Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active Fluopyram in the Product Luna Privilege Fungicide

APVMA Product Number 63642

APRIL 2015

ISSN: 1443-1335 (electronic)
ISBN: 978-1-922188-81-6 (electronic)

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

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PREFACE

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

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health, Office of Chemical Safety (OCS), Department of Environment (DE), and State Departments of Primary Industries.

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

The information and technical data required by the APVMA to assess the safety of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined in the APVMA's publications *Ag MORAG: Manual of Requirements and Guidelines* and *Vet MORAG: Manual of Requirements and Guidelines*.

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

About this document

This is a Public Release Summary.

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

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

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

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of luna privilege 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 5 May 2015 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

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

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

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

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

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

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

Further information

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

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

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

1 INTRODUCTION

1.1 Purpose of application

Bayer CropScience Pty Ltd has applied to the APVMA for registration of the new product Luna Privilege Fungicide containing the new active constituent fluopyram (500 g/L) as a suspension concentrate formulation. This submission has been assessed under a joint review arrangement where registrations for the same formulation and similar uses have been submitted concurrently in Australia, Canada, Germany and the USA.

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

1.2 Mode of Action

Fluopyram is a broad-spectrum fungicide of the pyridinyl-ethyl-benzamides ('pyramide') group with preventative, systemic and curative properties for the control of certain crop diseases. The mode of action is a succinate dehydrogenase inhibitor within the fungal mitochondrial respiration chain, having penetrant and translaminar properties, and also translocated in xylem. For crop protection purposes Luna Privilege Fungicide is best suited for use in a preventative treatment program. For resistance management purposes fluopyram is included in the Fungicide Resistance Action Committee (FRAC) Group 7 Fungicides group.

1.3 Product Claims and usepattern

Luna Privilege Fungicide (the product) is intended for control of botrytis bunch rot and powdery mildew in grapes for dried fruit production and in table grapes. The product is intended to be used at a rate of 15 mL/100 L water (dilute spraying) for control of powdery mildew and at a rate of 40 mL/100 L water (dilute spraying) for control of botrytis bunch rot.

For application, the product may be applied using dilute or concentrate spraying methods using vineyard spraying equipment and is approved for ground application only.

1.4 Overseas registrations

Products containing fluopyram are currently registered overseas including in Canada, the European Union (EU), New Zealand and the USA. Fluopyram is also registered overseas in various co-formulations with other fungicides such as tebuconazole, prothioconazole, pyrimethanil and trifloxystrobin.

2 CHEMISTRY AND MANUFACTURE

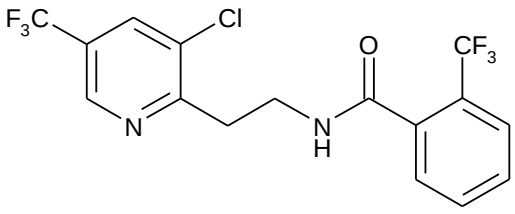
2.1 Active Constituent

Fluopyram is a new active constituent to be used as a fungicide in grapes. Fluopyram belongs to the chemical class pyridinyl ethylbenzamides (also known as pyramides).

Manufacturing Site

The active constituent fluopyram is manufactured by Bayer CropScience AG at Alte Heerstrasse, D-41538 Dormagen, Germany.

Chemical Characteristics of the Active Constituent

COMMON NAME:	Fluopyram (ISO, AS approved)
IUPAC NAME:	*N*-{2-[3-chloro-5-(trifluoromethyl)-2-pyridyl]ethyl}-α,α,α-trifluoro-o-toluamide
CAS NAME:	*N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl)benzamide
CAS REGISTRY NUMBER:	658066-35-4
MINIMUM PURITY:	960 g/kg
MOLECULAR FORMULA:	$C_{16}H_{11}ClF_6N_2O$
MOLECULAR WEIGHT:	396.72
STRUCTURE:	

APVMA Active Constituent Standard for Fluopyram

CONSTITUENT	SPECIFICATION	LEVEL
Fluopyram	**Fluopyram**	**Not less than 960 g/kg**

Physical and Chemical Characteristics of Pure Active Constituent

COLOUR:	White colourless
ODOUR:	No characteristic odour
PHYSICAL STATE:	Powder
MELTING POINT:	117.5 °C
RELATIVE DENSITY (20^{O}C):	1.53 g/cm^{3}
VAPOUR PRESSURE (20^{O}C):	1.2 x 10^{-6} Pa
FLAMMABILITY:	Not highly flammable, No self-ignition up to 400 °C
EXPLOSIVE PROPERTIES:	Not explosive
OXIDISING PROPERTIES:	Not an oxidizing agent
DANGEROUS GOODS CLASSIFICATION:	Not a dangerous goods according to ADG Code

2.2 Formulated Product

The product Luna Privilege Fungicide will be packaged and marketed in 1 to 100 L HDPE containers.

Physical and Chemical Properties of Formulated Product

FORMULATION TYPE:	Suspension concentrate
APPEARANCE:	Beige suspension
ACTIVE CONSTITUENT CONCENTRATION:	500 g/L fluopyram
PH OF A 1% AQUEOUS DILUTION:	6.1
RELATIVE DENSITY (20^{O}C):	1.205 g/cm^{3}
SURFACE TENSION (25^{O}C):	35 nM/mL
SAFETY PROPERTIES:	Not corrosive, flammable or explosive

2.3 Conclusion

The APVMA is satisfied that the chemistry and manufacture data requirements necessary for the registration of Luna Privilege Fungicide and approval of its active constituent, fluopyram, have been met.

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

Fluopyram is a member of the chemical class of pyridylethylamides. It is also identified as a member of the benzamide and pyridine class of fungicides. Its mode of action relies on the inhibition of succinate dehydrogenase within the fungal mitochondrial respiration chain. The proposed use of the product Luna Privilege Fungicide containing 500 g/L fluopyram is for the outdoor control of various fungal diseases in grapes. Luna Privilege Fungicide is not intended for domestic use. Luna Privilege Fungicide will be available in HDPE bottles of 1 to 100 L.

Fluopyram was quickly adsorbed and 90% of the administered dose was excreted within 168 hours. There was evidence of significant enterohepatic circulation. Only minor sex specific effects in toxicokinetics have been observed although systemic exposure was higher and enterohepatic circulation more pronounced in females. An analysis of metabolism revealed a number of metabolites. There were no significant gender differences in metabolic profiles.

Based on the findings of the acute toxicological studies evaluated, fluopyram is of low acute oral, dermal, and inhalation toxicity in rats, is not a skin or eye irritant in rabbits, and is not a skin sensitiser in mice (LLNA).

In short term and subchronic oral studies the liver proved to be the main target organ in rats, mice and dogs. Hepatotoxicity became apparent by a dose-related increase in organ weight, alterations of clinical chemical parameters and histopathological findings such as centrilobular hypertrophy or periportal or midzonal vacuolation or macrovacuolation.

The long-term toxicity and the oncogenic potential of fluopyram were assessed in both the mouse and rat. In both species, the liver, the thyroid and the kidney were the main target organs of chronic toxicity. Carcinogenic effects comprised of liver tumours in female rats and thyroid tumours in male mice but were confined to the highest dose levels in the respective studies. Overall it was considered that mechanistic studies only indicated a likely mode of action (MOA) for fluopyram induced liver tumours in female rats similar to that developed for phenobarbital, and further information is required on the association of fluopyram exposure and aryl hydrocarbon receptor activation and its possible influence on liver tumourigenicity. Consequently, in the absence of such data the relevance of these tumours to humans cannot be entirely dismissed. However, the weight of evidence supports a conclusion that these tumours occurred by a non-genotoxic mechanism in female rats at high doses (89 mg/kg bw/d), and a threshold for the induction of such tumours was identified (i.e. no treatment-related induction of liver tumours occurred in female rats at 8.6 mg/kg bw/d). In contrast, it was considered that the MOA deduced for fluopyram rodent thyroid tumours was not relevant to humans.

An impairment of motor and locomotor activity was seen in an acute neurotoxicity study in rats when fluopyram was administered by oral gavage, while no such findings were observed in a 90–day neurotoxicity study in rats when fluopyram was administered in the diet.

Fluopyram was not an *in vivo* genotoxicant, a reproductive or teratogenic toxicant, and studies on plant metabolites provided no data that indicates that the observed level of these metabolites and their limited toxicity profile presents a toxicological concern.

Based on the findings of the acute toxicological studies evaluated, the product Luna Privilege Fungicide has low acute oral, dermal and inhalational toxicity in rats, is not a skin or eye irritant in rabbits, and is not a skin sensitiser in mice (LLNA).

Based on an assessment of the toxicology, it was considered that there should be no adverse effects on human health from the use of Luna Privilege Fungicide when used in accordance with the label directions.

3.2 Evaluation of Toxicology

The toxicological database for fluopyram, which consists primarily of toxicity studies conducted in rats, mice, rabbits and dogs, is considered sufficient to determine the toxicology profile of fluopyram and characterise the risk to humans. In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species 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.

The toxicology assessment of fluopyram was conducted as part of a Global Joint Review (GJR) by scientists from the EU (Germany as the rapporteur), Health Canada Pest Management Regulatory Agency (PMRA), the United States Environmental Protection Agency (US EPA) and the Office of Chemical Safety (OCS) within the Department of Health. Australian independent toxicology assessments have used the terms of no observed effect level (NOEL) and lowest observed effect level (LOEL). However, since this report relies significantly on the international work share assessment, the OCS adopted the no observed adverse effect level (NOAEL) and low observed adverse effect level (LOAEL) approach using scientific justification for their adoption, which are included within this assessment. Since the GJR assessment additional mechanistic studies have become available to assist in the interpretation of the rodent tumour findings, which OCS have reviewed nationally.

Chemical class

Fluopyram is a member of the chemical class of pyridylethylamides. It is also identified as a member of the benzamide and pyridine class of fungicides. Its mode of action relies on the inhibition of succinate dehydrogenase within the fungal mitochondrial respiration chain.

Toxicokinetics and metabolism

Fluopyram was rapidly absorbed from the gastrointestinal tract of male and female rats. Absorption commenced immediately after oral dosing with absorption half-lives of 0.1–0.5 h. More than 93% of a dose was absorbed. Fluopyram was widely distributed in the body with highest concentrations found in liver, kidney, erythrocytes and adrenals. The majority of the administered dose had been excreted 168 h post dosing with faecal excretion accounting for 47-64% and urinary excretion for 35–45%. Considerable enterohepatic circulation was demonstrated with a high biliary (78.5% within 48 h in males) and low renal excretion in a bile fistulation test. The metabolite patterns in bile and urine were different. Elimination via exhalation was negligible in all tests.

For most organs of the central compartment (e.g. liver, kidney), and the peripheral tissues fat, muscle, some glands (e.g. adrenal, thyroid, Harderian) and nasal mucosa, concentrations were higher than in blood at the peak concentration time (t_{max}) and at t_{168h}, suggesting a rapid clearance from blood and distribution to organs and tissues.

Fluopyram was extensively metabolized in rats. The main metabolic reactions were hydroxylation of the ethylene bridge of the molecule resulting in fluopyram-7-hydroxy, fluopyram-8-hydroxy. Hydroxylation was also observed in the phenyl-ring. Hydroxylated compounds were conjugated mainly with glucuronic acid and sulfuric acid. The parent compound was of minor importance in low dose tests and represented < 2% of the administered dose in faeces of male and female rats, and amounted to 10.5% in male and to 16.7% in female rats of high dose tests, respectively.

From peak values reached during the first day of dosing, a continuous but slow decline of radioactivity concentrations in organs and tissues was observed over 168 h post dosing. Retention of fluopyram related radioactivity in any of the organs and tissues investigated was considered unlikely, noting that the toxicokinetic profile in general was not different following repeated dosing.

Percutaneous absorption

Percutaneous absorption of fluopyram was evaluated on the basis of a so-called ‘Triple pack’ approach, *i.e.*, an *in vivo* study on rats was corrected by the ratio in permeability between human and rat skin *in vitro* to give a reliable estimate for dermal absorption in humans *in vivo*. In both studies, the test material was the proposed product, a suspension concentrate (SC) containing 500 g/L fluopyram that was applied as a concentrate at a topical concentration of about 5 mg/cm^2 and as a representative 1:1000 spray dilution at about 0.005 mg/cm^2.

Based on the study findings, OCS considers that values of 1.3 % and 2.6 % are assumed to reflect the dermal absorption rate that is expected for humans if they became exposed to either the SC 500 neat formulation of fluopyram or its 1:1000 spray dilution respectively. Because of the uncertainties that are inherent to dermal absorption studies, OCS typically rounds down numeric values to whole figures. Consequently, dermal absorption values of 1 % (concentrate) and 3 % (dilution) were used for the exposure calculations.

Acute toxicity

Fluopyram is of low acute toxicity by the oral (LD_{50} >2000 mg/kg bw with no deaths), dermal (LD_{50} >2000 mg/kg bw with no deaths), and inhalational routes (4–hr LC_{50} >5.1 mg/L the maximum obtainable concentration with no deaths) in rats. It is not a skin or eye irritant in rabbits, and was not a skin sensitiser in mice (LLNA).

Luna Privilege Fungicide is of low acute toxicity by the oral (LD_{50} >2000 mg/kg bw with no deaths), dermal (LD_{50} >2000 mg/kg bw with no deaths), and inhalational routes (4–hr LC_{50} >2.1 mg/L the maximum obtainable concentration with no deaths). It is not a skin or eye irritant in rabbits, and was not a skin sensitiser in mice (LLNA).

Systemic toxicity

In short term and subchronic oral studies the liver proved to be the main target organ in rats, mice and dogs. Hepatotoxicity became apparent by a dose-related increase in organ weight, alterations of clinical chemical parameters and histopathological findings such as centrilobular hypertrophy or periportal or midzonal vacuolation or macrovacuolation. Liver and, in rats, kidney pathology, produced the endpoints on which, in most studies, the NOAELs are based. In general, the adverse effects of fluopyram were more pronounced in rodents than in dogs. The lowest relevant NOAEL was 12.5 mg/kg/d from the 90–day feeding study in rats, based on liver and kidney effects (organ weight increase, clinical chemistry and histopathological findings (hyaline droplet nephropathy in the kidney)) at the next highest dose level of 60.5 mg/kg bw/d. In chronic oral studies the liver and kidneys remained the main target organs with an increase in organ weight that was sometimes accompanied by gross pathological findings, though in mice follicular cell hyperplasia in the thyroid gland was also observed.

In a rat short term dermal study, increased cholesterol, increased prothrombin time and increased liver weights associated with hepatocellular hypertrophy were seen at 1000 mg/kg bw/d. A NOAEL of 300 mg/kg bw/d was established based on these findings.

Because of the low acute inhalation toxicity and taking into account the physical properties of this compound, a study with repeated inhalational exposure was not considered necessary.

Genotoxicity and Carcinogenicity

Fluopyram was not mutagenic or genotoxic *in vitro* with and without metabolic activation up to cytotoxic or limit concentrations, and was not genotoxic *in vivo.*

In a rat 2–year dietary study, the only treatment related carcinogenic finding was an increased incidence of combined hepatocellular adenoma and carcinoma in females at the top dose of 1500 ppm equivalent to 89 mg/kg bw/d (11/59 animals including 3 animals with carcinoma, compared to 2/60 in controls). No such finding was seen in males, noting that the top dose level of 750 ppm was reduced to 375 ppm from week 85 onwards due to the high mortality seen at 750 ppm, to give an overall study phase dose estimated to be 29 mg/kg bw/d at the top dose level.

