Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active Metamitron in the Product Brevis Fruit Thinner

APVMA Product Number 84928

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PREFACE

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

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

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

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

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

About this document

This is a Public Release Summary.

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

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

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

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for approval of the active metamitron and registration of the product **Brevis Fruit Thinner** should be granted. Submissions should relate only to

matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of **public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade,** and **efficacy and target crop or animal safety**. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **12 July 2018** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

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

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

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

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

Further information

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

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

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

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

1 INTRODUCTION

1.1 Purpose of application

Adama Australia Pty Limited has applied to the APVMA for approval of the new active metamitron and to register the new product, Brevis Fruit Thinner, containing metamitron at 150 g/kg in a water soluble granular (SG) formulation. The product is a plant growth regulator intended for commercial use for fruit thinning in apples. The product is proposed to be applied in a water-based dilution by ground-based airblast application.

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

1.2 Product claims and use pattern

Brevis Fruit Thinner is a photosynthesis inhibitor for use on apple trees. Brevis Fruit Thinner is applied post-fruit set, when the diameter of the central fruitlets is 8 – 16 mm, to thin excess fruitlets and assist with optimising fruit load and fruit size. Brevis Fruit Thinner can be applied up to a maximum of 2.2 kg/ha per season with the product application rate ranging from 1.1 to 2.2 kg/ha, in water volumes from 1000 to 2000 L/ha, according to either of the following spray programs:

1. A single application at 1.1 to 2.2 kg/ha; OR

2. Two applications of 1.1 kg/ha with a minimum spray interval of 5 days between applications.

A single spray program of Brevis Fruit Thinner can be used for greater flexibility of application timing depending on crop and weather conditions. The lower rate is used to thin fewer fruitlets, and on easy to thin cultivars. The higher rate is used to increase thinning, on normal to thin cultivars and/or when applying later in the Brevis Fruit Thinner application window of 8-16 mm central fruitlet size.

1.3 Mode of Action

Metamitron, a triazinone-based herbicide, acts by inhibiting photosynthesis in susceptible plants via disruption of the electron transport in photosystem II. A temporary inhibition of photosynthesis increases fruit drop in apples and pears, such that the weakest fruit within a cluster (i.e. those with lowest growth rate and no seeds) drop first.

1.4 Overseas Registrations

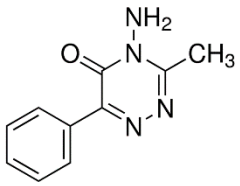
Metamitron is registered in many countries, including Austria, Belgium, Chile, France, Germany, Greece, Israel, Italy, New Zealand, Netherlands, Poland, Portugal, Serbia, Slovenia, South Africa, Spain, Switzerland, Turkey and U.K.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

The active constituent metamitron will be manufactured overseas, and imported into Australia either as the technical active for formulation, or as the fully formulated end use product.

Metamitron is a yellow crystalline powder at room temperature, with a melting point of 166 °C. It is very slightly volatile. It is slightly soluble in water (1.77 g/L at pH 5) with little pH dependence of solubility. Solutions were seen to be unstable at higher pH's due to decomposition of the active substance. It is readily soluble in polar solvents, and moderately soluble in n-heptane. The Log K_{ow} value is 0.96 at ambient temperature, indicating low fat solubility and low potential for bioaccumulation. Metamitron does not dissociate in aqueous solution, with low pH solutions seen to be stable for long periods of time (DT50 of >350 days at pH<7). Higher pH solutions show more unstable behaviour with a DT50 of 8.5 days at pH 9.

COMMON NAME (ISO):	Metamitron
CHEMICAL NAME (IUPAC):	4-Amino-3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one
CAS REGISTRY NUMBER:	41394-05-2
EMPIRICAL FORMULA:	$C_{10}H_{10}N_4O$
MOLECULAR WEIGHT:	202.21
STRUCTURAL FORMULA:	
CHEMICAL FAMILY:	Triazinone

Physico-chemical properties of metamitron active constituent

PHYSICAL FORM:	Yellowish to beige solid crystalline powder
ODOUR:	No odour detected
MELTING POINT:	Melting point: 166 °C; Decomposition observed at 250 °C
RELATIVE DENSITY AT 20°C:	1.270
VAPOUR PRESSURE	3.01×10^{-7} Pa at 20 °C; 7.44×10^{-7} Pa at 25 °C
HENRY'S LAW CONSTANT	3.62×10^{-8} Pa m^3mol^{-1}
PARTITION COEFFICIENT	Log P_{ow} = 0.96 at ambient temperature
SOLUBILITY IN WATER	pH Solubility g/L 5 1.77 7 1.68 9 solutions not stable
SOLUBILITY IN SOLVENTS (FOR TECHNICAL ACTIVE)	See table below
SAFETY PROPERTIES	No explosive and oxidising properties, not highly flammable
STABILITY:	Stable at 54°C for 2 weeks when stored in a lacquered steel or HDPE container

Solvent	Solubility at 20°C (g/L)
n-Heptane	< 0.1
Xylene	2
Dichloromethane	33
2-Propanol	18
1-Octanol	6
Polyethylene glycol	71
Acetone	37
Ethylacetate	20
Acetonitrile	35
Dimethyl sulphoxide	> 250

The APVMA has evaluated the chemistry aspects of metamitron active constituent (identification, physico-chemical properties, stability, manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable. The stability data indicates that technical metamitron is expected to remain stable for at least two years when stored under normal conditions.

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

APVMA Active Constituent Standard for Metamitron

CONSTITUENT	SPECIFICATION	LEVEL
Metamitron	Metamitron	980 g/kg minimum

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

2.2 Formulated product

The product Brevis Fruit Thinner will be manufactured both overseas and in Australia. It is a water soluble granular (SG) product containing 150 g/kg metamitron as the only active constituent. Brevis Fruit Thinner will be packaged in polyethylene bag in cartons, or in HDPE containers with screw caps. Suitable details of the product formulation, specifications for the ingredients, formulation and quality control processes, product specifications, stability data for the product when stored in the proposed packaging, analytical methods for the active constituent in the product, and details of the proposed containers, were provided and evaluated.

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

PRODUCT NAME:	Brevis Fruit Thinner
FORMULATION TYPE:	Water soluble granules (SG)
ACTIVE CONSTITUENT CONCENTRATION:	150 g/kg metamitron

Physical and chemical properties of product

PHYSICAL FORM:	Off-white granules (1-5 mm length)
ODOUR:	Light characteristic odour
PH VALUE:	pH: 7.0 (1% aqueous dilution in deionised water)
SAFETY PROPERTIES:	No explosive and oxidising properties, not highly flammable
PACK SIZES:	1 L – 20 L
PACKAGING MATERIAL:	Polyethylene bag in cartons, or HDPE containers
PRODUCT STABILITY:	Stable at 54 °C for 2 weeks and at ambient temperature (10 - 30°C) for 2 years

2.3 Recommendations

Based on a review of the chemistry and manufacturing details provided by the applicant, the registration of Brevis Fruit Thinner is supported from a chemistry perspective.

3 TOXICOLOGICAL ASSESSMENT

3.1 Evaluation of toxicology

The toxicological database for metamitron is considered sufficient to determine its toxicology profile and to characterise the risk to humans. The data package provided included metabolism studies, acute toxicity studies (active constituent and comparable product), short-term toxicity studies (oral and dermal), long-term oral toxicity studies (including carcinogenicity), reproductive and developmental toxicity studies, genotoxicity studies, and other information to address the human safety criteria.

