LITRES

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

EC Formulation type **Emulsifiable Concentrate**

Restraints

DO NOT apply by aircraft.

DO NOT apply if heavy rains or storms are forecast within 3 days.

DO NOT irrigate to the point of runoff for at least 3 days after application.

DO NOT use on broken skin, cover any skin wounds with an impermeable dressing before using.

DO NOT continue using if skin, eye or respiratory irritation occurs.

DO NOT apply more than one application per season.

DO NOT apply later than 80% capfall (E-L25).

Spray Drift Restraints

Specific definitions for terms used in this section of the label can be found at apvma.gov.au/spraydrift.
DO NOT allow bystanders to come into contact with spray cloud.
DO NOT apply in a manner that may cause an unacceptable impact to native vegetation, agricultural crops, landscaped gardens and aquaculture production, or cause contamination of plant or livestock commodities, outside the application site from spray drift. The buffer zones in the relevant buffer zone table below provide guidance but may not be sufficient in all situations. Wherever possible, correctly use application equipment designed to reduce spray drift and apply when the wind direction is away from these sensitive areas.
DO NOT apply unless the wind speed is between 3 and 20 kilometres per hour at the application site during the time of application.
DO NOT apply if there are hazardous surface temperature inversion conditions present at the application site during the time of application. Surface temperature inversion conditions exist most evenings one to two hours before sunset and persist until one to two hours after sunrise.
DO NOT apply by vertical sprayer unless the following requirements are met:

- Spray is not directed above the target canopy
- The outside of the sprayer is turned off when turning at the end of rows and when spraying the outer row on each side of the application site
- For dilute water rates, minimum distances between the application site and downwind sensitive areas (see "**Mandatory buffer zones**" section of the following table titled "**Buffer zones for vertical sprayers**") are observed

Buffer zones for vertical sprayers

Type of target canopy and dilute water rates	Mandatory buffer zones				
	Bystander areas	Natural aquatic areas	Pollinator areas	Vegetation areas	Livestock areas
All canopy types Maximum dilute water rate of 1500 L/ha	0 metres	55 metres	0 metres	0 metres	5 metres

DIRECTIONS FOR USE

Crop	Disease	Rate	Critical Comments
Wine grapes	Powdery mildew (*Uncinula necator*)	40 mL/100 L	Apply SEEKER® Duo fungicide within a protectant fungicide program with products from other mode of action groups aimed at controlling powdery mildew. Apply by dilute or concentrate spraying equipment applying the same total amount of product to the crop. Ensure thorough coverage of the crop canopy regardless of application method. Refer to Application Section for calculations. DO NOT apply more than one (1) application per season. DO NOT apply later than 80% capfall (EL-25). DO NOT apply at more than 3X concentration. DO NOT apply to canopies which require water volumes greater than 1500L/ha. This use is subject to a CropLife Australia Fungicide Resistance Management strategy.

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

WITHHOLDING PERIODS:

HARVEST

Wine Grapes: **NOT REQUIRED WHEN USED AS DIRECTED**

GRAZING

DO NOT GRAZE TREATED VINEYARDS FOR 12 WEEKS AFTER APPLICATION

EXPORT OF TREATED PRODUCE

Growers should note that appropriate MRLs or import tolerances may not be established in all markets for fruit harvested from SEEKER® Duo fungicide treated grapes. If you are growing grapes for export, please check with the Australian Wine Research Institute (in regard to wine) or Syngenta Australia for the latest information on MRLs and import tolerances before using SEEKER® Duo fungicide.

GENERAL INSTRUCTIONS

Mixing

SEEKER® Duo fungicide is an Emulsifiable Concentrate (EC) formulation that mixes readily with water and is applied as a spray.

1. Partly fill the spray tank with water.
2. Start the agitation.
3. Add the correct amount of product to the spray tank with the agitation system running.
4. Continue agitation while topping up the tank with water and while spraying.
5. Use the spray mix as soon as possible after preparation.

Application

Ground Application only

Ensure thorough coverage of foliage and fruit. Apply 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: 2X (ie, 1000 L / 500 L = 2)
4. If the dilute label rate is 40 mL/100 L, then the concentrate rate becomes 2 x 40, that is 80 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
SEEKER® Duo fungicide is compatible with a range of commonly used fungicides, insecticides, herbicides, and fertilisers. Always consult your Syngenta representative before mixing SEEKER® Duo fungicide 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** | **5** | **3** | **FUNGICIDE**

SEEKER® Duo fungicide is a combination of an amine and a demethylation inhibitor (DMI) fungicide. For fungicide resistance management SEEKER® Duo fungicide is both a Group 5 and a Group 3 fungicide. Some naturally occurring individual fungi resistant to SEEKER® Duo fungicide and other Group 5 and/or Group 3 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 SEEKER® Duo fungicide or other Group 5 and/or Group 3 fungicides, thus resulting in a reduction in efficacy and possible yield loss. Apply SEEKER® Duo fungicide in alternation with fungicides from different mode of action groups and follow CropLife Australia Fungicide Resistance Management strategies. 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 SEEKER® Duo fungicide to control resistant fungi.