Mechanistic studies were performed to elucidate the mode of action behind tumour formation. It was proposed that the MOA for the observed liver tumours arose through activation of nuclear receptors constitutive androstan/pregnane X (CAR/PXR), and that the observed tumours arose by a phenobarbital mode of action (MOA). Noting that phenobarbital is known to induce liver tumours in rodents by CAR/PXR activation, but not causing tumours in humans even after many years of therapeutic use. From the available mechanistic studies, it was concluded that the data only indicated a likely MOA for fluopyram induced liver tumours in female rats similar to that developed for phenobarbital, as the data indicated that the aryl hydrocarbon receptor (AhR) receptor activation and decreased apoptosis as modulating events for fluopyram tumourigenicity cannot be definitively ruled out. Furthermore, while decreased apoptosis is also a known relevant accessory MOA for phenobarbital induced liver tumours, AhR activation is not regarded as playing a role in phenobarbital's carcinogenic MOA. Consequently, further information is required on the association of fluopyram exposure and AhR activation, and the possible influence on liver tumourigenicity, and in the current absence of such data the relevance of these tumours to humans cannot be dismissed. However, the weight of evidence supports a conclusion that these tumours occurred by a non-genotoxic mechanism in female rats at high doses (89 mg/kg bw/d), and a threshold for the induction of such tumours was identified (i.e. no treatment-related induction of liver tumours occurred in female rats at 8.6 mg/kg bw/d).

In a mouse 18–month dietary study, the only treatment related carcinogenic finding was an increased incidence of follicular cell adenoma in males at the top dose level of 750 ppm equivalent to 105 mg/kg bw/d (7/50 animals compared to 1/50 in controls). No such finding was seen in females at up to and including the top dose level of 750 ppm equivalent to 129 mg/kg bw/d.

However, there is available evidence that rodents are much more susceptible to thyroid tumours than humans, and that the greater sensitivity of (particularly) male rodents to perturbations of the pituitary-thyroid axis by xenobiotics or physiologic alterations compared to humans is the result of:

- higher circulating levels of thyroid stimulating hormone (TSH) in rodents (>25 times) than humans;
- shorter plasma half-life of thyroxine (T_4) in rodents (12–24 hours) than in humans (5–9 days); and
- serum T_4 binding with high specificity to thyroxine-binding globulin (TBG) in humans which is absent in rodents. TBG has binding affinities 3–5 orders of magnitude greater than albumin or pre-albumin. This means the higher unbound T_4 is very susceptible to physiological events, like induced uridine diphosphate glucuronyltransferase (UDPGT), that enhance its clearance from blood.

Furthermore, by analogy with other chemicals (e.g. phenobarbital) known to induce thyroid tumours in rodents by CAR/PXR associated increases in Phase II enzymes metabolising free T_4 (as proposed for fluopyram), but not causing tumours in humans even after many years of therapeutic use, the MOA deduced for fluopyram rodent thyroid tumours is not considered relevant to humans.

Reproductive and Developmental Toxicity

There were no treatment related reproductive findings in a dietary 2–generation rat study up to and including dose levels producing parental toxicity.

In a rat oral (gavage) developmental toxicity study, maternal bodyweight gain at 450 mg/kg bw/d remained static during GD 6–8 of treatment, resulting in an overall decrease in body weight gain of 16%. A similar but

lower level effect was at 150 mg/kg bw/d with an overall body weight gain reduction of 6%. Food consumption at 450 mg/kg bw/d was decreased between 13 and 15% between GD 6 and 14. Developmental toxicity was observed at 450 mg/kg bw/d in terms of slightly lower fetal body weight (5%), and a slightly increased incidence of two visceral ('thymic remnant present' and 'ureter convoluted and/or dilated') and two skeletal minor variations ('at least one thoracic centrum split/split cartilage' and 'at least one thoracic centrum dumbbell and/or bipartite/normal cartilage'). The observed fetal findings at 450 mg/kg bw/d were considered a secondary non-specific of the observed marked maternal toxicity as shown by an overall decrease in body weight gain of 16%.

In a rabbit oral (gavage) developmental toxicity study, at 75 mg/kg bw/d only slight increases in maternal body weight gain were seen between GD 14–18 and GD 18–22, that resulted in an overall decrease in body weight gain of 35% between GD 6–29. These findings at 75 mg/kg bw/d were associated with decreases in food consumption between 24 and 34% for all intervals between GD 14–26. Developmental toxicity was observed at 75 mg/kg bw/d in terms of an 11% decrease in fetal body weight and a slight increase in the incidence of very small foetus (classified as 'runts'). The observed fetal findings at 450 mg/kg bw/d were considered a secondary non-specific of the observed marked maternal toxicity as shown by an overall decrease in body weight gain of 35%.

Therefore, fluopyram was not considered a developmental toxicant in rats and rabbits.

Neurotoxicity

In a rat acute neurotoxicity study when fluopyram was administered by oral gavage, decreased motor and locomotor activity were seen on the day of dosing only at 100 mg/kg bw (with a NOAEL of 50 mg/kg bw), while in no such findings were observed in a 90–day neurotoxicity study in rats when fluopyram was administered in the diet up to and including 153/162 mg/kg bw/d in males/females.

Toxicity of Metabolites

An acute oral toxicity study, *in vitro* genotoxicity tests and a 28–day short term oral toxicity study was provided for each of two plant metabolites of fluopyram (fluopyram-pyridyl-carboxylic acid and fluopyram-methyl-sulfoxide) that had not been detected in rat metabolism studies. The studies conducted suggested that the plant metabolites were of no toxicological concern, as both metabolites exhibited a very low acute oral toxicity and proved negative in the *in vitro* for mutagenicity and genotoxicity with and without metabolic activation. Additionally, the subacute feeding studies revealed a lower toxicity of these metabolites when compared to fluopyram.

3.3 PUBLIC HEALTH STANDARDS

Poisons Scheduling

On the 5th February 2015 the delegate to the Secretary of the Department of Health published an interim scheduling decision to create a new Schedule 5 listing of fluopyram, with a cut-off to exempt at 50 per cent and an implementation date of 1 June 2015.

NOAEL/ADI /ARfD

The acceptable daily intake (ADI) for humans is level of intake of an agricultural or veterinary chemical which can be ingested daily over an entire lifetime without appreciable risk to health. It is calculated by dividing the overall NOAEL for the most sensitive toxicological endpoint from a suitable study (typically an animal study) by an appropriate safety factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans, intra-species variation, and the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

The critical effects of fluopyram identified in chronic toxicity studies is liver toxicity, nephropathy and thyroid follicular cell hypertrophy. Rats appeared to be the most sensitive species for fluopyram and the 2–year combined chronic/carcinogenicity study in this species had the lowest NOAEL (1.2 mg/kg bw/d) based treatment related effects in the liver, kidney and thyroid gland. The ADI for fluopyram was established at 0.01 mg/kg bw/d (rounding down) based on a NOAEL of 1.2 mg/kg bw/d in in a dietary 2-year rat study and applying a default 100-fold safety factor to account for potential inter-species and intraspecies variation.

The acute reference dose (ARfD) is the estimate of the amount of a substance in food or drinking water, expressed on a milligram per kilogram body weight basis, that can be ingested over a short period of time, usually in 1 meal or during 1 day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

An acute reference dose (ARfD) was established since fluopyram was considered likely to present an acute hazard to humans. Adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. The only relevant effect reported following an acute exposure was a slightly lower motor and locomotor activity on the day of treatment (together with urine stain and decreased body temperature) in the acute neurotoxicity study. This effect was observed at 500 mg/kg and above in males and at 125 mg/kg and above in females. A NOAEL of 125 and 50 mg/kg was established for males and females, respectively. Consequently, the ARfD for fluopyram was established at 0.5 mg/kg bw based on a NOAEL of 50 mg/kg bw in an oral acute neurotoxicity study in rats and applying a default 100-fold safety factor to account for potential inter-species and intra-species variation.

3.4 Conclusion

The APVMA is satisfied that the proposed use of Luna Privilege Fungicide, containing the active constituent fluopyram, is not likely to be harmful to human beings if used according to the product label instructions.

4 RESIDUES ASSESSMENT

4.1 Introduction

Luna Privilege Fungicide contains the new active constituent fluopyram (figure 1) and is proposed for use to control various fungal diseases in table grapes and grapes for drying. As part of the residues assessment for fluopyram, plant and animal metabolism studies, supervised residue trials and trade aspects were considered.

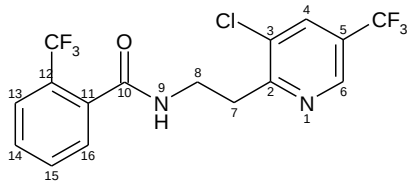


Figure 1: Fluopyram (AE C656948)

4.2 Metabolism

Plants

The metabolism of fluopyram was investigated in grapes, potatoes, beans and peppers using compound labelled in either the phenyl or pyridyl ring. The pepper studies involved application by drip irrigation.

Grapes

Three sprays of [phenyl-UL-^{14}C]AE C656948 or [pyridyl-2,6-^{14}C]AE C656948 were made to grapevines at growth stages BBCH 17-19, 71 and 81. The targeted application rates were 100, 200 and 200 g ai/ha for the first, second and third applications respectively. Grapes and leaves were harvested at maturity with a pre-harvest interval (PHI) of 18 days for grapes and 19 days for leaves. After the second application shoots and leaves ('summer cut') were taken for method development.

The total radioactive residues (TRR) in the summer cut amounted to 28.55–64.18 mg equiv/kg, in grapes to 1.70–1.86 mg equiv/kg and in leaves to 42.66–48.06 mg equiv/kg. A portion of 97.1-98.6% and 93.9–94.7% of the TRR in grapes and leaves, respectively, were extracted conventionally using acetonitrile (ACN)/water.

Parent compound and metabolites in the extracts were quantified by radio-HPLC. The TRRs consisted nearly quantitatively of unchanged parent. For the phenyl label parent compound represented 1.82 mg/kg (97.6% of the TRR) in grapes and 44.11 mg/kg (91.8% of the TRR) in leaves. For the pyridyl label parent compound represented 1.63 mg/kg (95.8% of the TRR) in grapes and 39.0 mg/kg (91.3% of the TRR) in leaves.

Potatoes

Three spray applications of [phenyl-UL-^{14}C]AE C656948 or [pyridyl-2,6-^{14}C]AE C656948 were made to potatoes at growth stages BBCH 16, 55 and 71. The target rate for each application was 167 g ai/ha. Potato leaves and tubers were harvested at maturity with a pre-harvest interval (PHI) of 51 days.

The TRR for tubers (0.008–0.012 mg equiv/kg) was very low while the TRR in leaves was 21.67–47.64 mg equiv/kg. A portion of 95.3–96.7% and 99.4–99.6% of the TRR in tubers and leaves, respectively, were extracted conventionally using ACN/water.

For the phenyl label a total of 77.1% of the TRR was identified in tubers and 99.2% in leaves. Parent compound amounted to 0.006 mg/kg (68.8% of the TRR) in tubers and 46.69 mg/kg (98.0% of the TRR) in leaves.

For the pyridyl label a total of 74.1% of the TRR was identified in tubers and 99.2% in leaves. Parent compound amounted to 0.003 mg/kg (23.2% of the TRR) in tubers and 21.26 mg/kg (98.1% of the TRR) in leaves.

Beans

Two sprays of [phenyl-UL-^{14}C]AE C656948 or [pyridyl-2,6-^{14}C]AE C656948 were made to beans at growth stages BBCH 51 and 75. The target rate for each application was 250 g ai/ha. The immature RACs green beans and foliage were taken four days after the second application. The mature RACs beans ('succulent beans') and straw were harvested 29 days after the last application. A portion of the mature beans were dried for 11 days and were analyzed as edible RAC 'dry beans'.

The TRRs in the edible RACs succulent and dry beans were very low and amounted to 0.07–0.17 mg equiv/kg and 0.12–0.31 mg equiv/kg, respectively. In green beans, foliage and straw TRRs amounted to 1.40–3.88 mg equiv/kg, 36.66–38.53 mg equiv/kg and 16.55–19.02 mg equiv/kg, respectively. The major amount of radioactivity (93.9–99.3% of the TRR) was effectively extracted with ACN/water from all RACs.

For the phenyl label parent compound represented 11–13% of the TRR in succulent and dry beans. In these RACs the main metabolite was AE C656948-benzamide which amounted to 0.04 mg equiv/kg (51.6% of the TRR) in succulent beans and 0.08 mg equiv/kg (64.0% of the TRR) in dry beans.

For the phenyl label in green beans, foliage and straw the TRRs consisted nearly quantitatively of unchanged parent compound which represented >90% of the TRRs. AE C656948-benzamide was either not detected or represented <1% of the TRR in these RACs.

For the pyridyl label parent compound represented 4.8-5.7% of the respective TRR in succulent and dry beans. In these RACs AE C656948-pyridyl-acetic acid (PAA) and AE C656948-pyridyl-carboxylic acid (PCA) were the main metabolites representing 23–33% of the respective TRRs. A third and minor label-specific metabolite, AE C656948-hydroxyethyl-glycoside, was detected and represented ≤3.1% of the low TRR.

For the pyridyl label in green beans the TRR consisted quantitatively of unchanged parent compound which represented 99.3% of the TRR. In foliage, parent compound amounted to 92.3% TRR and 6 minor metabolites were identified. In straw parent compound amounted to 87.1% of the TRR and 7 minor metabolites were identified.

Peppers

[Phenyl-UL-^{14}C]AE C656948 or [Pyridyl-2,6-^{14}C]AE C656948 was applied by drip application to red bell pepper growing on stone wool substrate. The targeted single application rate amounted to 5 mg a.s./plant. Additionally, an overdose experiment (4x) was conducted at 20 mg a.s./plant for method development and to facilitate identification of metabolites. The applications were performed when the fifth to seventh leaf of the main shoot was unfolded (BBCH 15–17).

A plant at an intermediate growth stage was harvested from the 4x experiment 33 days after application. Fruits were harvested at maturity from plants of the 1x experiment at three time points (55–96 days after application). The remaining plants were sampled one day after the third harvest of fruits (97 days after application).

The TRR in the mature fruits (1x) was very low and amounted to 0.038–0.06 mg equiv/kg. In the rest of the plant it amounted to 2.34–3.54 mg equiv/kg. The major amount of radioactivity (>95% of the TRR) was effectively extracted with ACN/water from all RACs.

For the phenyl label (1x) parent compound was the major part of the residue in the fruits and the rest of the plant (48.9% and 64.0% of the TRR, respectively). The main metabolite was the cleavage product AE C656948-benzamide (16.1% of the TRR in fruits and 10.0% of the TRR in remaining plants).

For the pyridyl label (1x) in the fruits parent compound amounted to 0.01 mg/kg (16.2% of the TRR). Metabolites were the cleavage product AE C656948-pyridyl-carboxylic acid (PCA) and two glycoside isomers of the AE C656948-pyridyl-acetic acid (PAA) amounting to 0.026 mg equiv/kg (43.5% TRR), 0.014 mg equiv/kg (23.8% TRR) and 0.009 mg equiv/kg (14.2% TRR), respectively.

Summary of plant metabolism

The major reactions observed were:

- Hydroxylation of AE C656948 leading to AE C656948-7-hydroxy and AE C656948-8-hydroxy.
- Conjugation of AE C656948-7-hydroxy with glucose, malonic acid, glycoside and glucuronic acid.
- Cleavage of the hydroxylated active substance leading to AE C656948-benzamide and AE C656948-pyridyl-carboxylic acid (PCA) and AE C656948-pyridyl acetic acid (PAA).

A summary of the main metabolic pathways for fluopyram in plants is given below in Figure 2.