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

Chemical class

Metamitron is a triazinone herbicide that acts by inhibiting photosynthesis in susceptible plants.

Toxicokinetics and metabolism

Metamitron was rapidly and completely absorbed after administration of a single oral dose in male and female rats. The peak plasma concentration was reached 20 to 40 minutes after administration of a single 2 to 5 mg/kg bw dose and 1 to 8 hours after administration of a single 200 mg/kg bw dose. Radioactivity from radiolabelled metamitron, was largely distributed in all organs and tissues with no evidence of accumulation in any organ. Elimination was nearly complete within 48 hours after administration of single low and high dose, and after repeated low dose administration. About half of the radioactivity was excreted in urine and faeces.

A metabolic pathway was described in rats, indicating that metamitron was rapidly and extensively metabolised with a fast initial desamination followed by several hydroxylation, conjugation and oxidation reactions. The main metabolites in urine and faeces were desamino-metamitron, hydroxylation products and triazinium-acetic acid. There were no apparent sex differences in the pattern of absorption, distribution, metabolism and excretion.

Acute toxicity

Metamitron has moderate acute oral toxicity (LD50 = 1183 mg/kg bw in male rats), low acute dermal toxicity (LD50 > 4000 mg/kg bw) and inhalational toxicity (4h LC50 =3910 mg/m3, 2/10 deaths) in male and female rats. It was not an eye or skin irritant in rabbits and was not a skin sensitiser in the guinea pig maximisation test.

Repeat-dose toxicity

The liver was the main target organ for metamitron-induced toxicity in rodents, dogs and rabbits, based on clinical chemistry parameters indicative of liver toxicity, organ weight and histopathological changes in the liver and effects on red blood cell parameters suggestive of anaemia.

In dogs dietary studies, effects on haematology and clinical chemistry indicative of liver toxicity were observed at ≥ 13.6 mg/kg bw/d in a 1-year study and increased cholesterol, considered to be indicative of impaired liver function, was observed at ≥ 11.3 mg/kg bw/d in a 2-year study.

In a 2-year rat dietary study, changes in red blood cell parameters and liver toxicity including increased cholesterol, increased relative liver weights and histopathological changes in the liver, were observed at ≥ 19.5 mg/kg bw/d. In an 18-month dietary study in mice, liver effects were observed at ≥ 35.9 mg/kg bw/d.

In a 28-day dermal toxicity study in rabbits, clinical chemistry parameters including increased AST and ALT, indicative of liver toxicity, were observed at 250 mg/kg bw/day.

Metamitron was not neurotoxic, mutagenic, genotoxic, carcinogenic or teratogenic.

Product acute toxicity

The acute toxicity of the formulated product, Brevis Fruit Thinner, containing 150 g/kg metamitron in a water soluble granular formulation, was based on the assessment of studies conducted with a comparable formulation. The product Brevis is expected to have moderate acute oral toxicity (rat, 300<LD50<2000 mg/kg bw), low acute dermal toxicity (rat LD50 > 2000 mg/kg bw, no deaths) and acute inhalational toxicity (rat LC50 > 5100 mg/m3, no deaths). It is expected to be a severe eye irritant (rabbit study), but non-irritant (rabbit study) and non-sensitising to the skin (mice LLNA).

3.2 Public health standards

Poisons scheduling

On 10 April 2018 the Delegate of the Secretary of the Department of Health published a final Scheduling decision to create a new Schedule 6 entry for metamitron. The reason for the Delegate's decision was moderate acute oral toxicity of metamitron. This decision was implemented on 1 June 2018.

Acceptable Daily Intake (ADI)

The Acceptable Daily Intake (ADI) is that quantity of a chemical compound that can safely be consumed on a daily basis for a lifetime. An ADI of 0.03 mg/kg bw/d has been established for metamitron based on a NOAEL of 3 mg/kg bw/d in a 2-year dietary dog study with increased plasma cholesterol level at the next higher dose of 11.3 mg/kg bw/d.

Acute Reference Dose (ARfD)

The Acute Reference Dose (ARfD) is the maximum quantity of a chemical that can safely be consumed over a short period of time, usually in one meal or during one day. An ARfD of 0.1 mg/kw has been established for metamitron based on acute CNS effects, in particular sedation and lower transient body temperature observed in a rat developmental study at doses above 10 mg/kg bw.

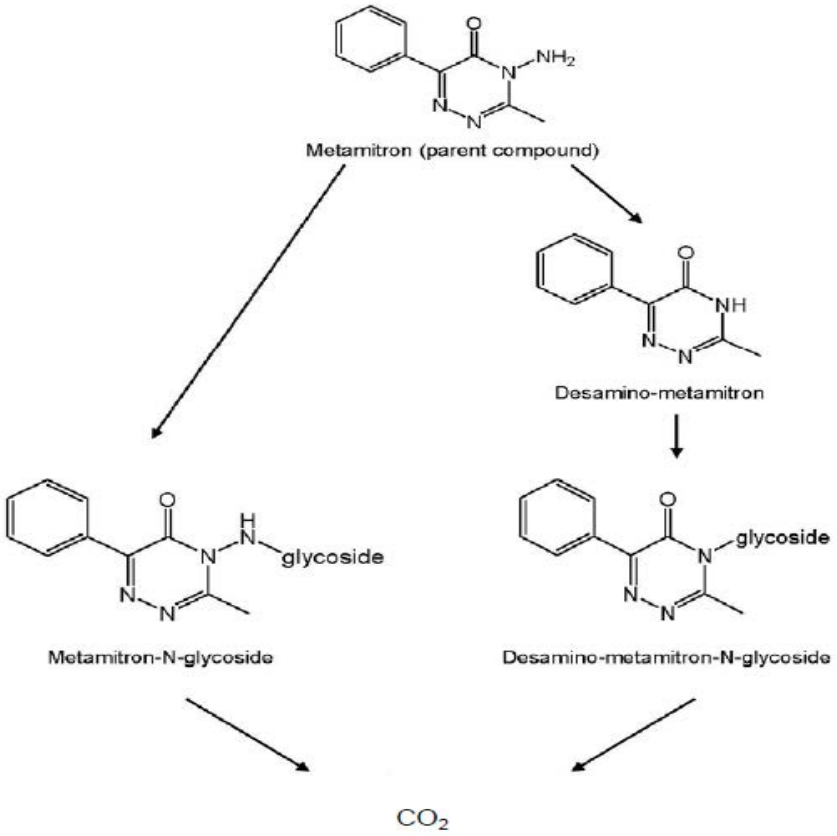
4 RESIDUES ASSESSMENT

4.1 Metabolism

Plants

The metabolism of metamitron has been investigated in apples. The [^{14}C] metamitron study involved two applications of radiolabelled metamitron formulated as metamitron 150 SG to apple trees (72 BBCH, spray interval 7 days) at rates of 0.35 kg ai/ha per application and 0.43 kg ai/ha per application. In apple fruit, parent metamitron represented approximately 40% of the TRR in immature fruit (1 DALA) and approximately 10% of the TRR at maturity (90 DALA). Desamino-metamitron (DAM) represented approximately 10% of the TRR in immature fruit (1 DALA) and approximately 25% of the TRR at maturity (90 DALA).