PRECAUTION
Re-entry Period
DO NOT enter treated areas until the spray has dried unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product or used containers.

PROTECTION OF CROPS, NATIVES AND OTHER NON-TARGET PLANTS

SEEKER® Duo fungicide may cause some minor crop phytotoxicity when applied pre-flowering during early shoot elongation. This phytotoxicity is transient and crops recover with no impact on yield or quality of grapes.

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

SAFETY DIRECTIONS

Warning – aspiration hazard. This product contains ingredients that may be fatal if swallowed. Harmful if inhaled. Will damage eyes. Will irritate the nose and throat and skin. Repeated exposure may cause allergic disorders. DO NOT inhale vapour or spray mist. Avoid contact with eyes and skin. When opening the container, preparing spray, and using the product, wear:

- **cotton overalls buttoned to the neck and wrist (or equivalent clothing)**
- **washable hat**
- **elbow-length chemical resistant gloves**
- **face shield**

Wash hands after use. After each day's use wash gloves, face shield and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone 131 126. If swallowed, do NOT induce vomiting. If skin contact occurs, remove contaminated clothing and wash skin thoroughly. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

May cause damage to organs (Central nervous system) through prolonged or repeated exposure.

SAFETY DATA SHEET

If additional hazard information is required refer to the Safety Data Sheet. For a copy visit our website at www.syngenta.com.au or use the QR code on this label.

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	

Acronyms and abbreviations

Shortened term	Full term
ACCS/ACMS	Advisory Committee for Chemicals Scheduling/Advisory Committee for Medicines Scheduling
ac	Active constituent
ADI	Acceptable daily intake (for humans)
A/G	Albumin/globulin
AHMAC	Australian Health Ministers Advisory Council
ai	Active ingredient
ALT	Alanine aminotransferase
AR	Applied radioactivity
ARfD	Acute reference dose
AST	Aspartate aminotransferase
AUC	Area under the curve. A measure of the plasma concentration of a chemical substance over a given period of time.
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	Bodyweight
C_{max}	The peak serum concentration of a chemical substance in a particular compartment of the body
CNS	Central nervous system
d	Day
DAT	Days after treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	Concentration at which the biomass of 50% of the test population is impacted
EC_{50}	Concentration at which 50% of the test population are immobilised
ED_{10}	Concentration at which 10% of the population shows an adverse effect
EEC	Estimated environmental concentration
E_rC_{50}	Concentration at which the rate of growth of 50% of the test population is impacted

Shortened term	Full term
EI	Export interval
EGI	Export grazing interval
ESI	Export slaughter interval
EUP	End use product
F_0	Original parent generation
FRAC	Fungicide Resistance Action Committee
g	Gram
GAP	Good agricultural practice
GCP	Good clinical practice
GD	Gestational date
Glob	Globulin
GLP	Good laboratory practice
GPMT	Guinea pig maximization test
GGPT	Gamma-glutamyl transpeptidase
GVP	Good veterinary practice
h	Hour
ha	Hectare
HC_5	Hazardous concentration to 5% of the species
Hct	Heamatocrit
Hb	Haemoglobin
HPLC	High pressure liquid chromatography *or* high-performance liquid chromatography
id	Intradermal
im	Intramuscular
ip	Intraperitoneal
IPM	Integrated pest management
iv	Intravenous
in vitro	Outside the living body and in an artificial environment

Shortened term	Full term
in vivo	Inside the living body of a plant or animal
kg	Kilogram
K_{OC}	Organic carbon partitioning coefficient
K_F	Soil adsorption coefficient
K_{FOC}	Organic carbon normalized Freundlich distribution coefficient
L	Litre
LC_{50}	Concentration that kills 50% of the test population of organisms
LD_{50}	Dosage of chemical that kills 50% of the test population of organisms
LLNA	Local lymph node assay
LOAEC	Lowest Observed Adverse Effect Concentration
LOD	Limit of Detection – level at which residues can be detected
Log K_{OW}	Log to base 10 of octanol water partitioning co-efficient, synonym P_{OW}
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	Milligram
mL	Millilitre
MRL	Maximum residue limit
MSDS	Material Safety Data Sheet
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short-Term Intake
ng	Nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No observable effect concentration level
NOAEL	No observed adverse effect level
OC	Organic carbon
OM	Organic matter
PAI	Purified active ingredient
PND	Post-natal Day