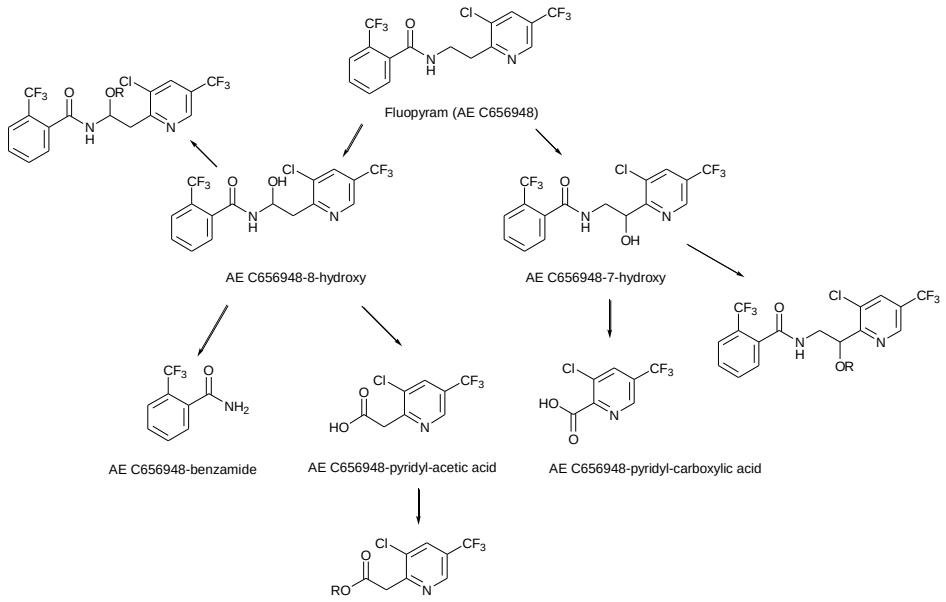


Figure 2: Proposed metabolic pathway for fluopyram in plants.

Metabolism in confined rotational crops

The metabolism of fluopyram (AE C656948) labelled in either the phenyl or pyridyl ring was investigated in the rotational crops wheat, Swiss chard and turnips from three consecutive rotations.

Phenyl label

[Phenyl-UL-^{14}C]AE C656948 was applied uniformly onto to bare soil in a planting container (area approx. 1 m^2) by spray application (day 0). The application rate was 534 g ai/ha. Crops of the 1st, 2nd and 3rd rotation were sown 30 days, 139 days and 280 days after soil application (plantback intervals or PBIs). TRRs were ≥0.01 mg equiv/kg in all rotated crop matrices except turnip roots from the 280 day PBI, as summarized below in Table 1.

TABLE 1: TOTAL RADIOACTIVE RESIDUES (TRRS) IN THE DIFFERENT RACS OF THE THREE ROTATIONS (EXPRESSED AS PARENT COMPOUND EQUIVALENTS, MG/KG) (PHENYL LABEL)

TRR	Wheat				Swiss	turnip	
[mg/kg]	forage	hay	straw	Grain	chard	leaves	roots
1st rotation (30 days)	0.100	1.783	6.156	0.167	0.540	0.884	0.065
2nd rotation (139 days)	0.785	1.120	3.450	0.054	0.377	0.113	0.013
3rd rotation (280 days)	0.197	1.527	1.032	0.023	0.164	0.103	0.009

Conventional extraction of the RACs using ACN/water released >96% of the radioactive residues in Swiss chard and turnip leaves and roots, 87–95% of the radioactive residues in wheat forage, hay and straw and 77– 85% of the radioactive residues in wheat grains. Turnip roots from the 280–day PBI were not subjected to extraction procedures due to low TRR. Post extraction solids of wheat hay, straw and grain were subjected to further extraction procedures including microwave extraction (hay and straw) and diastase treatment (grain). Non-extractable residues remaining after all extractions were <10% of the TRR in all rotated crop RACs from all plantback intervals, except 280–day PBI wheat grain in which the non-extractable residues were 21.9% of the TRR, but represented 0.005 mg equiv/kg.

Parent AE C656948 accounted for the major part of the residues in all RACs of all rotations and covered 56–84% of the TRR in the RACs of the 1st rotation, 33–78% of the TRR in the RACs of the 2nd rotation and 28–59% of the TRR in the RACs in the 3rd rotation. In general, the levels of the parent compound decreased with subsequent plantback intervals. AE C656948-7-hydroxy and its various conjugates with glucose, malonic acid (2 isomers) and sulphuric acid were important metabolites mainly in Swiss chard, where the AE C656948-7-hydroxy yielded 21% of the TRR in the 1st rotation increasing to about 35% of the TRR in the following rotations. In the other RACs, the amount of AE C656948-7-hydroxy was distinctively lower; <10% TRR, except in wheat hay and straw from the 3rd rotation in which AE C656948-7-hydroxy accounted for 12.3-12.6% TRR.

Two label specific metabolites were identified: AE C656948-benzamide and AE C656948-benzoic acid. AE C656948-benzoic acid accounted for 0.6–6.9% TRR in wheat forage, hay and grain, and turnip leaves and roots from the 30-day PBI; 0.3–0.4% TRR in wheat forage and hay, and 13.6% TRR in wheat grain from the 139–day PBI; and 13% TRR in wheat grain from the 280–day PBI. AE C656948-benzamide accounted for 2.8–9.7% TRR in wheat forage, hay, straw and grain, and turnip leaves and roots, and 11.1% TRR in Swiss chard from the 30–day PBI; 3.2–7.4% TRR in all RACs from the 139–day PBI; and 5.9–8.0% TRR in wheat forage, hay, straw and grain, and 10.3–11.7% TRR in Swiss chard and turnip leaves from the 280–day PBI.

Pyridyl label

[Pyridyl-2,6-^{14}C]AE C656948 was applied uniformly onto bare soil in a planting container (area approx. 1 m^2) by spray application (day 0). The application rate was 514 g ai/ha. Crops of the 1st, 2nd and 3rd rotation were sown 30 days, 139 days and 280 days after soil application, respectively. TRRs were ≥0.01 mg equiv/kg in all rotated crop matrices from all PBIs as summarized below in Table 2.

TABLE 2: TOTAL RADIOACTIVE RESIDUES (TRRS) IN THE DIFFERENT RACS OF THE THREE ROTATIONS (EXPRESSED AS PARENT COMPOUND EQUIVALENTS, MG/KG) (PYRIDYL LABEL)

TRR	wheat				Swiss	turnip	
[mg/kg]	forage	hay	straw	grain	chard	leaves	roots
1st rotation (30 days)	0.157	1.802	6.663	0.412	0.570	0.565	0.036
2nd rotation (139 days)	0.568	0.971	2.562	0.072	0.343	0.103	0.010
3rd rotation (280 days)	0.167	0.709	1.622	0.037	0.211	0.095	0.012

Conventional extraction of the RACs using ACN/water released >97% of the radioactive residues in Swiss chard and turnip leaves and roots, 85–96% of the radioactive residues in wheat forage, hay and straw and 82–92% of the radioactive residues in wheat grains. Post extraction solids of wheat hay, straw and grain were subjected to further extraction procedures including microwave extraction (hay and straw) and diastase treatment (grain). Non-extractable residues remaining after all extractions were <10% of the TRR in all rotated crop RACs from all plantback intervals, except 280–day PBI wheat grain in which the non-extractable residues were 17.8% of the TRR, but represented 0.007 mg equiv/kg.

Apart from wheat grain, the parent compound was the main compound in all RACs of all rotations and accounted for 57–86% of the TRR in the RACs of the 1st rotation, 37–95% of the TRR in the RACs of the 2nd rotation, and 39–92% of the TRR in the RACs in the 3rd rotation. In wheat grain the parent accounted for 20.4–33.4% of the TRR in the three rotations. AE C656948-7-hydroxy and its various conjugates with glucose, malonic acid (two isomers) and sulphuric acid were important metabolites mainly in Swiss chard, where the AE C656948-7-hydroxy yielded 28% of the TRR in the 1st rotation increasing to 37–39% of the TRR in the following rotations. In the other RACs, the amount of AE C656948-7-hydroxy was distinctively lower (≤10% of the TRR). The sulphuric acid conjugate of AE C656948-7-hydroxy, AE C656948-7-OH-SA, was also a prominent metabolite in Swiss chard increasing from 8% of TRR in the 1st rotation to 17% and 14% of the TRR in the 2nd and 3rd rotations, respectively; AE C656948-7-OH-SA was also found in turnip leaves from all plantback intervals at low levels (<1% TRR). AE C656948-7-hydroxy-glc, and AE C656948-7-hydroxy-glc-MA (isomers 1 and 2) were minor metabolites (<10% TRR) in wheat forage, hay and straw, Swiss chard and/or turnip leaves.

Two label specific metabolites were identified: AE C656948-pyridyl-carboxylic acid and AE C656948-methyl-sulfoxide. They formed the major part of the residues in wheat grain (in sum 48.9–65.4% of the TRR of the three rotations); AE C656948-pyridyl-carboxylic acid amounted to 56%, 16% and 29% of the TRRs of the 1st, 2nd and 3rd rotation, respectively, and AE C656948-methyl-sulfoxide amounted to 1.2%, 49% and 20% of the TRRs of the 1st, 2nd and 3rd rotation, respectively, in wheat grain. AE C656948-pyridyl-carboxylic acid and AE C656948-methyl sulfoxide were also detected in other rotated crop RACs. AE C656948-pyridyl-carboxylic acid accounted for 17% TRR in 30–day PBI wheat forage and <10% TRR in wheat forage from subsequent plantback intervals, as well as in wheat hay, wheat straw (found in 1st rotation only), Swiss chard, turnip leaves, and turnip roots (1st rotation only). AE C656948-methyl-sulfoxide was identified in wheat forage, hay and straw and Swiss chard at low levels (<5% TRR).

The main metabolic transformations detected in the two confined studies were:

- hydroxylation of the ethylene linking group of the parent compound forming AE C656948-7-hydroxy and -8-hydroxy metabolites,
- hydroxylation of the phenyl ring and subsequent conjugation with glucose,
- conjugation of the hydroxylated metabolites with glucose, malonic acid and sulphuric acid,
- hydrolytic cleavage and subsequent oxidation to AE C656948-benzamide and AE C656948-benzoic acid (phenyl label),
- hydrolytic cleavage and subsequent oxidation to AE C656948-pyridyl carboxylic acid and AE C656948-methyl sulfoxide (pyridyl label),

- formation of polar, probably natural compounds which were incorporated into the starch matrix of grains.

Animals

The metabolism of fluopyram has been investigated in laying hens and lactating goats using compound labelled in either the phenyl or pyridyl ring.

Laying hen (phenyl study)

Six hens were orally dosed with [phenyl-UL-^{14}C]AE C656948 for 14 consecutive days in 24 h intervals at 2.03 mg per kg body weight per day (corresponding to 26 ppm in the feed) and sacrificed about 24 hours after the last dose.

The TRR values in eggs ranged from 0.462 (day 1) to 3.901 mg equiv/kg (day 14). A more or less linear increase was observed until day 7 (3.243 mg equiv/kg). After that the residues only increased slightly to the test end and a residue plateau-level was nearly reached. The highest TRR-values were measured in the metabolizing and excretory organs, liver (9.536 mg equiv/kg) and kidney (5.759 mg equiv/kg). The residue levels of liver and kidney were followed in decreasing order by those determined in the muscle (3.290 mg equiv/kg), skin (2.533 mg equiv/kg), and subcutaneous fat (1.696 mg equiv/kg).

Samples were extracted with ACN/water. After SPE purification, the resulting extracts of eggs, muscle, fat, liver and excreta represented between ca. 92% and 99% of the TRR in the sample.

The major component in all the edible matrices was the metabolite AE C656948-benzamide (68.6% to 98.6% of the TRR). Other metabolites identified were AE C656948-Z-olefine (25.9% TRR in fat and ≤ 1.2% TRR in egg, muscle and liver), AE C656948-E-olefine (≤ 2.3% TRR in fat and liver), and AE C656948-benzoic acid (0.3% TRR in liver only). Parent compound was detected as a minor component only in eggs and fat at ≤ 2.5% TRR. Identification rates in the organs and tissues ranged from 93% to nearly 100% of the TRR.

Laying hen (pyridyl study)

Six hens were orally dosed with [pyridyl-2,6-^{14}C]AE C656948 for 14 consecutive days in 24 h intervals at 2.02 mg per kg body weight per day (corresponding to 26 ppm in the feed) and sacrificed about 24 hours after the last dose.

The TRR values in eggs ranged from 0.047 (day 1) to 0.321 mg equiv/kg (day 8). Until day 8, a linear increase was observed. After that the residues decreased slightly to 0.262 mg equiv/kg (days 13 and 14) and the residue plateau-level was reached. The TRR in liver and kidney corresponded to 0.538 mg equiv/kg and 0.242 mg equiv/kg respectively. The TRR in subcutaneous fat amounted to 0.498 mg equiv/kg and in skin to 0.152 mg equiv/kg. The lowest TRR was measured in the muscle (0.048 mg equiv/kg).

Samples were extracted with ACN and/or ACN/water (eggs, muscle, liver, and excreta) or with ACN/water and heptane (fat). After SPE purification, the resulting extracts of eggs, muscle, fat, liver, and excreta represented 43–54%, 58%, 99%, 32% and 92%, respectively, of the TRR. Alternatively, egg pools and liver were extracted after enzymatic digestion to try to solubilize more of the radioactive residues; 64–66% in eggs

and 82% in liver was recovered after SPE cleanup of the extract. Residual solids in egg pool day 7–14 following conventional extraction and in liver following enzymatic extraction were exhaustively extracted using microwave extraction releasing an additional 51.2% and 7.4% of the TRR, respectively. In these samples remaining non-extractable residues were 1% and 9.7% of the TRR.

The major component identified was the metabolite AE C656948-Z-olefine which accounted for 15.4–19.3% of the TRR in eggs day 7–14, 33.0% of the TRR in muscle, and 70.5% of the TRR in the fat, but only 4.1% of the TRR in eggs day 1–6, and 1.9–3.1% of the TRR in liver. The other isomer AE C656948-E-olefine was found at 11.8–13.9% of the TRR in fat and liver, and 1.0–3.9% of the TRR in eggs and muscle. Parent compound was a major residue identified in eggs day 1–6 at 14.7–17.9% of the TRR and 12.2% of the TRR in fat; the parent was identified as a minor residue (≤ 9.5% TRR) in eggs day 7–14 and muscle, and was not detected in liver. AE C656948-pyridyl-acetic acid (PAA) and AE C656948-7-hydroxy were only minor metabolites, each present at ≤ 6.4% of the TRR in eggs and liver.

The main metabolic pathways proposed for laying hens are:

- Cleavage of the aliphatic chain to form AE C656948-benzamide and AE C656948-pyridyl-acetic acid.
- Hydroxylation of the aliphatic chain followed by dehydration, yielding the olefins.
- Hydrolysis of the amide to a carboxylic group to form AE C656948-benzoic acid.

The proposed metabolic pathway for fluopyram in poultry is summarised below in figure 3.

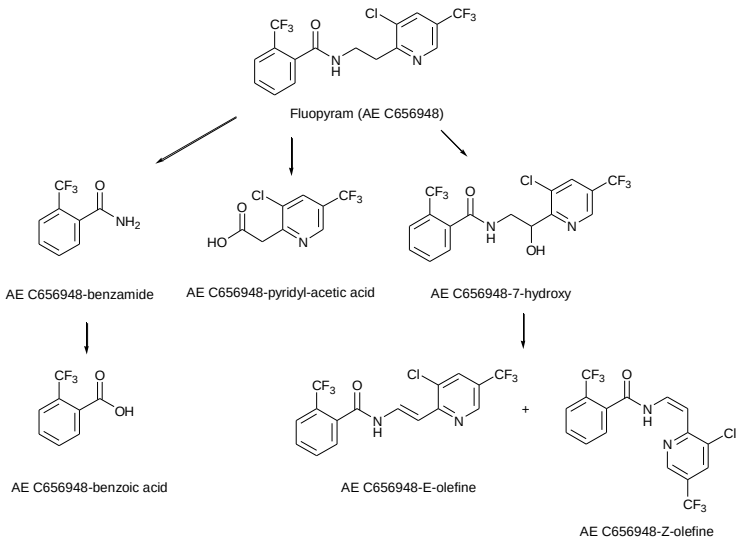


Figure 3: Proposed metabolic pathway for fluopyram in laying hens

Lactating goat (phenyl study)

The goat was orally dosed for five consecutive days, at 24 h intervals, with 1.91 mg [phenyl-UL-^{14}C]AE C656948 per kg body weight per day (corresponding to 46 ppm in the feed) and sacrificed at about 24 hours after the last dose.