The proposed metabolic pathway for metamitron in apples is summarised below:



Animals

Animal metabolism studies for goat and rat indicates that desamino-metamitron (DAM) is more prevalent in animal tissues than parent metamitron. It is noted that the expected animal exposure to metamitron associated with the proposed use in apples is negligible.

4.2 Analytical methods

Pome fruits

In the Australian apple and pear trials, metamitron residues were extracted from blended homogenous samples with acetonitrile and water. An aliquot of the extract was taken and diluted. Metamitron residues are determined by reverse phase Ultra Performance Liquid Chromatography (UPLC) coupled with tandem mass spectrometric detection (MS-MS). The LOQ and LOD for the method were 0.01 mg/kg and 0.002 mg/kg respectively. Recoveries of metamitron in apple fruit were within acceptable limits.

Animal commodities

Meat, liver, kidney, egg and milk was extracted with acetone. For liquid-liquid partition sodium chloride and ethyl acetate/cyclohexane were added and after repeated mixing the phases were separated. The evaporated residue of an aliquot of the organic phase was cleaned up by gel permeation chromatography (GPC). Fat specimens were directly dissolved using a mixture of ethyl acetate/cyclohexane and cleaned up by GPC. An aliquot of the purified extract was dissolved in acetonitrile acidified with acetic acid, and analysed by LC-MS/MS for residues of metamitron. The limit of quantification (LOQ) for metamitron meat, fat, liver, kidney, milk and egg was established at 0.05 mg/kg with an estimated limit of detection (LOD) of 0.015 mg/kg. Recoveries of metamitron were within acceptable limits.

4.3 Residue definition

A metabolism study for apples indicates that both parent metamitron and desamino-metamitron (DAM) can be significant components of the total residue in immature and mature apples. In European residue studies in which metamitron and DAM were measured demonstrates that levels of parent were significantly higher than DAM in immature apples and where finite residues were observed in mature apples, parent residues concentrations were equal to or greater than DAM. The majority of residue trials however demonstrate that residues of parent metamitron and DAM were <LOQ in mature apples. The toxicological assessment of metamitron and its metabolites did not identify a toxicological reason for the inclusion of DAM into the residue definition.

Based on the metabolism studies in plant (apples) and animals (rat and goat), the results of the residue trials in apples, the negligible expected exposure of metamitron to livestock, and the toxicological assessment of metamitron and its metabolites, it is concluded that the residue definition for commodities of plant and animal origin be parent metamitron for both the enforcement and dietary risk assessment. The residue definition for plant or animal commodities may be subject to change in the future should additional use patterns warrant a change.

4.4 Residue trials

The proposed use of metamitron in apples involves a single application at 165 – 330 g ai/ha per season or two applications made at the rate of 165g ai/ha each per season with a minimum re-treatment interval of 5 days. The Harvest withholding period is 'Not required when used as directed', and the 'DO NOT apply after the 16 mm stage' label statement applies.

At commercial harvest, residues of metamitron (parent) in apples (n=3 Australian and n=22 European) and pears (n=2 Australian) following 2 foliar applications administered at rates ranging from 323 – 438 g ai/ha (~0.98-1.37× the maximum proposed rate for one application) were <0.01 (LOQ) (n=26) and 0.01 (n=1) mg/kg. Based on the available information, an MRL of 0.01 mg/kg for metamitron on apples (FP 0226) is recommended for the proposed use.

It is noted that the data utilised for MRL setting purposes is conservative as trials involved 2 applications at 330 g ai/ha for the 5 Australian trials and 2 applications at 405 g ai/ha for the 21 European trials whereas the proposed use in Australia on apples involves one application at 330 g ai/ha or 2 applications at 165 g ai/ha. It is also noted that in the 5 Australian trials, metamitron residues were <LOD (0.002 mg/kg) following two applications at 660 g ai/ha.

4.5 Animal commodities and MRLs

Apple pomace is considered an animal feed commodity for mammalian livestock, however residues of metamitron above the LOQ (0.01 mg/kg) are not expected in apples or apple pomace as a result of the proposed use. The grazing restraint "DO NOT allow livestock to graze inter-rows in orchards treated" will apply. The exposure of metamitron to livestock is not expected from the proposed use on apples.

It is recommended that LOQ MRLs at *0.05 mg/kg for edible offal (mammalian), meat (mammalian) and milks at *0.05 mg/kg be established.

4.6 Fat solubility and potential for bioaccumulation

For metamitron, the Log P_{ow} = 0.96 at ambient temperature, Log P_{ow} = 0.85 at 21 °C indicating a low potential for bioaccumulation.

4.7 Spray drift

The product will be applied by ground application only. Based on the estimated residues in pasture downwind from the application area from airblast application, the available animal metabolism information and spray drift modelling for composite orchards, a no-spray zones of 80 m is required for the protection of international trade.

4.8 Dietary risk assessment

The chronic dietary exposure to metamitron is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived primarily from the 2011-12 National Nutritional and Physical Activity Survey. The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for metamitron is equivalent to <5% of the ADI. It is concluded that the chronic dietary exposure to metamitron is acceptable.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. The highest acute dietary intake was estimated at <5% of the ARfD. It is concluded that the acute dietary exposure is acceptable.

4.9 Recommendations

The following amendments are recommended to the MRL Standard:

Table 1

COMPOUND		FOOD	MRL (mg/kg)
ADD:			
Metamitron			
FP	0226	Apple	0.01
MO	0105	Edible offal (Mammalian)	*0.05
MM	0095	Meat [Mammalian]	*0.05
ML	0106	Milks	*0.05

Table 3

COMPOUND	RESIDUE
ADD:	
Metamitron	Metamitron

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Apples as well as meat and dairy products from animals that have been fed apple pomace containing residues arising from the use of metamitron may be exported[2].

5.2 Destination and value of exports

Australian exports of apples totalled 5 kt (value $13 million[3]) in 2016/17. The major export markets[4] for apples are the UK, Thailand, Indonesia, Malaysia, Singapore, Hong Kong, Papua New Guinea and UAE. The major destination for pear exports are Indonesia, Hong Kong, Malaysia, New Zealand, Singapore, Vietnam, Canada, Papua New Guinea, Thailand, New Caledonia, Fiji and French Polynesia.

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

5.3 Comparison of Australian MRLs with Codex and overseas MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex MRLs have not been established for metamitron. However, EU has established the following relevant MRLs for metamitron:

COMMODITIES	METAMITRON (EU[5] MRLS, MG/KG)	METAMITRON (PROPOSED AUSTRALIAN MRLS, MG/KG)
Pome fruits		
Apples	0.1*	0.01

[2] https://apvma.gov.au/node/1017#major_export_food_commodity_groups

[3] http://www.agriculture.gov.au/abares/research-topics/agricultural-commodities/report

[4] https://horticulture.com.au/wp-content/uploads/2017/07/Q1_2017_Apple-and-pear-trade-intelligence-report.pdf

[5] http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.detail&language=EN&selectedID=1558

COMMODITIES	METAMITRON (EU[5] MRLS, MG/KG)	METAMITRON (PROPOSED AUSTRALIAN MRLS, MG/KG)
Pears	0.1*	
Others	0.1*	
PRODUCTS OF ANIMAL ORIGIN -TERRESTRIAL ANIMALS		
Muscle	0.05*	
Fat tissue	0.05*	*0.05
Liver	0.05*	
Kidney	0.05*	*0.05
Milk	0.05*	*0.05

5.4 Potential risk to trade

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

Metamitron MRLs have not been established in the Codex or in key international markets. EU has established metamitron MRLs on various commodities including apple at 0.1 mg/kg. The proposed Australian MRL on apples is 0.01 mg/kg (at the LOQ). In 5 Australian trials, metamitron residues were <LOD (0.002 mg/kg) in mature apples following application at 1x and 2x the maximum proposed seasonal rate. The risk to trade for apples is considered to be low.

