Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active Cyflufenamid in the Product

Cyflamid 50EW Fungicide

APVMA Product Number 63036

DECEMBER 2012

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PREFACE

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

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

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

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

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

About this document

This is a Public Release Summary.

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

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

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

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of **CYFLAMID 50EW 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 **31 January 2013** 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:

Contact Officer
Pesticides Program
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604
Australia

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

Phone: 02 6210 4748
Fax: 02 6210 4776
Email: pesticides@apvma.gov.au

Further information

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

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

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

1 INTRODUCTION

Nippon Soda Co., Limited has applied to the APVMA for approval of the new active constituent cyflufenamid and the registration of the new product Cyflamid 50EW Fungicide. The product is an oil in water emulsion containing 50 g/L of the new active constituent cyflufenamid.

Cyflufenamid belongs to the amidoxime class of fungicides and the mode of action at this stage has not been established. Cyflufenamid is in the new group U6 (unspecified) for fungicides resistance management.

The proposed use in Australia is for control of powdery mildew in grapevines (*Erysiphe necator*) and cucurbits (*Podosphaera xanthii*). Cyflamid 50EW Fungicide is intended to be used at a rate of 250mL product/ha in cucurbits and 35mL product/100L water (dilute application rate), or by concentrate application methods in grapevines.

Cyflamid 50EW Fungicide will be imported fully formulated and be available in 1L, 2.5L, 5L, 10L and 20L pack sizes.

Cyflufenamid and cyflufenamid formulations are currently registered for use in Japan, Korea, USA and the EU. Cyflamid 50EW Fungicide is currently registered in the EU.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of **Cyflamid 50EW Fungicide**, and approval of the new active constituent, **Cyflufenamid**.

2 CHEMISTRY AND MANUFACTURE

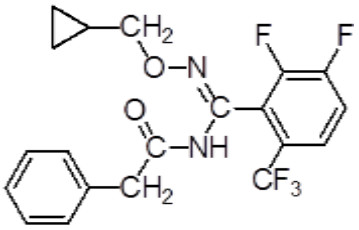
2.1 Active Constituent

Cyflufenamid is a new active constituent to be used as a fungicide in grapevines and cucurbits for the control of powdery mildew.

Manufacturing site

The active constituent cyflufenamid is manufactured by Nippon Soda Co., Ltd, in Nisso Fine Chemicals Co. Ltd., Koriyama Plant, 1-176 Sasagawa, Koriyama-shi, Fukushima 963-0108, Japan.

Chemical Characteristics of the Active Constituent

COMMON NAME (ISO):	Cyflufenamid
IUPAC NAME:	(*Z*)-*N*-[α-(cyclopropylmethoxyimino)-2,3-difluoro-6-(trifluoromethyl)benzyl]-2-phenylacetamide
CAS NAME:	(Z)-N-[[(cyclopropylmethoxy)amino][2,3-difluoro-6-(trifluoromethyl)phenyl]methylene]benzeneacetamide
CAS REGISTRY NUMBER:	180409-60-3
MANUFACTURER'S CODES:	NF-149
MINIMUM PURITY:	980 g/kg
MOLECULAR FORMULA	$C_{20}H_{17}F_5N_2O_2$
MOLECULAR WEIGHT:	412.35
STRUCTURE:	
CHEMICAL FAMILY	Amidoxime fungicide