The TRR in milk samples ranged from 0.045 to 0.454 mg equiv/kg. The highest value was detected just before sacrifice. The highest TRR was determined in the liver (8.379 mg equiv/kg) which shows the significance of this organ for metabolism. The following values were calculated in decreasing order for the other organs and tissues: 2.295 mg equiv/kg (kidneys), 0.737 mg equiv/kg (muscle) and 0.399 mg equiv/kg (fat).

The total radioactive residue was extracted efficiently (97 to 99% of the TRR) from milk and fat using conventional solvent extraction. For muscle, liver, and kidney, 68–77% of the TRR was extracted using conventional solvent extraction; an additional exhaustive extraction step with microwave assistance at increased temperature was used to solubilize an additional 17–32% TRR from these tissues. Non extractable residues were ≤ 6% of the TRR in all goat matrices.

The major component in all the edible matrices was the metabolite AE C656948-benzamide (49.1% to 97.6% of the TRR). Other major compounds identified were AE C656948-Z-olefine and the parent compound, which were found at 13.1% and 18.2% TRR, respectively, in fat. AE C656948-Z-olefine was identified as a minor residue (< 1% TRR) in milk and liver and was not found in muscle and kidney. The parent compound was identified as a minor component in milk, liver, and kidney, at ≤ 1.7% TRR, and was not detected in muscle. The following additional metabolites were identified as minor residues (< 9% TRR each) in goat matrices: AE C656948-benzamide-SA, AE C656948-7-OH-GA (isomers 1 and 2), AE C656948-di-OH-GA (kidney only), AE C656948-phenol-GA (liver and kidney only), AE C656948-8-OH-GA (isomer 2; liver and kidney only), AE C656948-7-hydroxy, and AE C656948-E-olefine (fat and liver only). Identification rates in the organs and tissues ranged from 93.5–98.9% of the TRR.

Lactating goat (pyridyl study)

The goat was orally dosed for five consecutive days, in 24 h intervals, with 2.0 mg [pyridyl-2,6-^{14}C]AE C656948 per kg body weight per day (corresponding to 45 ppm in the feed) and sacrificed at about 24 hours after the last dose.

The TRR-values in milk samples ranged from 0.017 to 0.063 mg equiv/kg. The highest value was detected at 32 h after the first dose followed by a decrease to 0.026 mg/kg at sacrifice.

The highest TRR was determined in liver (1.427 mg equiv/kg). The following TRRs were calculated in decreasing order for the other organs and tissues: 0.403 mg equiv/kg (kidneys), 0.372 mg equiv/kg (fat) and 0.042 mg equiv/kg (muscle).

The total radioactive residue was extracted efficiently (89% to 97% of the TRRs) from milk (pooled evening samples), muscle, fat and kidneys by conventional solvent extraction. For liver, only 55% of the TRR was released with conventional solvent extraction. In liver, non-extractable residues were 24.2% of the TRR (0.346 mg equiv/kg) following microwave extraction. Additional microwave extraction of liver solids with

ACN/aqueous NH_3 solubilized all of the residues; however, the extracts could not be chromatographically analyzed due to low radioactivity in the fractions or because of matrix interference.

The parent compound was identified as a major component in milk, muscle, and fat (27.3–46.4% TRR) but was only found as a minor residue in liver (7.7% TRR) and was not found in kidney. The metabolite AE C656948-Z-olefine was identified as a major metabolite in milk, muscle, and fat, at 12.9–33.7% TRR; it was found at 5.7% TRR in liver and was not found in kidney. The other isomer AE C656948-E-olefine was found at < 5% TRR in milk, muscle, fat, and liver. AE C656948-7-hydroxy was also found to be a major component of milk, muscle, and fat, at 12.8–21.6% TRR, but a minor residue (≤ 6% TRR) in liver and kidney. Other major identified metabolites included AE C656948-7-OH-GA (isomer 1), at 24.2–35.1% TRR in liver and kidney, AE C656948-7-OH-GA (isomer 2), at 16.3% TRR in kidney, and AE C656948-8-OH-GA (isomer 2) in kidney; these metabolites were also found at < 10% TRR in milk, muscle, and liver. AE C656948-pyridyl-acetic acid, AE C656948-hydroxyethyl-GA, AE C656948-di-OH-GA, and AE C656948-phenol-GA were only minor metabolites, each present at ≤ 8.6% of the TRR in liver and kidney.

The main metabolic pathways proposed for lactating goats are:

- Hydroxylation of the ethylene bridge of the molecule resulting in AE C656948-7-hydroxy, AE C656948-8-hydroxy, and a di-hydroxylated compound.
- Hydroxylation of the phenyl ring leading to AE C656948-phenol.
- Conjugation of the hydroxylated metabolites with glucuronic acid.
- Elimination of water from compounds hydroxylated in the ethylene bridge leading to AE C656948-Z-olefine and E-olefine.
- Molecular cleavage to AE C656948-benzamide.
- Hydroxylation of AE C656948-benzamide followed by conjugation with sulfate.
- Molecular cleavage to AE C656948-pyridyl-hydroxyethyl followed by conjugation with glucuronic acid.
- Oxidation of AE C656948-pyridyl-hydroxyethyl to AE C656948-pyridyl-acetic acid.

The proposed metabolic pathway for fluopyram in goats is summarised below in figure 4.

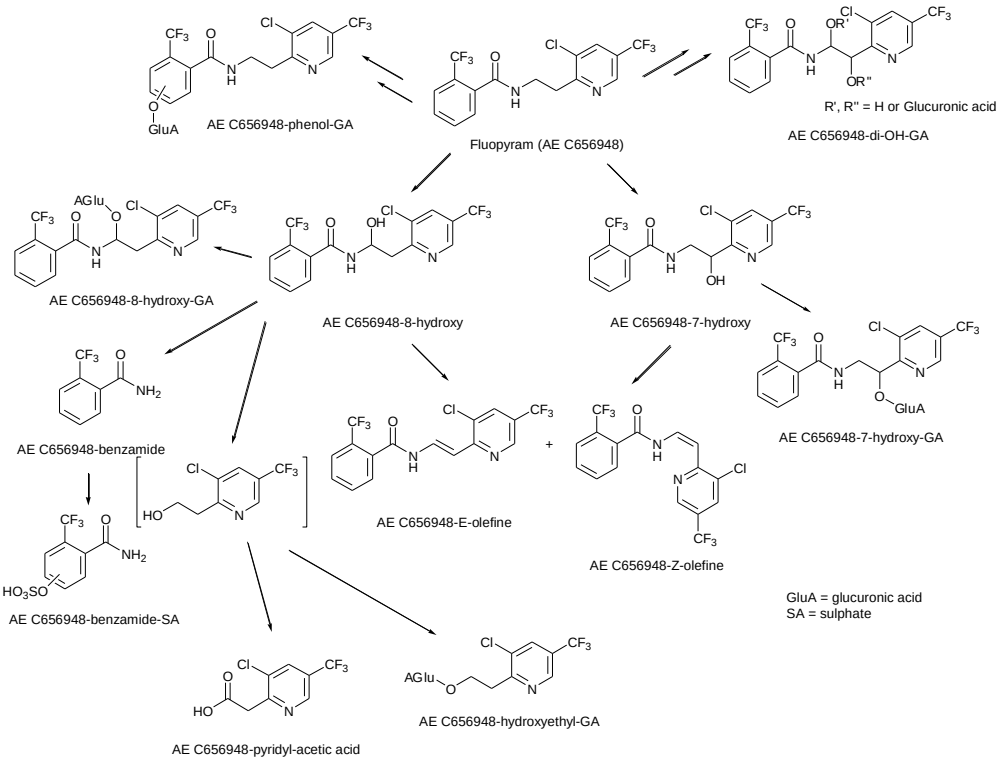


Figure 4: Proposed metabolic pathway for fluopyram in goats.

4.3 Analytical methods

Plant commodities

In the Australian residue trials provided in support of the application, fluopyram (parent) was extracted from test samples with water/acetonitrile. Extracts were filtered using a polyethylene frit and diluted in water/acetonitrile with 0.1% acetic acid. Residues were quantified by high performance liquid chromatography coupled to a triple quadrupole mass spectrometer. Quantification was achieved with the aid of a stable isotopically labelled internal standard. The LOQ for fluopyram (parent) was 0.01 mg/kg. Recoveries of fluopyram from fortified control samples were within acceptable limits.

Animal commodities

In the animal transfer studies provided with the application samples were analyzed for AE C656948 and its metabolites AE C656948-benzamide, and AE C656948-olefine (E- and Z-isomers) using a high performance liquid chromatography-electrospray ionization / tandem mass spectrometry (HPLC-MS/MS) method, using isotopically labelled internal standards. Samples were extracted with acetonitrile water (with microwave extraction for bovine liver, kidney and muscle) and cleaned up by SPE prior to analysis. The limit of

quantitation (LOQ) was 0.01 mg/kg for AE C656948 and the AE C656948-benzamide metabolite, expressed as parent equivalents. In case of the AE C656948-olefines, the total residue of olefines was calculated as sum of the two individual olefine isomers, expressed as parent equivalents. For these studies the LOQ of the total residue of olefines was set to 0.02 mg/kg for all matrices. Concurrent recoveries from fortified samples were generally acceptable.

Stability of pesticide residues in stored analytical samples

AE C656948 (fluopyram) and its metabolites AE C656948-benzamide, and AE C656948-pyridyl-acetic acid were shown to be stable for at least 24 months at ca. -18°C or below in/on lettuce (head), wheat (grain), rape seed and dry pea (seed). The metabolite AE C656948-pyridyl-carboxylic acid was shown to be stable for at least 24 months at ca. minus 18°C or below in/on dry pea (seed) and rape seed. The metabolite AE C656948-7-hydroxy was shown to be stable for at least 24 months at ca. minus 18°C or below in/on lettuce and wheat (grain).

A separate study was conducted in order to investigate the stability of residues of AE C656948 and its metabolites AE C656948-benzamide (AE F148815), AE C656948-pyridyl-carboxylic acid (AE C57188), AE C656948-pyridyl-acetic acid (BCS-AA10139) in orange under freezer conditions at about -18°C or below. Other than AE C656948-pyridyl-acetic acid, recoveries measured for the remaining 3 compounds at the 7 storage intervals in orange were all > 90%. For the pyridylacetic acid, recoveries declined gradually from 103% at 0 month to 69% at 24 months.

The maximum period between sampling and analysis in the Australian trials was 28 weeks, which is within the period of the storage stability studies.

4.4 Residue Definition

Plant commodities

Fluopyram is the major residue in treated plant commodities and in rotational crops, where residues occur. Metabolites identified in the plant metabolism studies at more than 10% TRR are benzamide, PCA and PAA. For grapes and green beans these metabolites were not more than 1% of TRR and below 0.02 mg/kg. Higher levels (up to 60% TRR but at relatively low concentrations up to 0.1 mg/kg) were found in commodities not directly exposed to spray applications (drip irrigated peppers, potato tubers and beans without pods). In wheat grown as a rotational crop PCA was found in grain at up to 56% TRR and 0.23 mg/kg.

In the available Australian residue trials samples were generally analysed for parent only. The 2010 JMPR noted that in supervised crop field trials, residues of benzamide, PCA and to a lesser extent PAA were sometimes detected in a number of commodities, mostly at longer PHIs of 10–21 days and generally at levels below 0.02 mg/kg. Higher levels of benzamide and less frequently, PCA and its methyl sulphoxide (up to 0.1 mg/kg) and PAA (rarely more than 0.05 mg/kg) were found occasionally in some legumes and brassicas, rape seed, grapes, lettuce and strawberries. The related parent residues are usually more than twice the metabolite levels.

Two of the main metabolites in plants (benzamide and PAA) are also observed in the animal metabolism studies. The 2010 JMPR noted that sufficient toxicology information is available to confirm that the PCA metabolite and its methyl sulphoxide, common metabolites with fluopicolide, are significantly less toxic than fluopyram. This was confirmed in the evaluation by OCS.

It is therefore not necessary to include the benzamide, PCA and PAA metabolites in the plant commodity residue definitions for MRL enforcement or estimation of dietary intake.

The recommended residue definition for fluopyram in plant commodities is fluopyram.

Animal commodities

In animal commodities, benzamide is the main residue in edible animal tissues, milk and eggs accounting for 49.1–98.6% of the TRR. The combined E/Z olefine isomers and the parent compound were major components only in fat of ruminants and poultry.

The US, EU and Canada have all recommended a tolerance residue definition for commodities of animal origin of fluopyram and the benzamide metabolite.[2] This is the same as has been proposed by the 2010 JMPR. More complex definitions including the E/Z olefine isomers have been proposed for risk assessment purposes. The Australian definitions will be recommended in line with those established overseas.

The recommended residue definition for fluopyram for MRL compliance in animal commodities is the sum of fluopyram and 2-(trifluoromethyl) benzamide, expressed as fluopyram.

The recommended residue definition for estimation of dietary intake for animal commodities is the sum of fluopyram, 2-(trifluoromethyl) benzamide and the combined residues of *N*-{(*E*)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-(trifluoromethyl) benzamide and *N*-{(*Z*)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-(trifluoromethyl) benzamide, all expressed as fluopyram.

4.5 Residue Trials

Australian residue data for grapes were provided. Overseas residue trials for grapes were also considered in support of the local data.

Grapes

The proposed use on grapes is for Table grapes and grapes for drying only (i.e. not for wine grapes). In the available Australian trials highest residues in grapes at 7 or more days after the last application at 20 g ai/100 L were 0.19, 0.29, 0.33, 0.44, 0.67, 0.74, 1.05 and 1.43 mg/kg. In overseas trials residues in grapes at 7 days after the last application at 250 g ai/ha were 0.10, 0.15 (n = 2), 0.19 (n = 2), 0.21, 0.27 (n = 2), 0.30, 0.32, 0.34, 0.35, 0.37 (n = 2), 0.43, 0.47, 0.48, 0.49, 0.52, 0.53, 0.55, 0.56 (n = 2), 0.57, 0.58, 0.60, 0.63, 0.70, 0.72, 0.75, 0.95, 0.96 and 1.0 mg/kg.

Given a highest residue of 1.43 mg/kg in the Australian trials (in a trial with a high spray volume) and a high residues of 1.0 mg/kg at 7 DALA in the overseas trials, an MRL of 2 mg/kg for fluopyram on FB 1235 Table-

[2] Report of the Residues of Concern Knowledgebase Subcommittee, 16th July 2009, USEPA

grapes is appropriate. It is noted that spray volumes for grapes could be as high as 2000 L/ha which would give a maximum rate per hectare of 400 g ai/ha for the Australian use pattern which is 1.6× the rate of the overseas trials. If the highest residue at 7 DALA in the overseas trials of 1 mg/kg is scaled for rate of 400 g ai/ha, the scaled HR is 1.6 mg/kg which is still within the proposed grape MRL.

4.6 Processing studies

As fluopyram will not be used on wine grapes it is not necessary to consider residues in wine, grape juice or grape pomace.

Applying the highest processing factor to raisins of 6.6× from European studies to the highest residue in grapes of 1.43 mg/kg in grapes gives a highest estimated residue of 9.44 mg/kg in dry grapes. An MRL of 15 mg/kg is recommended for fluopyram on DF 0269 Dried grapes.