The proposed MRL on mammalian commodities are at the LOQs (*0.05 mg/kg). Finite residues of metamitron are not expected in mammalian animal commodities that may be fed apple pomace derived from treated apples, thus the potential risk to trade in animal commodities is considered to be low.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Summary

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

Brevis Fruit Thinner is considered to have moderate acute oral toxicity, low acute dermal toxicity and low acute inhalation toxicity, it is considered to be a severe eye irritant, but non-irritant and non-sensitising to the skin. Based on the use pattern and this acute hazard profile, workers handling and preparing the product will need to wear eye protection.

In the absence of exposure monitoring data from persons preparing and applying Brevis Fruit Thinner under field conditions, dermal and inhalation exposures were estimated using the US EPA Pesticide Handler Exposure Database (PHED). The assessment indicated an acceptable margin of exposure (MOE) of greater than 100 for mixer / loaders preparing the product without wearing additional protective equipment. There were also acceptable MOEs for spray operators using airblast sprayers without wearing protective equipment.

Using the US EPA Re-Entry Interval Calculator, acceptable MOEs to foliar residues of metamitron were also determined for workers performing agricultural activities in treated crops on or after the day of application. The only risk management measure required to protect workers re-entering treated areas is a label statement directing them not to enter treated crops until the spray has dried. As Brevis Fruit Thinner is only intended for professional use in apple orchards, public exposure to the product is not likely to occur.

Based on the hazard, exposure and risk assessments for mixer / loaders, applicators and workers re-entering treated areas, First Aid Instructions and Safety Directions have been recommended for inclusion on the product label. With these risk mitigation measures in place, it was considered that there should be no adverse effects on workplace health and safety from the use of Brevis Fruit Thinner in accordance with the label directions.

6.2 Health hazards

Exposure during use

Farmers, agricultural workers and professional spray applicators will be the main users of Brevis Fruit Thinner. Workers may be exposed to the product when opening containers; pouring, diluting or mixing the product; and cleaning up spills and equipment. Exposure to metamitron in the finished spray mixture may also occur during loading, application and equipment clean-up or maintenance. The main potential route of

exposure is the skin, with some further potential for eye contact. Additional exposure via inhalation of respirable aerosols could occur during spray application.

Acute toxicological hazards of the product

Brevis Fruit Thinner is considered to have moderate acute oral toxicity (300<LD50<2000 mg/kg bw), low acute dermal toxicity (LD50 > 2000 mg/kg bw) and low acute inhalation toxicity (LC50 > 5100 mg/m3), it is considered to be a severe eye irritant (rabbit study), but non-irritant (rabbit study), and non-sensitising to the skin (mice LLNA).

Based on this hazard profile, workers handling the product are at risk of severe eye irritation, requiring the inclusion of suitable hazard and precaution statements on the product label together with directions to wear a faceshield or goggles when opening containers and preparing the spray mixture. Brevis Fruit Thinner is not expected to be an eye irritant once diluted for use. Therefore, eye protection is not required during application of the product.

Repeat-dose hazards of the active, metamitron

Brevis Fruit Thinner is expected to be applied for pome fruit thinning at an early stage of fruit formation (8-16 mm in diameter). Consequently, occupational exposure to metamitron may be repeated over a limited seasonal period of time. A suitable NOAEL for the assessment of occupational exposure was therefore chosen from among the available metamitron repeat-dose toxicity studies. The selected NOAEL of 50 mg/kg bw/d was established in a 28-day rabbit dermal toxicity study with elevated liver enzymes (AST, ALT) in plasma at the next higher dose of 250 mg/kg bw/d. The acceptable margin of exposure (MOE) from the WHS NOAEL was set at 100 to allow for differences when extrapolating between and within species.

6.3 Exposure

Exposure during mixing, loading and application

In the absence of exposure monitoring studies on workers preparing and applying Brevis Fruit Thinner, dermal and inhalation exposure to metamitron was estimated using the US EPA Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998). The assessment indicated an acceptable MOE of greater than 100 for workers, during open mixing and loading of Brevis Fruit Thinner without wearing additional protective equipment. There were also acceptable MOEs for application by airblast without the use of personal protective equipment (PPE). Therefore, PPE is not required during application of the product.

Exposure during re-entry to treated crops

In addition to becoming exposed to pesticides during their preparation for use and application, agricultural workers may also experience exposure to pesticide residues when re-entering previously treated crops to perform activities such as weeding, training, harvesting, scouting for pests and irrigation. The principal route of exposure is via the skin, through direct contact with contaminated foliage. Re-entry workers' exposure to foliar residues of metamitron were estimated using the US EPA Re-Entry Interval Calculator (March, 2013),

covering all re-entry activities in the crop group nominated by the applicant. The assessment included exposures after application of metamitron at the maximum label rate specified for the crop.

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

Exposure of bystanders and the public

As Brevis Fruit Thinner is only intended for use in apple orchards by professional horticulturalists and spray operators, public exposure to the product is not likely to occur.

Recommendations for safe use

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

First aid instructions

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

Safety directions

Harmful if swallowed. Will damage the eyes. Avoid contact with eyes. If product in eyes, wash it out immediately with water. When opening the container and preparing the spray, wear faceshield or goggles. Wash hands after use. After each day's use, wash faceshield or goggles.

Re-entry statement

DO NOT allow entry into treated areas until spray has dried.

6.4 Conclusions

The registration of Brevis Fruit Thinner, containing 150g/kg metamitron, for fruit thinning in pome fruit as proposed in the directions for use is supported. The product can be used safely if handled in accordance with the instructions on the product label.

7 ENVIRONMENTAL ASSESSMENT

A full data package on the environmental fate and ecotoxicity of metamitron and the formulated product Brevis Fruit Thinner was submitted by the applicant. These studies have been previously assessed by the European Union. The European assessments have been used to assist in the assessment of risks specific to the Australian environment.

7.1 Fate and behaviour in soil

Metamitron is considered to be readily degradable in soil. DT_{50} values ranged 2.2-44 days (geometric mean 19) under aerobic laboratory conditions and 6.6-22 days (geometric mean 11) under field conditions. Photolysis is not expected to be a significant route of degradation of metamitron in the soil. Batch adsorption and column leaching studies indicate metamitron is expected to be moderately mobile in soil. The K_f values ranged 0.36-5.9 mL/g (arithmetic mean 1.4) and the K_{foc} values ranged 22-392 mL/g (arithmetic mean 122). Information on ground water monitoring in the Netherlands indicated that metamitron has potential to reach groundwater under vulnerable soils conditions.