APVMA Active Constituent Standard for Cyflufenamid

Constituent	Specification	Level
Cyflufenamid	Cyflufenamid	Not less than 980 g/kg

Physical and Chemical Properties of Pure Active Constituent

PHYSICAL FORM	Solid powder		
COLOUR	White		
ODOUR	Weakly aromatic		
MELTING POINT:	61.5 to 62.5 ^{o}C		
DENSITY @ 20 °C:	1.347		
HENRY'S LAW CONSTANT @ 20 °C	2.81 x 10^{-2} Pa.m^3/mol		
WATER SOLUBILITY @ 20 °C	pH 4: 0.014 mg/L pH 6.3-6.9: 0.52 mg/L pH 10: 0.12 mg/L		
PARTITION CO-EFFICIENT (*N*-OCTANOL/WATER)	pH 4 : log Pow = 4.68 pH 6.75: log Pow = 4.70 pH 9.95: log Pow = 24.55		
VAPOUR PRESSURE AT 20^{O}C:	3.54 x 10^{-5} Pa		
DISSOCIATION CONSTANT	pKa = 12.08		
UV-VISIBLE SPECTRA	Sample solution	λ_{max} (nm)	ε (L/mol·cm)
	Acidic methanol solution (0.1N HCl)	207	2.11×10^4
		238	1.32×10^4
		361	1.78×10^2
	Neutral methanol solution	207	2.08×10^4
		238	1.29×10^4
	Basic methanol solution (0.1N NaOH)	220	1.30×10^4
		240	1.18×10^4
FLAMMABILITY INCLUDING AUTO-FLAMMABILITY	Not highly flammable; no potential for auto-flammability		
EXPLOSIVE PROPERTY	Has no explosive properties		
SURFACE TENSION @ 20 °C	66.5 mN/m*		
OXIDISING PROPERTIES	Not oxidising		

PH @ 25 °C (1% SUSPENSION IN DISTILLED H_2O)	6.1	
SOLUBILITY IN ORGANIC SOLVENTS @ 20 °C	Solvent	Solubility (g/L)
	Carbon tetrachloride	>399
	Chloroform	> 372
	Dichloromethane	>331
	Carbon disulphide	>316
	Dimethyl sulfoxide	>275
	Dimethylformamide	>237
	Ethylacetate	>225
	Ethanol acetate	>225
	Tetrahydrofuran	>222
	Benzene	>220
	Xylene	>217
	Toluene	>217
	Methanol	>198
	Acetone	>198
	Acetonitrile	>196
	n-octanol	76.9
	n -hexane	18.6
	n -heptane	15.7

2.2 Product

Cyflamid 50EW Fungicide

DISTINGUISHING NAME:	Cyflamid 50EW Fungicide
FORMULATION TYPE:	Oil in water emulsion (EW)
ACTIVE CONSTITUENT CONCENTRATION:	Cyflufenamid (50 g/L)

The product *Cyflamid 50EW Fungicide* will be manufactured overseas and imported into Australia in 1, 2.5, 5, 10, or 20 L Coex bottle with HDPE outer and nylon (polyamide) inner containers (or, Nylon-lined HDPE containers).

Physical and Chemical Properties of the product Cyflamid 50EW Fungicide

APPEARANCE:	Whitish emulsion solution with no separated or floating materials, with aromatic odour
PH VALUE:	5.7 (1%water solution) 5.0 (original liquid)
SPECIFIC GRAVITY	1.027
SURFACE TENSION	32 nM/m
VISCOSITY:	156.5-192.0 mPa.s with a shear rate of 1.15 s^{-1} at 23°C 49.4 mPa.s with a shear rate of 268.1 s^{-1} at 23°C
FLAMMABILITY:	Not flammable
EXPLOSIVE PROPERTIES:	Not explosive
OXIDISING PROPERTIES:	No oxidising properties
CORROSIVE HAZARD:	Not corrosive to nylon-lined HDPE containers
PERSISTENT FOAM	5 mL (after 1 min)
POURABILITY	Residue: 1.1% Rinsed residue: 0.2%
PACK SIZES	1, 2.5, 5, 10, or 20L
PACKAGING MATERIAL	Nylon-lined high density polyethylene (HDPE) containers
PRODUCT STABILITY	The product should remain within specifications for at least 2 years under normal conditions in nylon-lined HDPE containers

2.3 Recommendations

Based on a review of the chemistry and manufacturing details provided by the applicant, registration of Cyflamid 50EW Fungicide is supported.

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

Public Health Aspects & Toxicology

Cyflufenamid is new to the Australian market and belongs to the amidoxime class of fungicides. Currently, the mode of action of cyflufenamid is unknown. The product Cyflamid 50 EW Fungicide is an emulsion, oil in water, containing 50 g/L cyflufenamid that is intended for use in cucurbits and grapes as a protectant fungicide against powdery mildew.