4.7 Animal commodity MRLs

According to OECD guidelines grape pomace can form 20% of the diet for beef and dairy cattle in Australia. It can also form up to 20% of the diet for turkeys. However, use on grapevines will be restricted to table grapes and grapes for drying only. It is therefore not necessary to consider the livestock dietary exposure through residues in grape pomace. The following grazing withholding period statement is also included on the label: 'DO NOT graze livestock in treated vineyards'.

No changes are required to the current animal commodity MRLs for fluopyram which were recommended to cover uses under current research permits.

4.8 Estimated dietary intake

The chronic dietary exposure to fluopyram 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 from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines[3] and is a conservative estimate of dietary exposure to chemical residues in food.

The NEDI for fluopyram is equivalent to 20% of the ADI.

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 from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food.

The NESTIs for all relevant commodities are acceptable at <10% of the ARfD for children (2–6 years) and <5% for the general population (2+ years).

3 Guidelines for predicting dietary intake of pesticide residues, WHO, 1997.

4.9 Bioaccumulation potential

The log K_{ow} for fluopyram is 3.3 at pH 6.5 suggesting it is fat soluble. However the benzamide metabolite (the major component of the residue in eggs, milk and animal tissues) is not fat soluble.

4.10 Spray drift

The draft label indicates that application should be by ground spray equipment only. Aerial application was therefore not considered. The label also includes a restraint that the product should not be applied with droplets smaller than medium, except for airblast application.

In the dairy cattle feeding study highest residues were observed in liver. The Japanese MRL of 0.7 mg/kg for fluopyram in Cattle edible offal will be taken as the target concentration for spray drift, noting that the applicant has indicated they have applied for import tolerances in Taiwan and Russia at this level.

Using the APVMA's standard scenario for airblast application to vineyards the average deposition over a 300 metre field downwind from the application area is 0.00213× the field rate. This corresponds to an average deposition of 0.426 g ai/ha (for a maximum rate of 20 g ai/100 L at 1000 L/ha). Assuming pasture consists of 1500 kg DM/ha an average deposition of 0.426 g ai/ha corresponds to 0.28 ppm in the feed. The lowest feeding level in the dairy cattle transfer study (1.5 ppm) gave highest residues in liver of 0.26 mg/kg parent and 0.10 mg/kg benzamide or 0.36 mg/kg total which is below the Japanese offal MRL.

A downwind no-spray zone is not required for airblast applications to grapes for protection of international trade.

4.11 Recommendations

The following amendments are proposed to the MRL Standard:

Table 1

COMPOUND		FOOD	MRL (MG/KG)
FLUOPYRAM			
DELETE:			
DF	0269	Dried grapes (=Currants, Raisins and Sultanas)	T15
FB	1235	Table-grapes	T2
ADD:			
DF	0269	Dried grapes (=Currants, Raisins and Sultanas)	15
FB	1235	Table-grapes	2

Table 3

COMPOUND	RESIDUE
DELETE:	
Fluopyram	{T} Commodities of plant origin: Fluopyram.
	{T} Commodities of animal origin for enforcement: Sum of fluopyram and 2-(trifluoromethyl)-benzamide, expressed as fluopyram.
	{T} Commodities of animal origin for dietary exposure assessment: sum of fluopyram, 2-(trifluoromethyl) benzamide and the combined residues of *N*-{(*E*)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-(trifluoromethyl) benzamide and *N*-{(*Z*)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-(trifluoromethyl) benzamide, all expressed as fluopyram.
ADD:	
Fluopyram	Commodities of plant origin: Fluopyram
	Commodities of animal origin for enforcement: sum of fluopyram and 2-(trifluoromethyl) benzamide, expressed as fluopyram.
	Commodities of animal origin for dietary exposure assessment: sum of fluopyram, 2-(trifluoromethyl) benzamide and the combined residues of *N*-{(*E*)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-(trifluoromethyl) benzamide and *N*-{(*Z*)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-(trifluoromethyl) benzamide, all expressed as fluopyram.

The following withholding periods are required in relation to the above MRLs:

Grapes: Do not harvest for 7 days after application.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Grapes and dried grapes are considered to be major export commodities.

5.2 Destination and Value of Exports

Exports of dried vine fruit amounted to 2.9 kt in 2013–14 and were worth $9.7 million (ABARES). Information provided by the applicant indicated that the key export markets for dried grapes are Germany, Canada, the United Kingdom, New Zealand and Italy.

Table grape exports in 2010/2011 were worth A$79.5 million, with significant markets including Hong Kong ($27.1 million), Indonesia ($12.6 million), Thailand ($9.87 million), Vietnam ($7.12 million), Singapore ($6.05 million), Russia ($1.78 million), and Taiwan ($1.24 million) (Australian Bureau of Statistics).

5.3 Proposed Australian use-pattern

LUNA PRIVILEGE FUNGICIDE (500 G/L FLUOPYRAM)

Crop	Pest	Rate	Critical Comments
Grapes for dried fruit production Table grapes	Powdery Mildew	**Dilute spraying** 15 mL/100 L (7.5 g ai/100 L)	**Powdery mildew** Apply as part of a preventative spray program, from when shoots are 10 cm through to veraison, with a 10–14 day spray interval. **Botrytis bunch rot** Apply as part of a preventative spray program, with applications at critical timings for bunch rot control, including, but not limited to, flowering, pre-bunch closure and veraison. **General** **Apply a maximum of 3 applications of Luna Privilege per season.** **Apply a maximum of 1 litre of Luna Privilege per hectare per season.** Apply thoroughly to ensure complete coverage. Apply by dilute or concentrate spraying equipment. Apply the same total amount of product to the target crop whether applying this product by dilute or concentrate spraying methods. For concentrate spraying, do not use at rates greater than two times the dilute spraying rate (i.e. at a concentration factor greater
	Botrytis bunch rot	**Dilute spraying** 40 mL/100 L (20 g ai/100 L) **Concentrate spraying** Refer to the **Mixing/Application** section	

Crop	Pest	Rate	Critical Comments
			than 2X) – refer '**Application'** section in GENERAL INSTRUCTIONS.

Withholding periods:
Do not harvest for 7 days after application.
DO NOT graze livestock on treated vineyards.

5.4 Overseas registration and approved label instructions

Products containing fluopyram are registered for use on various crops in the USA and the EU.

5.5 Comparison of Australian MRLs with Codex and overseas MRLs.

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods.

Fluopyram has been considered by Codex. MRLs have also been established in the EU and USA.

The following relevant MRLs have been established for plant commodities:

Commodity	Australia (proposed) mg/kg	Codex CXL (mg/kg)	USA MRL (mg/kg)	EU MRL (mg/kg)	Japan MRL (mg/kg)
Dried grapes	15	5			20 (Raisin)
Grapes	2	2	2 (Grape, wine)	1.5 (Table and wine grapes)	10

5.6 Potential risk to trade

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

A Codex MRL is established for grapes at the same level as that proposed for Australia. Relevant MRLs have also been established for grapes in the US and EU, although the EU MRL is lower than that proposed

for Australia. For dried grapes the Codex MRL is lower than proposed for Australia. Japan has established a higher MRL for raisins than proposed.

In order to mitigate the risk to trade the following export trade advice statement has been included on the draft label:

Export of treated produce

Growers should note that suitable MRLs or import tolerances may not exist in all markets for edible produce treated with Luna Privilege. If you are growing edible produce for export, please check with Bayer CropScience Pty Ltd for the latest information on MRLs and import tolerances and for advice on any potential trade issues and their management.

Comment is sought from the relevant industry groups on the perceived level of risk and whether any industry-initiated strategies are required to manage the risk.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Summary

Luna Privilege Fungicide (the product) will be used for commercial use situations, and farmers and their employees will be the main users of the product. Workers may be exposed to the product when opening containers, mixing/loading, application, and cleaning up spills and equipment. The main route of exposure to the product/spray will be dermal and inhalation, although ocular exposure is also possible.

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide was used to estimate exposure. Exposure to the product when preparing and using the spray for airblast and low and high pressure handwand application was at an acceptable level without the need for any specific personal protective equipment (PPE). Exposure to the product during backpack application was at an acceptable level when a single layer of clothing (cotton overalls or equivalent clothing) was worn during application. However for backpack/knapsack application exposure was at an acceptable level when cotton overalls buttoned to the neck and wrist (or equivalent clothing) are worn.

Based on the risk assessment, First Aid Instructions, Safety Directions and Re-entry statements have been recommended for the product label.

6.2 Health hazards

Fluopyram (CAS: 658066-35-4) is not listed on Safe Work Australia's Hazardous Substances Information System (HSIS) Database (SWA, 2015). Based on the available toxicology information, OCS classified fluopyram as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004), with the following human health risk phrase:

Xn; R40	Limited evidence of a carcinogenic effect

The following cut-off concentrations apply for fluopyram:

Conc. ≥ 1%	Xn; R40 (Carc. Cat. 3)

Based on the product toxicology information and/or concentrations of fluopyram and other ingredients in the product, Luna Privilege Fungicide containing fluopyram at 500 g/L is classified as a hazardous substance according to the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004), with the following human health risk phrase:

Xn; R40	Limited evidence of a carcinogenic effect

6.3 Formulation, packaging, transport, storage and retailing

The active constituent fluopyram will be manufactured overseas. Luna Privilege Fungicide will be marketed in Australia in 1 to 100 L HDPE containers.

6.4 Use pattern

The product Luna Privilege Fungicide is a suspension concentrate containing 500 g/L of fluopyram. It is intended for commercial use, for the control of various fungal diseases in grapes and is to be used in orchard situations.

Luna Privilege Fungicide will be applied via crop sprayers, broadcast air assisted sprayers and potentially hand held sprayers. The proposed use rate is up to 800 mL/ha (40 mL/100L × 2000 L/ha) for vineyards. The label restricts use to up to 3 applications per year in grapes at 10–14 day intervals. Therefore the pattern of exposure is expected to be of medium/sub-chronic duration.

6.5 Exposure during use

Farmers and their employees will be the main users of Luna Privilege Fungicide. Workers may be exposed to the product when opening containers, mixing/loading, application, and cleaning up spills and equipment. The main route of exposure to the product/spray will be dermal and inhalation, although ocular exposure is also possible.

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide was used to estimate exposure. The toxic endpoint of concern and identified NOAEL is derived from a repeat dose study in animals, and in this instance a margin of exposure (MOE) of 100 or above is considered acceptable. The MOE takes into account both potential inter-species extrapolation and intra-species variability. Based on the risk assessment for workers preparing and using the spray for airblast and low and high pressure handwand application the margins of exposure are all considered to be acceptable (i.e. >100) without the need for personal protective equipment (PPE). However for backpack/knapsack application base level PPE of cotton overalls buttoned to the neck and wrist (or equivalent clothing) was required to achieve an acceptable MOE (>100).

Application of Luna Privilege Fungicide may lead to unintended bystander exposure via chemical spray drift. This may be in the form of a single random exposure or repeat exposures of residents who reside adjacent to areas being treated with the product. Parameters for assessing bystander exposure have not been finalised by APVMA, though good agricultural practices are expected to be followed.

6.6 Exposure during re-entry

There are not expected to be re-entry risks associated with dermal contact with crops treated with Luna Privilege Fungicide after the spray has dried. The following re-entry statement has been included on the product label as good agricultural practice and for product stewardship reasons:

Do not allow entry into 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.

6.7 Recommendations for safe use

Users should follow the First Aid Instructions, Safety Directions and Re-entry statements on the product label.

Luna Privilege Fungicide can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product Safety Data Sheet.

6.8 Conclusion

The APVMA is satisfied that the proposed use of Luna Privilege Fungicide, containing 500 g/L fluopyram, when used according to the product label instructions, would not be an undue hazard to the safety of people exposed to it during its handling and use.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

Bayer CropScience Pty Ltd has applied for registration of the product Luna Privilege Fungicide containing the new active constituent fluopyram. The product is a suspension concentrate (SC) formulation containing 500 g/L fluopyram. It will be marketed for use to control powdery mildew and botrytis bunch rot in table grapes and grapes for dried fruit production.

Fluopyram is a member of the pyridylethylbenzamide ('pyramide') group of fungicides. The mode of action is a succinate dehydrogenase inhibitor having penetrant and translaminar properties, and also translocated in xylem.

7.2 Environmental fate

Comments on physicochemical properties

Fluopyram is moderately soluble in water (~15 mg/L at 20°C), very slightly volatile (1.2×10^{-6} Pa at 20°C) and very slightly volatile from water (non-dimensional Henry's Law Constant H = ~1.2×10^{8} at 20°C). The molecule does not dissociate at environmentally relevant pH. Based on the n-octanol/water partition coefficient (log K_{OW} = 3.3), fluopyram has potential to bioaccumulate and is expected to have low soil mobility.

Route and rate of degradation in soil

The route of degradation of fluopyram ([phenyl-UL-^{14}C] and [pyridyl-2,6-^{14}C] labelled) has been investigated in a series of laboratory and field studies under aerobic and anaerobic conditions. The potential effect of sunlight upon this degradation has also been studied.

Route of degradation under aerobic conditions

Under aerobic laboratory conditions the primary metabolic pathway of fluopyram in soil is hydroxylation in the 7–position of the molecule to form the hydroxylated metabolite, fluopyram-7-hydroxy, identified in all soils tested with a maximum of 3.3% (pyridyl label) to 4.2% AR (phenyl label). Fluopyram-7-hydroxy in turn is cleaved to form the metabolite pyridyl-carboxylic acid (max. 0.7% AR) containing the pyridine ring and benzamide (max. 1.1% AR) containing the phenyl ring. While the pyridyl-carboxylic acid (PCA) was metabolised to methyl-sulfoxide (max. 1.0% AR), no metabolites other than the benzamide have been detected from the phenyl ring. Microbial breakdown of this ring leads to the formation of carbon dioxide.

Rate of degradation under aerobic conditions

Degradation of fluopyram was studied under laboratory aerobic conditions in four German soils (silt loam, sandy loam, clay loam and sandy loam) and two US soils (silt clay loam and sandy loam).

Fluopyram degraded slowly in soils under aerobic conditions with DT50 values ranging from 162 to 464 days in German soils and 561 to 746 days in US soils. The DT90 values (538 to >1000 days) and residues at the

end of study periods indicated that fluopyram has a potential for residue carry over to the following crop season.

No major transformation products were detected in any of the soils under aerobic conditions. The following minor products were identified: fluopyram-7-hydroxy (max. 4.2% AR); fluopyram-pyridyl-carboxylic acid (max. 0.7% AR); fluopyram-methyl-sulfoxide (max. 1.0% AR) and fluopyram-benzamide (1.1% AR).

Degradation in anaerobic soil

The anaerobic degradation of [phenyl-UL-^{14}C] and [pyridyl-2,6-^{14}C]-fluopyram was studied in a German silt loam soil. Fluopyram was stable and no significant degradation was observed under anaerobic (flooded) conditions. No major transformation products were detected for either label during both the aerobic and anaerobic phase of the study. Less than 1.1% / 0.8% (phenyl- /pyridyl- label) CO_2 and no volatile organic compounds were produced throughout the anaerobic phase of the study. The SFO half-life for both labels was >1000 days (determined by extrapolation) and fluopyram is, therefore, considered as stable under anaerobic conditions in soil.

Soil photolysis

The phototransformation of [phenyl-UL-^{14}C]-fluopyram was studied on a sandy loam soil at 20 $\pm$ 2°C and 75% soil moisture of 1/3 bar. The study showed that fluopyram was stable to photolysis under the test conditions. Therefore no degradation rates for the decline of fluopyram could be calculated. Photolysis on soil surfaces is not an important route of transformation of fluopyram in the terrestrial environment.