The proposed degradation pathway of metamitron in soil is presented in Figure 1. Desamino-metamitron was a major soil metabolite occurring at a maximum of 17% AR and is considered to be fairly degradable in soil. DT_{50} values ranged 23-45 days (geometric mean 30) under aerobic laboratory conditions and 17- 40 days (geometric mean 31) under field conditions. Batch adsorptions and column leaching studies indicate desamino-metamitron is expected to be mobile in soil. The K_f values ranged 0.80-2.5 mL/g (arithmetic mean 1.7) and the K_{foc} values ranged 66-139 mL/g (arithmetic mean 62).

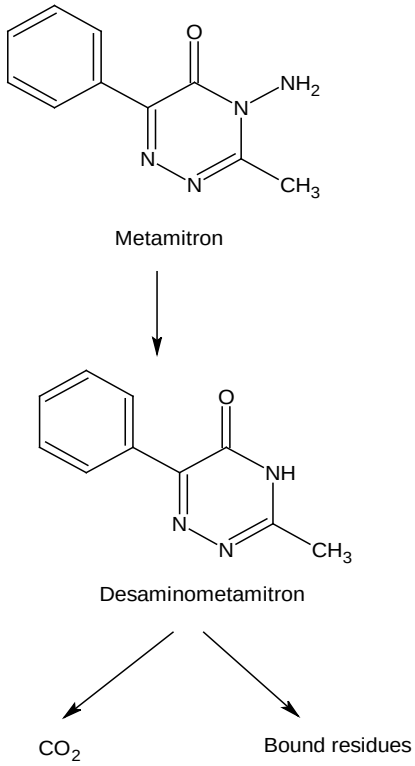


Figure 1 Proposed degradation pathway of metamitron in soil

7.2 Fate and behaviour in water

Metamitron is moderately soluble in water and is considered to be fairly degradable in aquatic systems based on DT_{50} values ranging 11-49 days (geometric mean 20). Hydrolysis is expected to play a minor role in its degradation when compared to competing processes such as photolysis, biodegradation and partitioning to sediment, but could be significant in higher pH water bodies. Photodegradation may be a significant route of degradation under field conditions, particularly close to the surface of natural water bodies where indirect photolysis may be significant due to the presence of photosensitizers.

Desamino-metamitron was the only major aquatic metabolite which peaked at 28% in the sediment and 54% in the water. Desamino-metamitron is slightly soluble in water and is considered to be readily degradable in aquatic systems based on the DT_{50} value of 11 days. Photolysis is not expected to be a significant route of degradation of desamino-metamitron in aquatic systems.

7.3 Fate and behaviour in air

Based on their vapour pressures, metamitron and its major metabolite desamino-metamitron are considered to be very slightly volatile, indicating losses from soil and water surfaces due to volatilisation are expected to

be minimal. Based on its predicted photochemical oxidative DT_{50} of 20 hours, any metamitron that does volatilise into the air would be unlikely to be subject to long range atmospheric transport.

7.4 Risk to terrestrial vertebrates

The acute LD_{50} for mammals was 644 mg ac/kg bw for metamitron. Ecologically relevant effects (ie, reduction in parental and pup weight) following long-term dietary exposure were observed in mammals at 97 mg ac/kg bw/d (NOAEL 36 mg ac/kg bw/d).

The acute LD_{50} and short-term LD_{50} values for birds were 1326 mg ac/kg bw and >904 mg ac/kg bw/d for metamitron, respectively. Reproductive effects (ie, eggshell thinning, reduced number of eggs laid, reduced offspring survival and weight) following long-term dietary exposure were observed in birds at 392 mg ac/kg bw/d (NOAEL 82 mg ac/kg bw/d).

The major potential routes of exposure of terrestrial vertebrates were considered to be feeding on food items (e.g. vegetation and invertebrates) directly contaminated from spray application of the product. The acute and reproductive risk for terrestrial vertebrates following dietary exposure to contaminated food items was assessed using a tiered approach which is in line with current EFSA (2009) guidance. Based on available data and assuming terrestrial vertebrates feed exclusively on dietary items exposed to the treatment at the maximum seasonal rate, the screening level assessment indicated no adverse effects are expected. Therefore, risks of the proposed use of Brevis Fruit Thinner to birds and mammals were considered to be acceptable.

7.5 Risk to aquatic species

Metamitron is considered to be very toxic to aquatic species (specifically algae and aquatic plants). The lowest short-term toxicity values were LC_{50} 194 mg ac/L for fish, EC_{50} 5.7 mg ac/L for aquatic invertebrates, E_rC_{50} 0.82 mg ac/L for algae, and E_rC_{50} 0.45 mg ac/L for aquatic plants. Following long-term exposure to 22 mg ac/L, increased mortality was observed in fish (NOEC 7.0 mg ac/L). Reduced reproductive output was observed in aquatic invertebrates following long-term exposure to 18 mg ac/L (NOEC 10 mg ac/L). Bioconcentration is not expected since the log K_{ow} of metamitron is <3. The major metabolite, desamino-metamitron, was less toxic than the parent for all of the taxonomic groups assessed.

The major potential routes of exposure of aquatic species are considered to be spray drift or runoff from the treatment area. The acute and chronic risks to aquatic species are assessed using a tiered approach which is in line with current EPHC (2009) guidance. Although the product is not applied to water, a screening level risk assessment assumes the worst-case scenario of a direct overspray of shallow aquatic habitat in order to identify those substances and associated uses that do not pose a risk to aquatic species. A screening level assessment for the proposed use of Brevis Fruit Thinner indicates no adverse effects are expected for fish or aquatic invertebrates.

An outdoor microcosm study performed in the Netherlands was available to consider the toxicity of metamitron to algae and aquatic plants under realistic conditions. Pronounced effects on oxygen and pH levels at 4.5 mg ac/L were considered to be ecologically relevant (NOEAEC 1.1 mg ac/L). An assessment

factor of 3 was applied to the NOEAEC to derive the regulatory acceptable concentration of 0.37 mg ac/L in aquatic systems. Considering the higher tier endpoint based on the microcosm study, risks to algae and aquatic plants were determined to be acceptable at the screening level (ie, assuming direct overspray). As a result, no mitigation measures are required for the protection of aquatic species.

7.6 Risk to bees

Acute oral and contact toxicity studies were conducted with metamitron and its representative SC and SG formulation. The formulated products did not appear to modify the toxicity of metamitron. The contact LD_{50} was >200 µg ac/bee and the oral LD_{50} was 123 µg ac/bee. The oral NOEL was 70 µg ac/bee which was the highest dose with acceptable mortality. This value was used as a surrogate for chronic dietary toxicity. The oral toxicity values for the adult bees were also used as surrogate for larvae.

Bees could be directly exposed to metamitron residues when visiting over-sprayed plants in bloom during or after treatment. Although apple crops are not expected to be in bloom during treatment (applied to full canopy at BBCH 69-72), weeds or plants within or adjacent to the treatment area could be in bloom at the time of application. Residues in pollen and nectar are not expected when application occurs outside of the blooming period because metamitron is translocated acropetally (upward) via the xylem for which residues tend to accumulate in the outer tissue of the plant.

The acute and chronic risks to bees are assessed using a tiered approach which is in line with current APVMA (2017) guidance. A screening level risk assessment assumes the worst-case scenario of a direct overspray of blooming plants that are frequented by bees in order to identify those substances and associated uses that do not pose a risk. A screening level assessment for the proposed use of Brevis Fruit Thinner indicates no adverse effects are expected. Therefore, risks of the proposed use of Brevis Fruit Thinner to adult bees and larvae are considered to be acceptable.