In rats, following oral administration, cyflufenamid was rapidly absorbed with a minimum of 70% of the administered dose absorbed, and widely distributed to organs and tissues, with the highest levels detected in the kidneys, muscle, fat, liver and GI tract. It is extensively metabolised in the rat and rapidly eliminated from the body, predominantly via the faeces with the urine a lesser route of elimination. There was evidence in the rat that limited enterohepatic circulation may occur. There was no evidence of bioaccumulation following repeated oral dosing in rats.

Based on the submitted data, cyflufenamid was of low acute oral toxicity in the rat and mouse, and low acute dermal and inhalational toxicity in the rat. It was not a skin irritant in rabbits but is a slight eye irritant in the same species, and was not a skin sensitiser in guinea pigs.

In a formulation product similar to Cyflamid 50 EW Fungicide, it was estimated that in vivo human dermal absorption of cyflufenamid was limited.

Following repeat oral dosing in rats, mice and dogs, in general body weight changes, clinical chemistry alterations and histopathological changes in the liver and kidneys were seen in all species, along with histopathological changes in additional organs observed with increased study duration. Cyflufenamid was not mutagenic or genotoxic in vitro with and without metabolic activation and in vivo was not genotoxic in mice and did not induce DNA damage in rat liver. There was no evidence from rats and mice that cyflufenamid would be a carcinogenic hazard to humans and furthermore, cyflufenamid was not a reproductive toxicant in rats or a developmental toxicant in rats and rabbits. Cyflufenamid was not neurotoxic in a subchronic toxicity study in rats, and did not elicit oestrogenic activity in vitro or in ovariectomised rats in vivo.

Acute oral toxicity studies on a range of cyflufenamid impurities and metabolites revealed mainly low acute toxicity, with moderate acute toxicity seen in both sexes for one impurity and in males only for one metabolite. Additionally, all tested impurities and metabolites were negative in bacterial reverse mutation studies with and without metabolic activation.

Cyflamid 50 EW Fungicide is of low acute oral toxicity in rats and mice, and low acute dermal and inhalational toxicity in rats, is a moderate skin irritant in the rabbit and a slight eye irritant in the same species, and is not a skin sensitiser in guinea pigs.

Based on an assessment of the toxicology studies evaluated, it was considered that there should be no adverse effects on human health from the use of Cyflamid 50 EW Fungicide when used in accordance with the label directions.

3.2 Evaluation of Toxicology

The toxicological database for cyflufenamid, which consists primarily of toxicity tests conducted using animals, is extensive. 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. Such dose levels as the No-Observable-Effect-Level (NOEL) are generally used to develop acceptable limits for dietary or other intakes (ADI and ARfD) at which no adverse health effects in humans would be expected.

Chemical Class

Cyflufenamid is a novel fungicide of the amidoxime class of fungicides. Currently, the mode of action of cyflufenamid is unknown.

Toxicokinetics and Metabolism

Following single oral administration of [Fluorinated phenyl-U-^{14}C]-cyflufenamid to rats at the low dose (10 mg/kg bw), cyflufenamid was absorbed rapidly (T_{max} 1–4 hours) and excreted rapidly with > 95 % elimination of administered radiolabel in excreta by 72 hours post-dose. A slight sex-specific difference in the excretion profile was observed, with a larger proportion of radiolabel excreted in urine of male rats (24–31 %) compared with females (10–18 %). Repeated low-dose administration of radiolabelled cyflufenamid to rats yielded similar absorption and excretion profiles after the final dose was administered. Bile cannulation studies in rats indicated that approximately 70 % (males) and 85 % (females) was absorbed after a single low-dose, indicating that only a fraction of orally administered material is unabsorbed. Comparison of the excretion profiles between cannulated and orally dosed rats indicates that limited enterohepatic circulation of cyflufenamid may occur, as the proportion of radiolabel eliminated in bile and faeces in cannula-dosed rats was slightly higher than the proportion of radiolabel identified in the faeces in orally dosed animals.