European field studies: Dissipation

Soil dissipation of fluopyram 250 SC under European field conditions was investigated at six sites in bare soil plots in Burscheid, Germany (silt loam), Little Shelford, United Kingdom (sandy loam), Staffanstorp, Sweden (loam), Vatteville, Northern France (silt loam), Vilobi d'Onyar, Spain (loam) and in Albaro, Italy (silt loam).

Quantifiable residues of fluopyram were detected to a maximum depth of 20 cm. Only at the Italian site, slight amounts of AE C656948 (between LOD and LOQ) were detected at a single sampling event in the 20–30 cm soil layer.

Fluopyram dissipated from the top 20 cm of the soil with DT50 values ranging from 21 to 386 days (most not Simple First Order [SFO] kinetics – DT90 values 487 to > 1000 days) under European field conditions.

European field studies: Long term accumulation

Long term accumulation of fluopyram in soil under European field conditions was studied at two sites Monheim, Germany (sandy loam) and Tarascon, France (silt loam), which come under ecoregions northern and southern Europe, respectively. The interim results over a period of two years have been presented.

According to the interim results, single application of fluopyram (250 g ac/ha) resulted in an accumulation of 29% of first application 0-day concentration in German sandy loam soil at the end of 353 days and 53% in France silt loam soil at the end of 334 days. Two consecutive annual applications resulted 57% (710 days) and 59% (697 days) of initial 0-day second application, respectively. The maximum concentrations of 234

and 250 µg ac/kg soils were detected in German sandy loam and France silt loam soils, respectively, at the 0–day third application. These interim results indicate that fluopyram has a potential for accumulation in soils under field conditions. Most of the residues were detected in the 0–30 cm soil depth, except in France silt loam where 0.75 µg ac/kg (< LOD) was detected after the third application in the 30–40 cm soil depth.

In general, concentrations slightly increased at the end of each winter period. At each site evaluation is being continued until the plateau concentration is attained.

US field studies

Five terrestrial field dissipation studies with fluopyram were carried out on bare soil plots in Washington (WA), New York (NY), North Dakota (ND), Georgia (GA), and California (CA). Fluopyram SC 500 formulation was applied to the bare plots at a rate of 500 g ac/ha.

Supplemental irrigation was supplied to maintain at least 110% of long term average rainfall for NY (126% of 30 y average), ND (177% of 10 y average), and GA (149% of 10 y average). For the highly irrigated regions of CA and WA, irrigation was carried out to meet water demand for a cropped field, although those were bare ground studies. For CA the total water input was 125% of the evapotranspiration of orchards (391% of the bare ground evapotranspiration and 546% of 10 y average rainfall), and for WA the total water input was 131% of the evapotranspiration for apple (623% of 10 y average rainfall).

Under these conditions the parent compound dissipated with DFOP DT50 values of 163, 539, 83, 24 and 174 days for WA, NY, ND, GA and CA soils, respectively.

The transformation products, fluopyram-7-hydroxy, fluopyram-benzamide, and fluopyram-PCA were detected at all the sites in minor amounts. Only at the CA site two major transformation products, fluopyram-benzamide and fluopyram-PCA with maximum concentrations 19% and 16% were observed. The maximum concentrations of these metabolites on the other four US field locations were < 10% or less than 2 × 5% for consecutive dates.

Long term soil accumulation – calculated worst case

In the absence of completed soil accumulation studies, DE has estimated worst case concentrations in soil based on the results of the field dissipation studies provided by the applicant for 11 sites (using SFO half-lives to facilitate modeling). All PECsoil calculations were performed assuming a soil bulk density of 1.5 g/cm^3 and equal distribution in the top 10 cm. Calculations were performed using the worst-case half-life value of 682 days (New York site) and also the mean value of all 11 studies (299 days). It was assumed that the maximum cumulative annual rate of fluopyram was applied on a single occasion each year (500 g/ha), with application occurring every year.

With the worst case half-life, 69% carryover is predicted, while with the mean value estimated carryover is 43% (this compares to 57% and 59% from the second year at the two sites in the long term accumulation studies: carryover of 57-59% suggests SFO half-lives of ~450-480 days). The predicted maximum cumulative soil concentration under the worst case assumptions is 1.07 mg ac/kg soil, ie ~3.2 × the concentration immediately after the first annual application. The predicted maximum cumulative soil concentration based on the average field dissipation half-life is 0.58 mg ac/kg soil, ie ~1.7 × the concentration immediately after the first annual application.

Mobility in soil

The adsorption $K_{d(ads)}$ values for fluopyram ranged from 3.16 to 8.37 mL/g and the $K_{oc(ads)}$ ranged from 266 to 460 mL/g. $K_{oc(des)}$ values ranged from 444 to 834 mL/g and were higher than the $K_{oc\ (ads)}$ values, indicating a strengthened binding of the test material once adsorbed to the soil. Although adsorption and desorption constants do not appear to be dependent on the pH of the soil, the pH values are not divergent enough to determine pH dependence.

The adsorption $K_{d(ads)}$ values of the minor metabolite fluopyram-7-hydroxy ranged from 1.03 to 2.54 mL/g and the corresponding $K_{oc\ (ads)}$ values were 91, 159, 86 and 94 mL/g. The amount of fluopyram-7-hydroxy desorbed from the adsorbed material ranged from 18 to 38%. $K_{oc(des)}$ values were higher than the $K_{oc(ads)}$ values, indicating a strengthened binding of the test material once adsorbed to the soil.

Fate and behaviour in water

Hydrolysis

Fluopyram is hydrolytically stable under acidic, neutral and alkaline conditions. No major degradation products were detected at pH 4, pH 7 and pH 9.

Aqueous photolysis

Direct phototransformation in aqueous solution does not contribute to the overall transformation of fluopyram in the environment as fluopyram does not absorb light at wavelengths greater than 292 nm. By indirect photolytic processes under laboratory conditions in sterile buffer solution of pH 7 one major transformation product fluopyram-lactam with 13% AR was detected. Under non-sterile conditions in natural water no major metabolite was observed. The maximum concentration of fluopyram-lactam under these conditions was 1.2% AR. It is concluded that phototransformation would not be a principal route of transformation in natural waters.

Fate in water and sediment

In water/sediment systems under aerobic conditions, fluopyram steadily dissipated through partition to the sediment. No major degradates were formed in either sediment/water system. The maximum CO_2 evolved was 1.8% AR. The DFOP DT50 values in the water phase were 25.5 days and 15.5 days for the German and U.S. systems, respectively. Corresponding SFO half-lives in the total system were greater than 648 days in each sediment system, which indicate that fluopyram is persistent in the aquatic systems. Aerobic biotransformation would not be an important transformation route of fluopyram in the aquatic environment.

DT50 and DT90 values of > 1000 d were calculated for fluopyram under anaerobic aquatic conditions, which indicated that anaerobic biotransformation would not be a route of transformation for fluopyram.

Fate and behaviour in air

Based on calculation for a 12 h day, a half-life time in air of 1.7 to 2.6 days was estimated, depending on the model input parameter of the mean concentration of hydroxyl radicals present in the troposphere. However,

fluopyram is not expected to partition to the atmosphere due to its relatively low vapour pressure (1.2×10^{-6} Pa) and Henry's Law Constant ($H = \sim 1.2 \times 10^{-8}$ at 20°C). Therefore volatilisation is not expected to be a significant route of dissipation for fluopyram and is not expected to result in long range atmospheric transport, despite the estimated persistence in air.

Bioconcentration

A bioconcentration study conducted with bluegill sunfish using [pyridyl-2,6-^{14}C]fluopyram indicated rapid uptake (time to reach 95% steady state was 7.7 to 14.8 days), a low bioconcentration factor (whole fish = 18; whole fish, normalized to 6% lipid content = 16 [taking into account that ~22-25% of total radioactive residues were identified as fluopyram]), and very rapid clearance (half-life = 1.8 to 3.4 days). This information indicates low fish bioaccumulation potential and also a low potential for secondary poisoning of fish eating birds and wild mammals. After 14 days in uncontaminated water, a maximum of 25% of the absorbed quantity of fluopyram remained (i.e. as total radioactive residues) in fish. While a relatively large percentage, this remaining quantity can still be considered as very low and environmentally not relevant when compared to the plateau concentration of absorption that corresponds to a very low BCF value of 16.

7.3 Environmental effects

In addition to fluopyram, the toxicity of the 500 g ac/L SC formulation was evaluated. The only metabolite evaluated was fluopyram-lactam, which was only a significant metabolite in a laboratory photolysis study under sterile conditions. Studies were generally conducted to standard test guidelines (e.g. OECD and US EPA).

Birds

Fluopyram is practically nontoxic to birds with acute oral or short term dietary exposure (acute oral LD50 > 2,000 mg ac/kg bw for bobwhite quail and zebra finch; 5 d dietary LC50 > 4785 ppm for bobwhite quail and > 4604 ppm mallard duck). Reproduction studies indicated NOECs of 46.7 ppm for bobwhite quail and 428 ppm for mallard duck. The value for bobwhite quail is based on statistical significance, but the resulting effect on 14–day survivor bodyweight was < 10% and the NOEC may more appropriately be determined to be 75.7 ppm diet.

Aquatic organisms

Aquatic testing was affected by the limit of solubility of fluopyram in the test media and most of the acute toxicity studies indicated endpoint values above the practical limit of water solubility for fluopyram according to the conditions of testing. They indicated a variability of this limit of water solubility for fluopyram depending on temperature (cold – 12°C to warm water 21°C) and salt concentration of dilution waters.

Fish

Based on the results of acute toxicity studies conducted with the active constituent, fluopyram would be categorised as at worst moderately toxic to fish, with little or no toxicity up to the limit of solubility in the test

media (96 h LC50 to rainbow trout, bluegill sunfish and fathead minnow and sheepshead minnow, respectively, > 1.78, > 5.17, > 4.95 and > 0.98 mg ac/L).

An acute toxicity study was conducted with the SC 500 formulation, but the results were possibly affected by undissolved test material, which was observed at the three highest test concentrations (nominal 21–120 mg formulation/L, 8.72–49.8 mg ac/L - TWA measured concentration 8.27-46.4 mg ac/L). Based on the results recorded for mortality, the formulation would be classified as no more than slightly toxic to rainbow trout (96 h LC50 > 120 mg formulation [nominal], > 46.4 mg ac/L [TWA measured concentration]). However, sublethal effects were evident at all but the lowest test concentration (NOAEC = 3.6 mg formulation/L [nominal] or 1.31 mg ac/L [TWA measured concentration]).

A 33–day chronic toxicity study of fluopyram to the early life stage of fathead minnow indicated 33 d NOAEC and LOAEC values of 0.135 and 0.269 mg ac/L, respectively, based on clinical signs of toxicity, the most sensitive endpoint. Thus fluopyram can be classified as slightly toxic to fish with chronic exposure (NOEC = 0.1–1 mg ac/L).

Aquatic invertebrates

Based on the results of acute toxicity studies conducted with the active constituent, fluopyram would be classified as no more than slightly toxic to the freshwater daphnid *Daphnia magna* (48 h EC50 > 17 mg ac/L) and, at worst, as highly toxic to the marine/estuarine aquatic invertebrates mysid shrimp (96 h LC50 > 0.51 mg ac/L) and eastern oyster (96 h EC50 > 0.43 mg ac/L), in all cases with little or no toxicity up to the limit of solubility in the test media.

An acute toxicity study conducted with the SC 500 formulation indicated that the formulation would be classified as no more than slightly toxic to *Daphnia magna* (48 h EC50 > 100 mg formulation [nominal], > 38.2 mg ac/L [mean measured concentration]).

A 21 day chronic toxicity study of fluopyram to *Daphnia magna* indicated 21 d NOAEC and LOAEC values of 1.214 and 2.996 mg ac/L, respectively, based upon treatment-related effects on offspring production and terminal body lengths of surviving females. Thus fluopyram can be classified as very slightly toxic to aquatic invertebrates with chronic exposure (NOEC > 1 mg ac/L).

Benthic invertebrates

Studies were conducted with three benthic invertebrate species. [Pyridyl-2,6-^{14}C]-labelled fluopyram was used in the studies where sediment was spiked, with results expressed in terms of measured total radioactive residues (TRR).

A 10 day (acute exposure) study with the marine amphipod *Leptocheirus plumulosus* indicated a 10 d LC50 > 100 mg TRR/kg dw sediment and NOAEC for survival = 100 mg TRR/kg dw sediment (Table 14). Fluopyram can therefore be classified as practically non-toxic to immature marine amphipods with acute exposure, based on measurement of total radioactive residues from the initially applied test substance.

A 28–day sub-chronic toxicity with *Leptocheirus plumulosus* indicated a 28 day NOAEC = 36 mg TRR/kg dw sediment (corresponding with 2.5 mg TRR/L pore water and 0.55 mg TRR/L overlying water), based upon a statistically-significant reduction in dry weight (growth) relative to the negative control, at the 92 mg TRR/kg

sediment level (corresponding with 5.9 mg TRR/L pore water and 1.19 mg TRR/L overlying water). Reliable conclusions could not be drawn regarding impacts on reproduction (number of offspring per amphipod), as there was a very poor dose-response for this endpoint, and the reviewer's analysis detected a significant difference between the negative and solvent control groups for this endpoint, with significantly fewer (25%) offspring produced in the solvent control [treatments were not significantly different from the solvent control, but compared to the negative control were reduced at all levels (6–41%), significantly so ($p < 0.05$) at the second lowest treatment level (6.3 mg TRR/kg)].

A 54 day life-cycle toxicity with the freshwater dipteran midge *Chironomus tentans* indicated a 54 day NOAEC of 26 mg TRR/kg dw sediment (corresponding with 3.8 mg TRR/L pore water and 0.14 mg TRR/L overlying water), based upon statistically-significant reductions in larval survival and percent emergence. Midge growth (assessed on day 20) and development rate for both sexes were statistically-reduced at the 96 mg TRR/kg sediment level. No treatment-related effects on time to death for mated adults, number of eggs per female, or percent hatch of egg masses were indicated.

A 28 day sub-chronic toxicity study of technical-grade fluopyram to the freshwater dipteran *Chironomus riparius* was also conducted (static conditions, with treatment of the water, with sediment present). The more sensitive endpoint was emergence ratio, with the 28 day NOAEC = 0.525 mg ac/L overlying water based on TWA concentrations and LOAEC = 1.63 mg ac/L overlying water (sediment and pore water concentrations not measured).

Algae and aquatic plants

Studies indicated that based on the toxicity results for biomass (area under the growth curve [E_bC50], and growth rate [E_rC50]), fluopyram can be classified as moderately toxic to green and blue-green algae and diatoms. The species tested were a freshwater green alga (*Pseudokirchneriella subcapitata* – 96 h E_bC50 = 4.3 mg ac/L, E_rC50 = 6.0 mg ac/L), a blue-green alga (*Anabaena flos-aquae* – 96 h E_bC50, E_rC50 > 9.69 mg ac/L), a freshwater diatom (*Navicula pelliculosa* – 96 h E_bC50 = 6.1 mg ac/L, E_rC50 = 9.6 mg ac/L), and a marine diatom (*Skeletonema costatum* - 96 h E_bC50, E_rC50 > 1.13 mg ac/L). Similarly, a study with the freshwater duckweed *Lemna gibba* indicated fluopyram can be classified as moderately toxic to aquatic plants (7 d EC50 = 2.6 mg ac/L).

Studies with the SC 500 formulation indicated similar toxicity of fluopyram applied as the formulation (72 h EC50 [cell density] = 8.2 mg formulation/L, 3.4 mg ac/L to *Pseudokirchneriella subcapitata*; 7 d EC50 = 7.0 mg formulation/L, 2.9 mg ac/L to *Lemna gibba* - based on measured concentrations).