7.7 Risk to other non-target arthropods

The standard test species for beneficial arthropods are *Aphidius rhopalosiphi* (a parasitoid hymenopteran insect) and *Typhlodromus pyri* (a predatory phytoseiid mite). These standard indicator species have been shown to be relatively sensitive and representative of non-target arthropods in a comparative study of arthropods of nine families exposed to 95 plant protection products (Candolfi et al. 1999) and are therefore suitable as indicator species for this group of terrestrial non-target arthropods.

Standard laboratory tests on an inert (glass) substrate were conducted with an SC formulation and the indicator species (LR_{50} and ER_{50} values >14,700 g ac/ha for both species). Extended laboratory tests on natural (plants/leaves) substrates were also conducted with the same indicator species using the proposed SG formulation (LR_{50} and ER_{50} values >810 g ac/ha for both species). In addition, laboratory tests were conducted with ground-dwelling (*Pardosa* spp.) and foliar dwelling (*Coccinella septempunctata*) predatory arthropods (LR_{50} and ER_{50} values >3500 g ac/ha for both species). The results of the tests indicate that

predatory and parasitic arthropods are not sensitive to fresh-dried residues of metamitron at exaggerated rates.

A screening level risk assessment assumes the non-target arthropods are exposed to fresh-dried residues within the treatment area immediately after application. A screening level assessment for the proposed use of *Brevis* indicates no adverse effects are expected. Therefore, risks of the proposed use of Brevis Fruit Thinner to predatory and parasitic arthropods are considered to be acceptable.

7.8 Risk to soil organisms

Acute toxicity values for earthworms were LC_{50} 914 mg ac/kg dry soil for technical metamitron and LC_{50corr} >500 mg/kg dry soil for the metabolite desamino-metamitron. No adverse effects of metamitron on earthworms were observed following long-term exposure to exaggerated soil concentrations (NOEC 60 mg ac/kg dry soil).

Since the field soil DT_{90} for desamino-metamitron was >100 days, an assessment of the potential effects on another soil macro-organism *Folsomia candida* from the exposure of this metabolite was conducted. A reduced reproductive output was observed at 1000 mg/kg dry soil ($NOEC_{corr}$ 50 mg/kg dry soil).

No effects exceeding 25% on soil respiration and nitrification were observed in tests at exaggerated rates of metamitron (NOEC 20 mg ac/kg dry soil) or desamino-metamitron (NOEC 22 mg/kg dry soil).

Soil organisms could be directly exposed to residues of metamitron in over-sprayed soil within the treatment area. The acute and chronic risks to soil organisms are assessed using a tiered approach which is in line with current EPHC (2009) guidance. A screening level risk assessment assumes the worst-case scenario of a direct overspray of soil without interception in order to identify those substances and associated uses that do not pose a risk to soil organisms. Based on available data, the screening level assessment for the proposed use of Brevis Fruit Thinner indicates no adverse effects on soil organisms are expected. Therefore, risks of the proposed use of Brevis Fruit Thinner to soil organisms are considered to be acceptable.

7.9 Risk to non-target terrestrial plants

Key studies on effects of the representative SG formulation on non-target terrestrial plants were evaluated on ten representative plant species: sugar beet, lettuce, tomato, soybean, oilseed rape, carrot, onion, oats, rye grass and corn. Lettuce was the most sensitive species following pre-emergent exposure (ER_{25} 69 g ac/ha, ER_{50} 121 g ac/ha) and post-emergent exposure (ER_{25} 86 g ac/ha, ER_{50} >405 g ac/ha).

Non-target terrestrial plants adjacent to the treatment area could be directly exposed to spray drift during treatment. Risks to non-target terrestrial plants are assessed using a tiered approach which is in line with current EPHC (2009) guidance. Although non-target plants are defined as non-crop plants located outside the treatment area, screening level risk assessment assumes the worst-case scenario of a direct exposure to the treatment in order to identify those substances and associated uses that do not pose a risk to non-target terrestrial plants. A screening level assessment indicated that pre-emergent exposure was identified as the route of greatest concern that required a spray drift assessment. A regulatory acceptable rate of 12 g ac/ha

for non-target terrestrial plants was derived based on the pre-emergent ER_{50} 121 g ac/ha and an assessment factor of 10. Using the APVMA standard spray drift scenario for 'composite orchards'[6], a mandatory no-spray zone of 25 metres was determined to be appropriate for the protection of non-target terrestrial plants.

7.10 Conclusions

When used according to label directions, Brevis Fruit Thinner is unlikely to have an unintended effect that is harmful to animals, plants or things or to the environment.

[6] https://apvma.gov.au/node/27931

8 EFFICACY AND SAFETY ASSESSMENT

Brevis Fruit Thinner is to be applied to apples during early fruit set to reduce the number of developing fruitlets and help growers to optimise fruit set, size and yield. Brevis Fruit Thinner differs from other thinning agents as it temporarily inhibits photosynthesis. Application rate ranges from 1.1 to 2.2 kg/ha and can be applied as a single application at 1.1 to 2.2 kg/ha; OR as two applications of 1.1 kg/ha with a minimum spray interval of 5 days between applications.

Between 2014 and 2017, eleven field trials were conducted in Australia to evaluate the efficacy and crop safety of Brevis Fruit Thinner in major apple growing regions and on a range of major cultivars. In addition seven overseas trials (New Zealand and Belgium) with a similar proposed use pattern was evaluated. Rates tested ranged from 1.1 to 2.2 kg/ha. All trials were conducted using appropriate field trial designs with randomisation and replication to enable statistical analysis and scientific interpretation of treatment effects, where present.

8.1 Effect on fruit thinning

Differences between the rate and number of applications were significant in a few trials and there were trends in most trials for increased efficacy with an increase in rate and number of applications. The trials showed varied levels of efficacy, however overall there is increased efficacy with Brevis Fruit Thinner compared to the controls though in most instances this was no greater than hand thinning.

Brevis Fruit Thinner performance was in general as good as or better than the standards used in the trials, in particular a registered product containing 500 g/L carbaryl which is currently approved for fruit thinning in pome fruit within Australia.

Brevis Fruit Thinner is applied post-fruit set when the central fruitlet diameter is between 8 mm and 16 mm and is not to be applied later than the 16 mm stage. In some trials the second application was made to fruit greater than 16 mm, in some cases up to 20 mm (BBCH 72). The later timing didn't appear to impact efficacy or safety and overall did not effectively thin fruit. In several trials, single applications of Brevis Fruit Thinner were compared at the early or later timings. Both timings were effective and safe, with some evidence that the earlier application was more efficacious than later. Therefore, if a single application only will be applied at the later timing, growers can use the higher rate to increase the number of fruitlets thinned.

The thinning effect of Brevis Fruit Thinner depends on a range of factors like orchard history, cloud cover (solar radiation), temperatures before/after application etc. A complete list of the factors influencing the efficacy of Brevis Fruit Thinner are provided on the proposed label, based on extensive global and local experience. Considering the Brevis Fruit Thinner label recommends that growers consider these factors before choosing the application rate/regime the proposed application rate is supported.

Trials included two applications, with a spray interval between 5-9 days. In all but two trials there was no significant effect of two applications compared to one with only trends of increased efficacy at two applications compared to one. Trial results indicate that the label instruction to "Maintain an interval of at least 5 days before or after application of *Brevis*®", is appropriate.