Single high-dose (200 mg/kg bw) oral administration of cyflufenamid to rats indicated that a large proportion (42–50 %) of cyflufenamid was excreted (unabsorbed) in faeces. Tissue distribution of absorbed cyflufenamid in rats was extensive, with highest concentrations noted in the GI tract, liver, fat and muscle, with similar distribution profiles observed regardless of the dose concentration or duration of administration. Elimination of radiolabel from tissues was essentially complete in rats 168 hours after the final dose, with only residual amounts (< 1 %) observed in the carcass.

Metabolic profiling of radiolabelled components in excreta, bile and selected tissues (liver, kidney and fat) revealed extensive metabolism of cyflufenamid. A number of metabolism processes were proposed, including hydrolysis, amidine reduction, deamination, di-hydroxylation/methoxy conversion, mono-hydroxylation, cleavage of the cyclopropylmethoxy moiety and glucuronide conjugation.

Dermal absorption of cyflufenamid was studied in vitro in rat skin, in vitro in human skin and in vivo in rats allowing a 'triple pack' approach to be taken to estimate human dermal absorption in vivo. In formulation products, cyflufenamid absorption is limited, with ~1 % dermal absorption arising from an EW formulation similar to the proposed product (Cyflamid 50 EW Fungicide containing 5% cyflufenamid), while dilute application formulations of 0.25 g/L and 0.0156 g/L cyflufenamid resulted in dermal absorption of approximately 8 % and 16 % respectively.

Acute Studies

Cyflufenamid has low acute oral toxicity in the rat and mouse (LD_{50} > 5000 mg/kg bw in both species), low acute dermal toxicity in the rat (LD_{50} > 2000 mg/kg bw) and low acute inhalational toxicity in the rat (4-hr LC_{50} > 4760 mg/m^3). Cyflufenamid was not a skin irritant in rabbit but is a slight eye irritant in the same species. It was not a skin sensitiser in guinea pigs.

The formulated product Cyflamid 50 EW Fungicide has low acute oral toxicity in the rat and mouse (LD_{50} > 5000 mg/kg bw in both species), low acute dermal toxicity in the rat (LD_{50} > 2000 mg/kg bw) and low acute inhalational toxicity in the rat (4-hr LC_{50} > 4410 mg/m^3). The product was a moderate skin irritant and slight eye irritant in the rabbit, but was not a skin sensitiser in guinea pigs.

Systemic Effects

Short-term (4-week) oral studies with cyflufenamid were conducted in order to determine appropriate dosing for subchronic toxicity studies. In general, treatment-related toxicity, including body weight changes, clinical chemistry alterations and histopathological changes in the liver and kidneys were found at mid-to-high dose levels (~200 mg/kg bw/d in rodents, ~100 mg/kg bw/day in dogs).

In subchronic (13-week) oral toxicity studies, treatment-related effects similar to those observed in short-term studies were noted in mice. At high doses (~800 mg/kg bw/d), additional treatment-related histopathological changes in the heart and testes were identified. In rats, changes in a range of clinical chemistry parameters and histopathological changes in liver, kidney, thyroid, testes and caecum were noted (~120 mg/kg bw/d). In dogs, changes in organ weights, clinical chemistry parameters and liver histopathology were seen at ~23 mg/kg bw/d, with changes in body weight, food consumption, additional clinical chemistry parameters and histopathological changes in the thymus and reproductive organs were also noted at ~70 mg/kg bw/d. Additionally in dogs at ~70 mg/kg bw/d, vacuolation in the brain (identified as myelin oedema under electron microscopy), along with occasional thinness in myelin membranes was observed which were reversible after a 26-week recovery period.