A study of the toxicity of the metabolite fluopyram-lactam indicated at most moderate toxicity to *Pseudokirchneriella subcapitata* (72 h E_bC50, E_rC50 > 8.87 mg as/L).

Other terrestrial vertebrates

The following endpoints and discussion for assessment of the risk to other terrestrial vertebrates are noted. These are drawn from the draft assessment report prepared through the Joint Review process and have not been examined by DEH.

Fluopyram and the SC 500 formulation are practically non-toxic to mammals (rat acute oral LD50 > 2,000 mg ac/kg bw and > 2,000 mg formulation/kg bw). The NOAEC for rats in a two-generation reproductive study was 220 ppm feed (corresponding to 14.5 mg ac/kg/day in males, 17.2 mg ac/kg/day in females; LOAEC = 1,200 ppm for parental systemic effects and offspring effects, NOAEC = 1,200 ppm for reproductive effects).

Bees

Acute exposure (48 h observation) limit tests were conducted with oral and contact exposure of the honeybee, *Apis mellifera*. With the active constituent, the 48 h LD50 was >103.2 µg ac/bee (NOAEL = 100 µg ac/bee) with oral exposure, and with contact exposure the 48 h LD50 was > 100 µg ac/bee (NOAEL = 100 µg ac/bee). With the SC 500 formulation, the 48 h LD50 was >214 µg formulation (89 µg ac)/bee (NOAEL = 214 µg formulation/bee) with oral exposure, and with contact exposure the 48 h LD50 was > 200 µg formulation (89 µg ac)/bee (NOAEL = 200 µg ac/bee). Fluopyram would therefore be categorized as very slightly toxic to honeybees on both an acute oral and contact toxicity basis.

Terrestrial arthropod species other than bees

Tier 1 rate response laboratory studies were provided for two terrestrial invertebrate predators/parasites, where the insects/mites were exposed to dried spray residues from the SC 500 formulation in small enclosures. The 48 h exposure LR50 (mortality) and EC50 (subsequent reproduction) for the cereal aphid parasitoid wasp *Aphidius rhopalosiphi* were both > 2 L formulation/ha. The 7 d LR50 and 14 d EC50 (reproduction) for the predatory mite *Typhlodromus pyri* were also both > 2 L formulation/ha.

A Tier 2 extended laboratory study was conducted with the rove beetle (*Aleochara bilineata*), a ground-dwelling predaceous species with larvae that are parasitic of root maggot eggs, larvae and pupae. In this test the SC 500 formulation was applied at rates up to 2 L formulation/ha to the surface of soil in plastic containers, after which adult male and female beetles were introduced. After a 28 day exposure phase adult mortality was determined and a hatching phase then commenced to evaluate reproduction (emergence of adults from onion fly pupae mixed into the substrate at days 7, 14 and 21 of the exposure period). Statistical analysis revealed no significant differences in adult mortality or reproductive capacity between the control and all test item treatment groups.

Earthworms and other soil non-target macro-organisms

Acute and chronic/reproductive toxicity to earthworms

Fluopyram active constituent and the SC 500 formulation proposed for Luna® Privilege Fungicide are both very slightly toxic to the earthworm species *Eisenia foetida* with acute exposure (14 d LC50 > 1,000 mg ac/kg soil dw and > 1,000 mg formulation [414 mg ac]/kg soil dw, nominal initial concentrations). An earthworm reproduction study with the SC 500 formulation produced a NOEC of 5.62 L formulation/ha applied to the surface of the artificial soil in test containers (equivalent to 27.3 formulation [11.4 mg ac]/kg soil dw). In the reproduction study, at day 56 statistically significantly different values for the number of juveniles per test vessel relative to the control were observed at the highest application rate of 10.0 L formulation/ha (48.6 mg formulation/kg soil dw), but mortality of adult earthworms or change in worm biomass relative to the control after the initial 28 days of exposure were not significantly affected at any of the rates tested.

Other soil non-target macro-organisms

In a 14 day study corresponding to the new OECD Guideline 226, the overall NOEC for mortality and reproduction for the soil mite species *Hypoaspis aculeifer* was 1,000 mg Fluopyram SC 500/kg soil dw, the highest soil concentration tested. The LOEC was >1,000 mg Fluopyram SC 500/kg soil dw.

In a 28 day study corresponding to the new OECD Guideline 232, the overall NOEC for mortality and reproduction for the Collembola species *Folsomia candida* was 250 mg Fluopyram SC 500/kg soil dw, the highest soil concentration tested. The LOEC was >250 mg Fluopyram SC 500/kg soil dw.

Effect on organic matter breakdown

A litter bag study was conducted with the SC 500 formulation applied at rates to produce soil concentrations simulating ongoing annual use at 300 g ac/ha, assuming 40% interception of an application rate of 500 g ac/ha. The plateau concentration of Fluopyram SC 500 was calculated to be 0.428 mg ac/kg soil, based on a preliminary mean DT50 value of 300 days for the active substance and calculated for a depth of 0–10 cm. The total nominal soil concentration was therefore 628 mg ac/kg soil (plateau concentration in surface 10 cm soil = 428 mg ac/kg soil [642 g ac/ha incorporated by harrows] + 200 mg ac/kg soil from a single application at 300 g ac/ha to the soil surface after burial of the litter bags). The study showed no significant differences in litter mass loss between control (76.2%) and treatment groups (76.9%) after 6 months. Therefore it can be concluded that under the conditions of this study with maximum measured soil residues of fluopyram of 0.514 mg ac/kg soil there was no influence on organic matter breakdown.

Soil microbial activity

Nitrogen and carbon transformation

The effects of fluopyram on carbon and nitrogen transformation by soil micro-organisms was examined in studies to OECD guidelines with fluopyram and with the SC 500 formulation. Tested soil concentrations of fluopyram were 0.33 mg and 3.33 mg ac/kg soil dw (corresponding to application rates of 1× and 10× an application rate of 250 g ac/ha), and tested concentrations of Fluopyram SC 500 were 0.67 mL and 6.7 mL formulation/kg soil dw (corresponding to application rates of 1× and 10× an application rate of 0.5 L formulation/ha).

With both fluopyram and fluopyram SC500 and at both application rates, differences in the rates of nitrate formation between the treatment and control were below 25% at each of the 0-7, 7–14 and 14–28 day intervals. In all cases, differences in carbon dioxide production rates between control soil samples and treated soil samples were also < 25% when tested after 7, 14 or 28 days incubation. Thus the trigger values of the guidelines for termination of the studies at 28 days were met and it can be concluded that there was no harmful impact on nitrogen or carbon transformation with either fluopyram or fluopyram SC 500 at the tested application rates (NOEC = 3.3 mg ac/kg soil dw).

Growth of soil fungi

Tests were conducted with fluopyram ac and five species of soil fungi/water moulds grown on soil-malt extract-agar plates in the laboratory in the dark at 20 ± 2°C. The species tested were from three fungal phyla

(the Ascomycota [ascomycetes], Zygomycota and Basidiomycota) and one Oomycete species (now classified in the Kingdom Chromalveolata [water moulds]). EC25 values for the species *Phytophthora nicotianae*, *Agrocybe aegerita* and *Cladorrhinum foecundissimum* were > 30 mg ac/kg soil dw, but were 2.0 mg ac/kg soil dw for *Mucor circinelloides* var. *griseocyanus* (EC10 = ~0.5 mg ac/kg soil dw) and 3.7 mg ac/kg soil dw for *Penicillium simplicissimum* (EC10 = ~0.9 mg ac/kg soil dw).

Terrestrial plants

Studies were conducted of the toxicity of the SC 500 formulation to terrestrial plants, with application of spray to the soil surface or incorporated into the soil prior to planting, or application to the foliage of young plant seedlings. In each case 10 standard crop/pasture species were tested at the Tier I level, including four monocotyledonous species ('monocots'—barley or onion, maize, perennial ryegrass and oat) and six dicotyledonous species ('dicots'—buckwheat, cucumber, oilseed rape, soybean, sugarbeet and sunflower).

In a standard Tier I guideline study with the formulation applied to soil at planting at 498 g ac/ha, no harmful effects were evident on % emergence or 21 d survival, and no visual symptoms of phytotoxicity were observed in any of the species tested. No monocot species exhibited harmful effects on growth and most dicot species also exhibited at most mild growth effects. However, for buckwheat there was 50.4% growth inhibition (dry weight) compared to the negative control. Thus the ER50 and ER25 were both > 498 g ac/ha for monocot species, while for dicots the ER50 was ~498 g ac/ha and the ER25 < 498 g ac/ha. In the Tier II study (buckwheat only), there were no harmful effects on plant survival or shoot length, while inhibition in buckwheat dry weight ranged from mild to relatively high, with no clear dose-dependent pattern. The maximum inhibition was 40.1% in the 250 g ac/ha treatment group (though not statistically significant), but inhibition was only 6.2% at the next (highest) treatment level. Inhibition in height was very mild across all test concentrations. No phytotoxic effects were observed. Based on these results, the ER50 was determined to be > 498 g ac/ha, ER25 < 249 g ac/ha and NOER = 62.8 g ac/ha. Another Tier II study with buckwheat would need to be conducted to clarify the ER25 and ER05 endpoints, using additional replicates to improve the statistical power.

In a standard Tier I guideline study with the formulation applied to young seedlings at 250 g ac/ha, survival was not affected by fluopyram treatment. Inhibition in dry weight was relatively mild across all treatments, with sugarbeet having the highest level of inhibition of 20.2% (< 25%) in comparison to the negative control. Inhibition in height was very mild across all treatments, with no species exhibiting inhibitions of ≥ 5% in comparison to the negative control. The most sensitive monocot and dicot species could not be determined. The NOER and ER25 for all species was 250 and > 250 g ac/ha, respectively. There were no compound-related phytotoxic effects.

A non-standard study with fluopyram (as the SC 500 formulation) incorporated into soil at 125, 250 and 500 g ac/ha prior to planting found no effects on plant emergence across species, except for oat and ryegrass, which experienced effects at the first two treatment levels. Due to promotion of growth at the highest treatment level, a dose-response relationship cannot be inferred. There was no crop damage in any species, and there was no effect of the treatment on fresh weight across all species. It was concluded that the ER25 and ER50 were > 500 g ac/ha and the NOER = 500 g ac/ha.

Biological methods of sewage treatment

An activated sludge, respiration inhibition test indicated < 20% inhibition from fluopyram concentrations up to 10,000 mg ac/L, indicating low toxicity to sewage microorganisms.

7.4 Risk assessment

Luna Privilege Fungicide will be applied to grapevines by ground application only, therefore the risk assessment has considered application by orchard airblast sprayer. The maximum cumulative application rate per annum for grapes is 1000 mL product (500 g ac)/ha. For use by orchard airblast application to grapes, for simplicity a worst case situation of a single application at 1000 mL/ha was considered.

An acceptable risk to birds and mammals with acute or chronic exposure was indicated, based on worst case scenarios where 100% of the diet was obtained from contaminated feed.

For aquatic exposure, predicted concentrations in water in a 15 cm deep, 3 m wide pond downwind of the treated area were compared to endpoints for acute exposure (mysid shrimp 96 h LC50 > 510 µg ac/L, *Lemna gibba* 7 d EC50 = 2600 µg ac/L) and chronic exposure (fathead minnow 33 d NOEC = 0.135 mg ac/L). For consideration of multiple applications, DT50s of 55.2 days from water and > 648 days from the whole system were assumed. A risk to aquatic organisms with chronic exposure was indicated with direct overspray on one or more occasions at 250 mL product/ha, thus direct overspray must be avoided with vineyard use. However, evaluation of spray drift indicated that no downwind no-spray zone buffers are required to protect organisms living in water or sediment from spray drift. Modelling also indicated that the risk to aquatic ecosystems from the run-off of fluopyram is acceptable for both the aquatic and sediment compartments. Based on a worst case screening model, it was concluded that because fluopyram has medium mobility and is very slow to degrade, over long time periods it may reach groundwater in highly susceptible situations, but at very low concentrations well below harmful levels to aquatic organisms.

The risk to bees from direct or indirect exposure to spray at the maximum individual application rates to grapes is acceptable, and higher tier tests were not required. Consideration of Tier I and II laboratory studies indicates that no unacceptable effects on populations of various insect and mite predators and parasites should be expected from the proposed uses.

Comparison of worst case predicted soil concentrations with acute and chronic exposure endpoints for earthworms indicated an acceptable risk to earthworms with acute or chronic exposure to fluopyram or the Luna Privilege formulation, even after repeated long-term application. Comparison of predicted worst case concentrations in soil with the endpoints from collembola and soil mite studies also indicate an acceptable risk. A litter bag study also indicates that the risk to non-target soil macro-organisms and the breakdown of organic matter is acceptable under the proposed use pattern. The risk to soil microorganisms from residues of fluopyram was also found acceptable.

In the terrestrial plant studies provided most species were not harmed at a rate of 500 g ac/ha, thus even with direct overspray most species would not be harmed at that rate. It is concluded that no harmful effects on off field non-target terrestrial plant species are expected at the maximum single application rates of 400 g ac/ha to grapevines or the maximum cumulative rate of 500 g ac/ha.

In considering the submitted data, DE has given particular attention to the potential risk to organisms in the environment arising from persistence of fluopyram in soil and sediment. Based on the submitted data, the risk to birds, mammals, plants, bees, earthworms and other non-target terrestrial invertebrates was found acceptable, and no harmful impact on soil nitrogen and carbon metabolism is expected from the proposed uses. Based on the acute and chronic aquatic toxicity studies provided, with the proposed uses the risk to aquatic and sediment-dwelling organisms from spray drift, run-off or if groundwater were returned to the surface were found acceptable, with no Downwind No-Spray Zone being required.

7.5 Conclusion

The APVMA is satisfied that the proposed use of Luna Privilege Fungicide, containing 500 g/L fluopyram, when used according to the product label instructions, would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed usepattern

Fluopyram is a broad-spectrum fungicide of the pyridinyl-ethyl-benzamides ('pyramide') group with preventative, systemic and curative properties for the control of certain crop diseases. The mode of action is a succinate dehydrogenase inhibitor within the fungal mitochondrial respiration chain, having penetrant and translaminar properties, and also translocated in xylem. For crop protection purposes Luna Privilege Fungicide is best suited for use in a preventative treatment program. For resistance management purposes fluopyram is included in the Fungicide Resistance Action Committee (FRAC) Group 7 Fungicides group.

Luna Privilege Fungicide (the product) is intended for control of botrytis bunch rot (*Botrytis cinerea*) and powdery mildew (*Uncinula necator*) in grapes for dried fruit production and in table grapes. The product is intended to be used at a rate of 15 mL/100L water (dilute spraying) for control of powdery mildew and at a rate of 40 mL/100L water (dilute spraying) for control of botrytis bunch rot.

For powdery mildew control the product is to be applied as part of a preventative spray program, from when shoots are 10cm through to veraison, with a 10–14 day spray interval. For botrytis bunch rot control the product is to be applied as part of a preventative spray program, with applications at critical timings for bunch rot control, including, but not limited to, flowering, pre-bunch closure and veraison.

The product may be applied using dilute or concentrate spraying methods using orchard spraying equipment and is approved for ground application only. A maximum of 3 applications of the product may be made per season with a total maximum of 1 litre (500 g.a.i.) product per hectare per season. The use is subject to a CropLife Australia fungicide resistance management strategy which limits the total number and consecutive number of applications of the product.

8.2 Assessment of study/trial data

Data were supplied from 24 Australian field trials conducted in grapes in Victoria, New South Wales, South Australia, Western Australia and Tasmania to demonstrate the efficacy of Luna Privilege Fungicide (the product) against powdery mildew (*Uncinula necator*) (in 13 of the trials) and botrytis bunch rot or grey mould (*Botrytis cinerea*) (in 16 of the trials). Sufficient disease pressure was present in all except one of the trials, which was still relied on for crop safety evaluation purposes. Crop safety parameters, as evidenced by safety to leaves, flowers and fruit, were measured in all 24 trials.