All cultivars on the label have been tested in field trials. Most apples showed a positive response to Brevis Fruit Thinner and the data supports the proposed use in Granny Smith, Rubens, Red Delicious, Royal Gala, Pink Lady, Fuji and Envy.

8.2 Crop safety

Across the trials there was some evidence of phytotoxicity on the foliage and fruit but in most cases the damage dissipated by harvest and had no impact on yield. Overall phytotoxicity didn't impact fruit quality or return growth in the following season. Brevis Fruit Thinner caused slight to moderate phytotoxicity two weeks after application which generally dissipated within four weeks of application. Fruit treated with Brevis Fruit Thinner had no more skin russet at harvest than fruit from untreated trees.

Rates are presented as both per hectare and per 100 L depending on the target water volume. Irrespective of the water volume, the rate recommendations are designed to deliver a specific dose range per hectare. These label statements are supported, in particular for reducing crop phytotixicity.

Use of Brevis Fruit Thinner on apple orchards over 4 years is recommended as most trails were conducted on trees older than four years. The data supports the proposed label statements regarding temperature.

Location did not appear to have an impact on safety or efficacy and an all-states registration is justified by the supporting data.

8.3 Conclusions

Brevis Fruit Thinner when used as directed is expected to provide effective fruit thinning in apples and acceptable levels of crop safety when used as directed.

9 LABELLING REQUIREMENTS

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

BREVIS®
FRUIT THINNER

ACTIVE INGREDIENT: 150 g/kg METAMITRON

Crop: ***Apples***

Uses: ***Fruit thinning***

adama.com Net contents: 1 - 20 Kg

RESTRAINTS
DO NOT apply more than two applications of BREVIS® per season or more than 2.2 kg per hectare, per growing season.
DO NOT apply later than 16 mm stage of central fruitlet.
DO NOT apply by aircraft. Apply only by ground based application methods.
DO NOT use on trees to be used for propagation.
DO NOT apply herbicides that have the potential to volatilise and be taken up by foliage in the 7 days before or after BREVIS® application.
DO NOT apply to wet foliage e.g. early in the morning after a dew or shortly after rain.
DO NOT apply within 5 days of a frost or when frost is expected.
DO NOT allow drift onto non-target crops, especially stone fruit as drift may cause scorching of the foliage.

SPRAY DRIFT RESTRAINTS
DO NOT apply when wind speed is less than 3 or more than 20 kilometres per hour, as measured at the application site.
DO NOT apply during surface temperature inversion conditions at the application site.

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

Users of this product **MUST make an accurate written record** of the details of each spray application within 24 hours following application, and must KEEP this record for at least 2 years. The spray application details that must be recorded are:
1. date with start and finish times of application **2.** location address and paddock(s) sprayed **3**. full name of this product **4**. amount of product used per hectare and number of hectares applied to **5**. crop or situation and weed or pest **6**. wind speed and direction during application **7**. air temperature and relative humidity during application **8.** nozzle brand, type, spray angle, nozzle capacity and spray system pressure measured during application **9.** name and address of person applying this product. (Additional record details may be required by the state or territory where this product is used.)

MANDATORY NO-SPRAY ZONES

No-spray zones for protection of the terrestrial environment:

DO NOT apply if there are sensitive crops, gardens, landscaping vegetation, protected native vegetation or protected animal habitat within **25 metres** downwind from the application area.

No-spray Zones for Protection of International Trade of animal commodities:

DO NOT apply if there are livestock, pasture or any land that is producing feed for livestock downwind from the application area and within **80 meters** downwind from the application area.

DIRECTIONS FOR USE

BREVIS® is a photosynthesis inhibitor for use on apple trees. BREVIS® is applied post-fruit set to thin excess fruitlets and assist with optimising fruit load and fruit size.
It is recommended to apply BREVIS® only to well-maintained orchards with adequate pest and disease control and good irrigation and nutrition.

BREVIS® is a photosynthesis inhibitor and factors influencing photosynthesis can impact the thinning effect. These factors need to be considered when deciding the appropriate application rate, number of applications and timing of the application.

Table 1. Factors increasing the activity/thinning effect of BREVIS®

PARAMETER	COMMENTS
Application of: • Oil based products such as summer oils, adjuvants and crop protection products that contain oils (e.g. Penthiopyrad) • Other fruit thinners, applied either before/after or in a tank mix with BREVIS®.	For oil-based products, maintain an interval of at least 7 days before or after application of BREVIS®. Other fruit thinners: refer to the "Other Fruit Thinning Products" section in the General Instructions.
Warm night-time temperatures (>10° C) the week prior to and post application. Reduction in sunlight/light intensity (e.g. Cloud cover or overcast conditions, hail nets, etc.). The use of hail nets may increase the effectiveness of BREVIS® due to reductions in solar radiation and the existence of a microclimate.	Application should be postponed if trees are under stress e.g. after a period of cloudy weather, high day and/or unusually high night temperatures, drought, hail damage etc.; or when a stressful period is expected. If conditions favour over-thinning, postpone application or decrease the application rate and/or reconsider the need for a second application.
Orchard Management: Cultivars and clones respond differently to fruit thinning agents. Not all cultivars/clones have been tested for crop safety under all environmental conditions and growing circumstances. In addition to seasonal weather conditions occurring prior to and after flowering, other factors can play an important role in the response to chemical thinning agents including: • Tree age • Training systems • Rootstock • Tree vigour • Stress on trees • Orchard cropping history/orchard management practices • Other thinning sprays/plant growth regulators applied to the block In orchards with vigorous growth, the activity of BREVIS® may be increased due to competition for photosynthates between the vegetation itself and the fruits. Strong and vigorous trees generally respond more to chemical fruit thinning.	DO NOT use on areas with a history of poor or variable fruit set or poor fruit retention or on trees with poor tree health/under stress e.g. frost damage, water stress, heat stress. DO NOT apply higher rates on varieties or trees with a history of issues with poor fruit retention or over-thinning responses to other thinning products. Use of BREVIS® on young apple orchards under 4 years is not recommended. Caution must be exercised when using the product for the first time or on new areas or blocks, to avoid over-thinning the crop. If the block history is unknown or there is a history of variable responses to fruit thinners, evaluate BREVIS® before commercially treating whole blocks by applying only to a small trial section within each block for 1-2 years.

Table 2. Apples

Before applying BREVIS®, refer to **Table 1** for critical information about factors increasing the thinning effect of BREVIS®. Growers should consider all factors and orchard history before selecting the rate and the number of applications. If the block history is unknown or there is a history of variable responses to fruit thinners, evaluate BREVIS® by applying only to a small trial section within each block for 1-2 years before commercially treating whole blocks.

<table>
<tr><th>CULTIVARS</th><th>RATE</th><th>CRITICAL COMMENTS</th></tr>
<tr><td>Granny Smith,
Rubens,
Red Delicious,
Royal Gala,
Pink Lady,
Fuji,
Envy</td><td>1.1 to 2.2 kg/ha</td><td>
Timing of application:
BREVIS® should be applied when the diameter of the central fruitlets is 8-16 mm. DO NOT apply later than the 16 mm stage.

For best results, apply BREVIS® when daily temperatures range between 10°C and 25°C. If weather conditions prior to application are outside the recommended range and trees are under stress, postpone application until conditions are more suitable for applying BREVIS®.

Refer to Table 1 for factors increasing the effect of BREVIS® or causing tree stress.