In long-term oral studies (52 - 104 weeks), in dogs treatment-related alterations in ALP levels were observed in both sexes at the high dose of ~17 mg/kg bw/d, with histopathological changes in the adrenals also observed at this dose in females only. No evidence of the previously observed myelin oedema and thinness in myelin membranes seen in the subchronic dog study at ~70 mg/kg bw/d was observed in the long term

dog study up to and including the top dose level of ~17 mg/kg bw/d. In mice, treatment-related deaths, decreased body weight gain and histopathological changes in the liver in both sexes, as well as histopathological changes in the heart and kidneys in females only, were observed at the top dose level of ~325 and ~400 mg/kg bw/d in males and females respectively. In rats, a range of treatment-related clinical symptoms were noted at the top dose tested ~230/115 mg/kg bw/day in males/females, including perigenital staining, decreased body weight gain, clinical chemistry changes and histopathological changes in the liver, kidney, heart and thyroid during the first 52 weeks of dosing, with additional histopathological changes in the adrenals, pancreas, lungs and lachrymal glands seen in the carcinogenicity phase of the study at 104 weeks (study termination).

In a 4-week dermal toxicity study in rats no treatment-related effects were seen up to and including the top, and limit, dose level of 1000 mg/kg bw/d.

Carcinogenicity

In a 78-week dietary study in mice, a slight increase in the frequency of hepatocellular adenomas (34.0%) was seen in males at the top dose level (at which males were administered 403.6 mg/kg bw/d for 20 weeks which was then reduced to 324.8 mg/kg bw/d for the remainder of the study due to the observance of treatment related deaths) that was outside the upper historical control range (30.8%). However, this slight increase in benign liver tumours in one sex was seen at a dose level that produced a 25.1% decrease in body weight gain over the study period. Thus, the maximum tolerated dose (MTD) was substantially exceeded at the top dose level. Consequently, the study provided no robust evidence of a carcinogenic potential in male rats. Additionally, a supplementary carcinogenicity study in mice provided no macroscopic evidence (microscopy was not undertaken) that cyflufenamid induced liver tumours in male mice at 174.1 mg/kg bw/d, the only dose tested in addition to a concurrent control group.

In female mice, a slight increase seen in the frequency of bronchiolar-alveolar neoplasms at the top dose level was within the historical control range.

In a 104-week dietary study in rats, in male rats only a slight increased incidence in thyroid follicular cell adenomas (8.3%) and carcinomas (3.3%) was seen at the top dose level of 228.7 mg/kg bw/d which was outside the upper historical control range (6 and 2% respectively). However, these treatment-related findings were considered to be of limited relevance to humans based on mechanistic data provided indicating that neoplastic effects were likely due to hepatic enzyme induction and hormonal imbalances resulting in increased thyroid activity and subsequent thyroid tumours. Furthermore, a broader consideration of the mode of action (MOA) behind thyroid adenomas was undertaken using the IPCS Framework for the Relevance of a Cancer MOA to Humans, which concluded that the marginal increase was of limited relevance to humans.

In female rats, a marginal increase in pancreatic islet cell carcinoma but not adenoma was noted at the top dose level of 115.4 mg/kg bw/d (3.3%) that was outside the upper historical control range (2%). However, noting the absence of a clear sequential progression (e.g. over-stimulation leading to hyperplasia through to neoplasm), it is considered that this marginal increase in one sex only is likely incidental and not treatment-related.

Genotoxicity

Cyflufenamid was not mutagenic in bacteria or mammalian cells *in vitro* with and without metabolic activation. Additionally, cyflufenamid was not genotoxic in an *in vitro* chromosome aberration assay with and without metabolic activation. *In vivo*, cyflufenamid was not genotoxic in a micronucleus assay in mice, and did not induce DNA damage in the rat liver in a UDS assay.

Reproductive Toxicity

In a dietary two-generation reproductive study in rats, cyflufenamid was not a reproductive toxicant. No treatment-related effect was seen on reproductive parameters up to and including the top dose level of 57.4 and 65.7 mg/kg bw/d in males and females respectively. Parental toxicity was observed at the top dose level (increased liver and thyroid weight in males and females) as was toxicity in offspring (reduced body weight gain in both generations).