Control (measured as % incidence and severity) of powdery mildew was 75–100%, using the product at the proposed label rate of 15 mL/100L with disease pressure of 4.5–100% incidence in the untreated control (UTC). Control of botrytis bunch rot was measured as significant reduction in incidence and severity to 100%, using the product at the proposed label rate of 40 mL/100L with disease pressure of 5.8–100% incidence in the untreated control (UTC).

The formulations tested were consistent with, or comparable to, those proposed for registration and a range of rates were tested to determine an optimal application rate and application regime.

Control when using the product in a program was demonstrated, evidenced by statistically significant equivalent or superior performance to a wide range of various industry standard fungicides in 23 of the 24 trials, and in two of the trials in an alternating program with suitable industry standard fungicides. All trials were conducted using suitable methodology, appropriate parameters were assessed and satisfactory evidence of efficacy under normal commercial growing conditions was provided.

Crop safety was assessed in all 24 trials at up to 1.25 x maximum label rate on grapes. There was no evidence of phytotoxicity from the use of the product to leaves, flowers or fruit in any treatment.

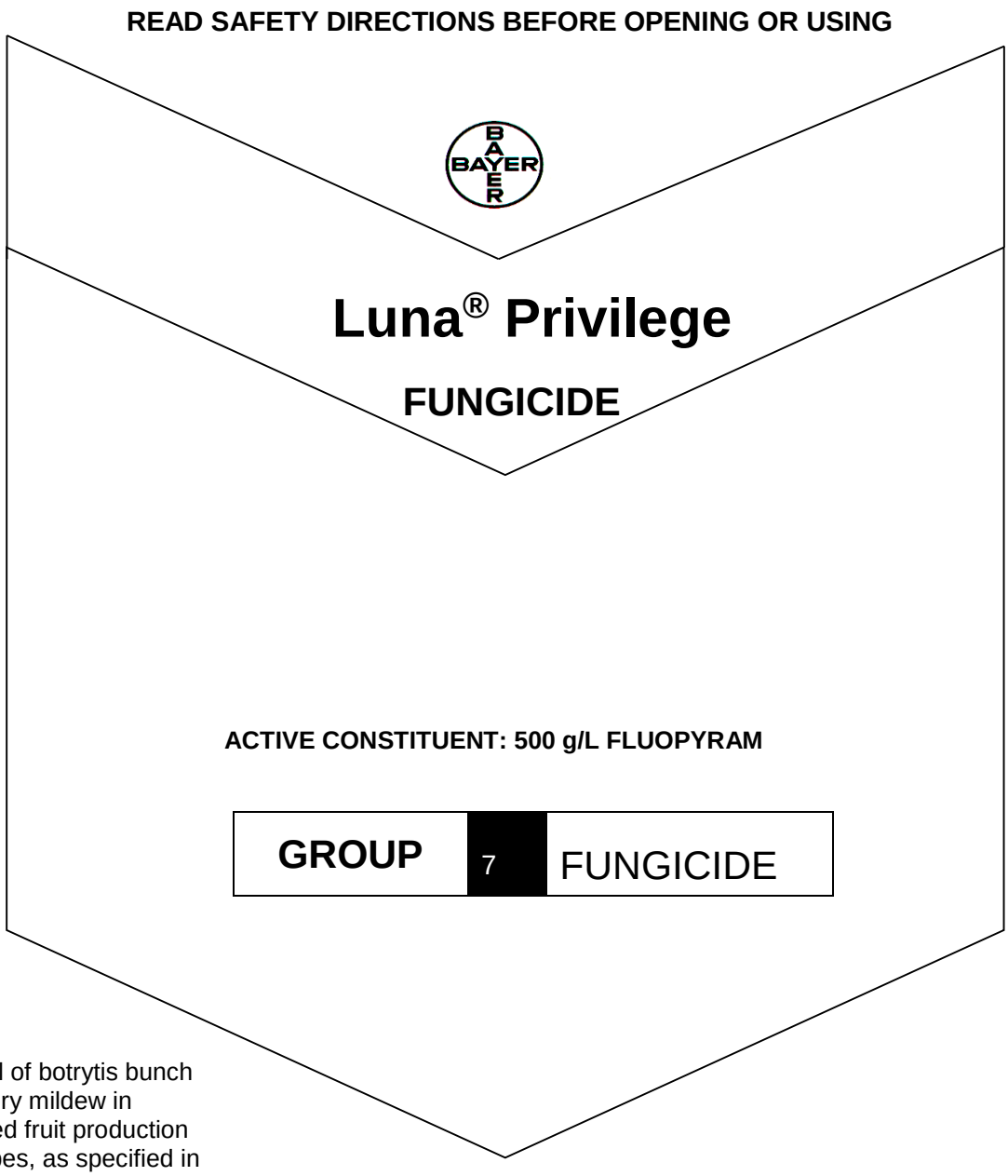
8.3 General conclusions

The label claims and instructions proposed in the Claims for use statement and the Directions for use and other label instructions are consistent with the results of the trials and other information presented.

The APVMA is satisfied, based on the trial data submitted and the advice provided, that the product Luna Privilege Fungicide is expected to be safe and efficacious when used as proposed.

9 LABELLING REQUIREMENTS

MAIN PANEL



For the control of botrytis bunch rot and powdery mildew in grapes for dried fruit production and table grapes, as specified in the DIRECTIONS FOR USE table

*** L**

(label code)

* 1 - 100 L

REAR PANEL

DIRECTIONS FOR USE
DO NOT apply with aircraft

SPRAY DRIFT RESTRAINTS
Except when applying with vineyard airblast equipment, **DO NOT** apply with spray droplets smaller than a **MEDIUM** spray droplet size category according to nozzle manufacturer specifications that refer to the ASAE S572 Standard or the BCPC Guideline.

DO NOT apply when wind speed is less than 3 or more than 20 kilometres per hour as measured at the application site.

DO NOT apply during surface temperature inversion conditions at the application site.

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

CROP	DISEASE	RATE	CRITICAL COMMENTS
Grapes for dried fruit production Table grapes	Powdery Mildew	**Dilute spraying** 15 mL/100 L **Concentrate spraying** Refer to the **Application** section	**Powdery mildew** Apply as part of a preventative spray program, from when shoots are 10 cm through to veraison, with a 10-14 day spray interval. **Botrytis bunch rot** Apply as part of a preventative spray program, with applications at critical timings for bunch rot control, including, but not limited to, flowering, pre-bunch closure and veraison. **General** **Apply a maximum of 3 applications of Luna Privilege per season.** **Apply a maximum of 1 litre of Luna Privilege per hectare per season.** Apply thoroughly to ensure complete coverage. Apply by dilute or concentrate spraying equipment. Apply the same total amount of product to the target crop whether applying this product by dilute or concentrate spraying methods. For concentrate spraying, do not use at rates greater than two times the dilute spraying rate (i.e. at a concentration factor greater than 2X) – refer '**Application**' section in GENERAL INSTRUCTIONS. **Resistance Management** This use is subject to a CropLife Australia fungicide resistance management strategy which limits the total number and consecutive number of applications of Luna Privilege.
	Botrytis bunch rot	**Dilute spraying** 40 mL/100 L **Concentrate spraying** Refer to the **Application** section	

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

WITHHOLDING PERIOD
Grapes: DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION

DO NOT graze livestock in treated vineyards

GENERAL INSTRUCTIONS

Fungicide Resistance Warning

GROUP	7	FUNGICIDE

Luna Privilege Fungicide is a member of the pyridylethylamide group of fungicides. For fungicide resistance management Luna Privilege is a Group 7 fungicide. Some naturally occurring individual fungi resistant to Luna Privilege and other Group 7 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungal population if these fungicides are used repeatedly. These resistant fungi will not be controlled by Luna Privilege and other Group 7 fungicides, thus resulting in a reduction in efficacy and possible yield loss. Since the occurrence of resistant fungi is difficult to detect prior to use, Bayer CropScience Pty Ltd accepts no liability for any losses that may result from the failure of Luna Privilege to control resistant fungi.

Luna Privilege may be subject to specific resistance management strategies. For further information contact your local supplier, Bayer CropScience representative, local agricultural department agronomist or refer to the CropLife Australia website.

Export of treated produce
Growers should note that suitable MRLs or import tolerances may not exist in all markets for edible produce treated with Luna Privilege. If you are growing edible produce for export, please check with Bayer CropScience Pty Ltd for the latest information on MRLs and import tolerances and for advice on any potential trade issues and their management.

Mixing
Shake well before use. Half fill the spray tank with water. Pour in the required quantity of Luna Privilege Fungicide with agitators running, then top up with water. Use spray mixture immediately after preparation, do not allow it to stand.

Application
Application should be by ground spray equipment only. Thorough coverage of the target area is essential.

Dilute Spraying
- Use a sprayer designed to apply high spray volumes, up to the point of run-off 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 run-off. Avoid excessive run-off.
- The required spray volume may be determined by applying different test volumes, using different settings on the sprayer, or 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 run-off.
- 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 spray volumes less than those required to reach the point of run-off) and matched to the crop being sprayed.
- Set up and operate the sprayer to achieve even coverage throughout the crop canopy using your chosen spray volume.
- Determine an appropriate dilute spray volume (See *Dilute Spraying* above) 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 1500 L/ha
2. Your chosen concentrate spray volume: For example 750 L/ha
3. The concentration factor in this example is 2 X (i.e. 1500 L ÷ 750 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.
- ♦ Do not use at a concentration factor greater than 2X (e.g. at a rate higher than 80 mL/100 L where a dilute spraying rate of 40 mL/100 L is specified).
- For further information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow industry best practice.

Sprayer Clean Up
If clean up of spray equipment is required, rinse equipment twice with clean water after use.

Compatibility

For information on the compatibility of Luna Privilege with other products, contact your local Bayer CropScience representative.

PRECAUTION

Re-entry period

Do not allow entry into 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

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

PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS

A spray drift minimisation strategy should be employed at all times. Spray drift may occur under adverse meteorological conditions or from certain spraying equipment. Do not allow spray to drift onto sensitive areas including, but not limited to, susceptible plants/crops, cropping land, pasture, natural streams, rivers, wetlands, waterways or human dwellings.

STORAGE AND DISPOSAL

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

1 litre pack

Triple-rinse container before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. Break, crush, or puncture and deliver empty container to an approved waste management facility. If an approved facility is not available, bury the empty container 500 mm below the surface in a disposal pit specifically marked and set up for this purpose, clear of waterways, desirable vegetation and tree roots, in compliance with relevant Local, State or Territory government regulations. Do not burn empty containers or product. Do not re-use empty container for any other purpose.

2 to 100 litre disposable packs

Triple-rinse container 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 container to an approved waste management facility. If an approved facility is not available, bury the empty container 500 mm below the surface in a disposal pit specifically marked and set up for this purpose, clear of waterways, desirable vegetation and tree roots, in compliance with relevant Local, State or Territory government regulations. Do not burn empty containers or product. Do not re-use empty container for any other purpose.

50 to 100 litre returnable packs

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

SAFETY DIRECTIONS

When opening the container and preparing the spray wear elbow-length chemical resistant gloves. If applying by spraying equipment carried on the back of the user, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length chemical resistant gloves. Wash hands after use. After each day's use, wash gloves and contaminated clothing.

FIRST AID
If poisoning occurs, contact a doctor or Poisons Information Centre (telephone 131126).

SAFETY DATA SHEET
Additional information is listed in the Safety Data Sheet, which can be obtained from www.bayercropscience.com.au.

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

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APVMA Approval No.:

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

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Batch Number: Date of Manufacture:

ABBREVIATIONS

AC/ac	active constituent
ACCS	Advisory Committee on Chemicals Scheduling
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
BBCH	Scale used to identify phenological developmental stages of plants (Biologische Bundesanstalt, Bundessortenamt and CHemical industry)
BCF	Bioconcentration factor
bw	bodyweight
°C	Degrees Centigrade
CHO	Chinese Hamster Ovary
CIPAC	Collaborative International Pesticides Analytical Council
Croplife	Croplife Australia
cm	centimetre
d	day
DAT	Days After Treatment
DFOP	Double First-Order in Parallel (dissipation kinetics)
DE	Department of Environment
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 adversely impacted or immobilised
EEC	Estimated Environmental Concentration

E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
$ER_{25/50}$	the rate that results in an undesirable change or alteration of 25%(or 50%) in the test endpoint being measured relative to the control
ESI	Export Slaughter Interval
EU	European Union
EUP	End Use Product
Fo	original parent generation
F1	First generation
FRAC	Fungicides Resistance Action Committee
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GI	Gastro Intestinal
GJR	Global Joint Review
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Heamatocrit
HDPE	High Density Polyethylene
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HR	highest residue
HR-P	Calculated highest residue - processed commodity
HSIS	Hazardous Substance Information System
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
JMPR	Joint FAO/WHO Meetings on Pesticide Residues
K_d	distribution coefficient for adsorption
$K_{d(ads)}$	distribution coefficient for adsorption
kg	kilogram
$K_{oc(ads)}$	apparent adsorption constant
$K_{oc(des)}$	apparent desorption constant
K_{oc}/ K_{foc}	organic carbon adsorption coefficient
L	litre
LC_{50}	concentration that kills 50% of the test population of organisms
LC/MS/MS	liquid chromatography-tandem mass spectrometer
LCT	Leydig Cell Tumours
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LH	Lutenising Hormone
LLNA	Local Lymph Node Assay
LOD	Limit of Detection – level at which residues can be detected
LOAEC	Lowest Observable Adverse Effect Concentration
LOAEL	Lowest Observable Adverse Effect Level
LOEL	Lowest Observable Effect Level
$\log K_{ow}$	Octanol-Water Partition Coefficient
LOQ	Limit of Quantitation – level at which residues can be quantified
LR_{50}	Application rate that kills 50% of the test population of organisms
m	metre
mg	milligram
mL	millilitre

MMAD	Mass Median Aerodynamic Diameter
MoA	Mode of Action
MOE	Margin Of Exposure
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
nAChR	nicotinic acetylcholine receptor
ND	Not Detectable
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
nm	nanometres
NOHSC	National Occupational Health and Safety Commission
NOAEC	No Observable Adverse Effect Concentration
NOEC	No Observable Effect Concentration
NOAEL	No Observable Adverse Effect Level
NOEL	No Observable Effect Level
NOER	No Observable Effect Rate
OC	Organic Carbon
OCS	Office of Chemical Safety (Department of Health and Ageing)
OECD	Organisation for Economic Cooperation and Development
OM	Organic Matter
Pa	Pascals
PEC	Predicted Environmental Concentration
PHED	Pesticide Handler Exposure Database
PHI	Post Harvest Interval
PMRA	Pest Management Regulatory Agency (Canada)
P_{ow}	octanol/water partition coefficient

ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
RAC	Confined Rotational Crop
RBC	Red Blood Cell
RSD	Relative Standard Deviation
s	second
SC	Suspension Concentrate
SFO	Single First-Order Rate model (dissipation kinetics)
STMR	Supervised Trials Median Residue
STMR-P	STMR corrected for processing
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SWA	Safe Work Australia
$T_{1/2}$	Elimination Half-Life
TGAC	Technical grade active constituent
T_{max}	Time to achieve maximum concentration
TRR	Total Radioactive Residue
µg	microgram
US EPA	U.S. Environmental Protection Agency
UTC	Untreated control
UV/VIS	Ultra Violet/Visible Light
VMT	Vehicle Mounted Tank
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

Australian Pesticides and Veterinary Medicines Authority 2008, *Ag MORAG: Manual of Requirements and Guidelines*, APVMA, Canberra.