Shortened term	Full term
POD	Point of Departure
po	Oral
ppb	Parts per billion
PPE	Personal protective equipment
ppm	Parts per million
QT	Time from the start of the Q wave to the end of a T wave on an electrocardiogram. It represents time taken for ventricular depolarisation and repolarisation or the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
Q-value	Quotient-value
RAL	Regulatory acceptable level
RBC	Red blood cell count
REI	Re-entry interval
s	Second
sc	Subcutaneous
SC	Suspension concentrate
SDMT	Spray Drift Management Tool
SDRAT	Spray Drift Risk Assessment Tool
SSD	Species specific diversity
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
$t_{1/2}$	Time required for plasma concentration (of a chemical substance) to decrease by half
T_{max}	Time to peak concentration
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
TRR	Total radioactive residue
TTC	Threshold of toxicological concern
µg	Microgram
vmd	Volume median diameter
WG	Water dispersible granule

Shortened term	Full term
WHP	Withholding period

Glossary

Term	Description
Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	Repels water
Leaching	Removal of a compound by use of a solvent
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

References

Australian Government Federal Register of Legislation, *Agricultural and Veterinary Chemicals Code Act (1994)* (Cth), Federal Register of Legislation website.

Australian Pesticides and Veterinary Medicines Authority (2018). *Spray Drift Risk Assessment Tool (SDRAT) – Version 1.0*, APVMA website.

Australian Pesticides and Veterinary Medicines Authority (2021a). *Acceptable daily intakes for agricultural and veterinary chemicals*, APVMA website.

Australian Pesticides and Veterinary Medicines Authority (2021b). *Acute reference doses for agricultural and veterinary chemicals*, APVMA website.

Australian Pesticides and Veterinary Medicines Authority (2021c). *FAISD Handbook,* APVMA website.

Australian Wine Research Institute (AWRI) (2010). *Understanding grapevine growth. Flowering and pollination*. AWRI website.

Bernard M, Wainer J, Carter V, Semeraro L, Yen AL, Wratten SD, 2006. Beneficial insects and spiders in vineyards – predators in Southeast Australia. The Australian and New Zealand Grapegrower and Winemaker 512: 37-48l.

ECETOC (2003). *Derivation of assessment factors for human health risk assessment*. European centre for ecotoxicology and toxicology of chemicals. Technical report No 86 pp 1-90 February 2003.

EFSA (European Food Safety Authority), 2009. G*uidance document on risk assessment for birds & mammals on request from EFSA*. EFSA Journal 7(12): 1438, doi: 10.2903/j.efsa.2009.1438.

EFSA (European Food Safety Authority), 2013. *Guidance on the risk assessment of plant protection products on bees (Apis mellifera, Bombus spp. and solitary bees).* EFSA Journal 11(7): 3295. 266 pp. doi:10.2903/j.efsa.2013.3295.

EFSA (European Food Safety Authority), 2014. *EFSA guidance document for evaluating laboratory and field dissipation studies to obtain DegT$_{50}$ values of active substances of plant protection products and transformation products of these active substances in soil*. EFSA Journal 12(5): 3662, 37 pp. doi:10.2903/j.efsa.2014.3662.

Ishii, S., Ishii, K., Nakadate, M. and Yamasaki, K. (2013). *Correlation study in skin and eye irritation between rabbits and humans based on published literatures*. Food Chem. Toxicol. 55 (596-601) DOI: 10.1016/j.fct.2013.02.004.

OECD (Organisation for Economic Co-operation and Development), 2018. *Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption*. OECD Series on Testing and Assessment, OECD Publishing, Paris.

Retallack M, 2021. *Natural predators of vineyard insects pests booklet: a guide to the natural enemies of grapevine pests in South Australia*.

The Therapeutic Goods Administration (TGA) (2023) *Therapeutic Goods (Poisons Standard-June 2023) Instrument 2023*, TGA website.

USDA (United States Department of Agriculture), 2017. *Attractiveness of agricultural corps to pollinating bees for the collection of nectar and/or pollen*. USDA website.

US EPA (2021a). *Occupational Pesticide Handler Exposure Calculator (OPHEC) (version date: May 2021). Occupational Pesticide Handler Exposure Data | Pesticide Science and Assessing Pesticide Risks*. US EPA website.

US EPA (2021b). *Occupational Pesticide Re-entry Exposure Calculator (OPREC)*. US EPA website.