Application rate:
BREVIS® can be applied up to a maximum of 2.2 kg/ha per season according to either of the following spray programs:
1. A single application at 1.1 to 2.2 kg/ha; OR
2. Two applications of 1.1 kg/ha
A single spray program of BREVIS® can be used for greater flexibility of application timing depending on crop and weather conditions. Use the lower rate to thin fewer fruitlets, and on easy to thin cultivars. Use the higher rate to increase thinning, on normal to thin cultivars and/or when applying later in the BREVIS® application window.

Apply BREVIS® as two applications of 1.1 kg/ha where the cultivar can be easily thinned by the higher rate of BREVIS®. When applying BREVIS® as a two spray program, use a minimum interval of 5 days between applications.

DO NOT apply more than 2.2 kg/ha of BREVIS® per season.

In certain situations such as heavy fruit set, hard to thin varieties and/or growing conditions not conducive to chemical thinning; hand-thinning may be required after the maximum seasonal rate of BREVIS® has been applied to the crop, to achieve the desired fruit size range/yield.

Spray application:
Apply in sufficient water volume to give good coverage. DO NOT apply past the point of runoff. The rate applied must be based on the target rate per hectare as listed above. The following application guide table can assist to convert the rate per hectare to a rate per 100 L for a range of target spray volumes.

Application guide for BREVIS®:
<table>
<tr><th>Rate
(kg/ha)</th><th>Water volume
(L/ha)</th><th>Rate
(g/100 L)</th></tr>
<tr><td rowspan="3">1.1</td><td>1000</td><td>110</td></tr>
<tr><td>1500</td><td>73</td></tr>
<tr><td>2000</td><td>55</td></tr>
<tr><td rowspan="3">2.2</td><td>1000</td><td>220</td></tr>
<tr><td>1500</td><td>147</td></tr>
<tr><td>2000</td><td>110</td></tr>
<tr><td colspan="3">DO NOT apply using concentrate spray volumes exceeding 220 g of BREVIS® per 100 L water.</td></tr>
</table>
</td></tr>
</table>

Table 2. Apples (continued)

Before applying BREVIS®, refer to **Table 1** for critical information about factors increasing the thinning effect of BREVIS®. Growers should consider all factors and orchard history before selecting the rate and the number of applications. If the block history is unknown or there is a history of variable responses to fruit thinners, evaluate BREVIS® by applying only to a small trial section within each block for 1-2 years before commercially treating whole blocks.		
CULTIVARS	**RATE**	**CRITICAL COMMENTS**
Granny Smith, Rubens, Red Delicious, Royal Gala, Pink Lady, Fuji, Envy	1.1 to 2.2 kg/ha	**Cultivar** The thinning effect of BREVIS® can vary by cultivar and the efficacy has not been tested on all cultivars. For advice on the use of BREVIS® by cultivar, contact your local ADAMA representative. **Crop Safety** BREVIS® can cause minor chlorotic/necrotic areas on leaves and some minor leaf drop. The leaf effects from BREVIS® applications had no impact on crop development or fruit yield/quality on any of the apple cultivars tested. However, BREVIS® has not been tested on all cultivars. For advice on the crop safety of BREVIS® by cultivar, contact your local ADAMA representative.

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

WITHHOLDING PERIODS
HARVEST: **NOT REQUIRED WHEN USED AS DIRECTED.**
GRAZING: **DO NOT ALLOW LIVESTOCK TO GRAZE INTER-ROWS IN ORCHARDS TREATED WITH BREVIS®.**

GENERAL INSTRUCTIONS

Mixing

Ensure the sprayer is clean and in good working order. Calibrate as per the sprayer manufacturer's recommendations.

Half fill the spray tank with clean water and begin agitation. Continue to fill the spray tank and slowly add the required quantity of BREVIS®. Triple rinse empty container and add rinsate to the spray tank. Continue agitation until spraying is complete.

Do not leave the sprayer standing with the spray mixture in it for prolonged periods.

Application

Ensure even and thorough coverage of foliage. BREVIS® has a thinning effect only on the treated parts of the trees and should only be applied to the parts of the crop canopy that require thinning. Application should be made using appropriate spray equipment and sufficient water to provide adequate penetration and coverage. Equipment setting and water volume may need to vary, depending on the tree height and canopy. See *Application rate guide for BREVIS®* section in **Table 2**, for water volume and corresponding rates for BREVIS®. Take care not to overlap sprays during application.

BREVIS® is rainfast in 2 hours for up to 10 mm of rainfall. Heavier rainfall after application may reduce the foliar uptake of BREVIS®. If >10 mm rainfall is forecast but will only marginally exceed 10 mm i.e. by ≤10 mm; use an 8 hour rainfastness interval. If heavier rainfall or prolonged cloudy/rainy conditions are forecast, it may be necessary to postpone application. Before application, review the recommendations in Tables 1 and 2 regarding weather conditions, light intensity and over-thinning risk.

Other Fruit Thinning Products

The use of BREVIS® in conjunction with other fruit thinners (primary or secondary thinners) has not been thoroughly evaluated under local conditions. Application of other thinners in conjunction with BREVIS® may impact the efficacy and/or crop safety. Adama Australia does not recommend tank-mixing BREVIS® with other fruit thinners.

Cleaning Spray Equipment
After using BREVIS®, empty the tank completely and drain the entire system clear of waterways and susceptible vegetation. Thoroughly wash out the spray tank using a minimum of 3 rinse cycles. Drain the tank and clean any tank, pump, line and nozzle filters.

Wetting Agents/Surfactants
The addition of a wetting agent/surfactant is not recommended.

Compatibility
BREVIS® should NOT be applied in a tank mix with other products.

RE-ENTRY
DO NOT allow entry into treated areas until the spray has dried.

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

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. This container can be recycled if it is clean, dry, free of visible residues and has the *drumMUSTER* logo visible. Triple-rinse container for disposal. Wash outside of the container and the cap. Store cleaned container in a sheltered place with cap removed. It will then be acceptable for recycling at any *drumMUSTER* collection or similar container management program site. The cap should not be replaced, but may be taken separately.
If not recycling, break, crush, or puncture and deliver empty packaging to an approved waste management facility. If an approved waste management facility is not available, bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose, clear of waterways, desirable vegetation and tree roots, in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product.

SAFETY DIRECTIONS
Harmful if swallowed. Will damage the eyes. Avoid contact with eyes. If product in eyes, wash it out immediately with water. When opening the container and preparing the spray, wear face shield or googles. Wash hands after use. After each day's use, wash face shield or googles.

FIRST AID
If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26.

SDS
A Safety Data Sheet (SDS) for this product is available at adama.com or from ADAMA Australia on request. Call Customer Service on 1800 423 262.

CONDITIONS OF SALE

The use of BREVIS® being beyond the control of the manufacturer, no warranty expressed or implied is given by ADAMA Australia regarding its suitability, fitness or efficiency for any purposes for which it is used by the buyer, whether in accordance with the Directions for Use or not. ADAMA Australia accepts no responsibility for any consequence whatsoever resulting from the use of this product.

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APVMA Approval No: XXXXX/XXXXX

Batch No.
Date of Manufacture

ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
ESI	Export Slaughter Interval
EUP	End Use Product
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice

h	hour
ha	hectare
Hct	Heamatocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram

NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	repels water
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

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