Developmental Toxicity

Cyflufenamid was not a developmental toxicant in an oral (gavage) developmental toxicity study in rats. No foetal effects were seen up to and including the limit dose level of 1000 mg/kg bw/d in the presence of maternal toxicity (increased salivation and increased absolute and relative liver weight at 300 mg/kg bw/d and greater).

In an oral (gavage) developmental toxicity study in rabbits, an increased incidence in skeletal findings were seen in foetuses at 60 mg/kg bw/d (cervical vertebral element incompletely ossified and unossified epiphyses) and 300 mg/kg bw/d (that included abnormalities included increases in enlarged anterior fontanelle, incompletely ossified cervical vertebral elements, unossified epiphyses and unossified cranial areas). However, in pregnant females a decrease in body weight gain of 27.8, 33.3 and 66.6% was seen from gestation day 6 to 29 at 10, 60 and 300 mg/kg bw/d respectively, along with decreases in food consumption of 9.9, 13.2 and 26.8%. Additionally, abortions observed at the top dose of 300 mg/kg bw/d were considered indicative of severe maternal toxicity as evidenced by the magnitude of the observed decrease in body weight gain. Thus, the observed skeletal findings in foetuses at 60 mg/kg bw/d were considered to be a secondary non-specific consequence of marked maternal toxicity, and cyflufenamid was not considered to be a developmental toxicant in rabbits.

Neurotoxicity

Based on cumulative evidence in a range of acute oral and repeat-dose studies indicating cyflufenamid was not a neurotoxicant the absence of an acute neurotoxicity study was not considered a critical data gap in this instance, while a dietary subchronic neurotoxicty study was available in the rat. In this study, no treatment-related changes in FOB parameters, behavioural signs, clinical chemistry, macroscopic or microscopic findings were seen up to and including the highest dose tested, equivalent to 453.1 and 571.8 mg/kg bw/d in males and females respectively.

Other studies

Acute oral toxicity studies on a range of cyflufenamid impurities and metabolites revealed mainly low acute toxicity, with moderate acute toxicity seen in both sexes for one impurity and in males only for one metabolite. Additionally, all tested impurities and metabolites were negative in bacterial reverse mutation studies with and without metabolic activation. In non-Guideline *in vitro* screening studies, cyflufenamid did not elicit oestrogenic activity in yeast and MCF-7 human breast adenocarcinomas cells, and no oestrogenic activity was seen in ovariectomised rats *in vivo*.

3.3 Public Health Standards

Poisons Scheduling

The delegate to the Secretary of the Department of Health and Ageing sought advice from the Advisory Committee on Chemical Scheduling (ACCS) on the scheduling of cyflufenamid.

Cyflufenamid was discussed at the February 2012 meeting of the ACCS. The delegate noted the ACCS discussion on cyflufenamid and made an interim decision on the 26th April 2012 to include cyflufenamid in Schedule 5 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) with no cut-off. This was the interim decision of the delegate. The delegate's final decision made on 30th May 2012 confirmed that cyflufenamid be included in Schedule 5 of the SUSMP with no cut-off, along with an implementation date of 1st September 2012.

NOEL/ADI

The acceptable daily intake (ADI) is that quantity of an agricultural or veterinary chemical which can safely be consumed on a daily basis for a lifetime and is based on the lowest NOEL obtained in the most sensitive species. This NOEL is then divided by a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

The ADI for cyflufenamid was established at 0.04 mg/kg bw/d (rounding down), based on a NOEL of 4.14 mg/kg bw/d in male dogs for elevated ALP levels in a 52-week oral study and applying a default safety factor of 100 for potential interspecies and intraspecies variability.

ARfD

The acute reference dose (ARfD) is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated event. The ARfD is derived from the lowest NOAEL as a single or short-term dose which causes no adverse effect in the most sensitive species of experimental animal tested, together with a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

An acute reference dose (ARfD) was established since cyflufenamid will be used in food crops and was considered to present a potential acute hazard in humans. The ARfD was established at 0.1 mg/kg bw based on a NOEL of 10 mg/kg bw/d from an oral rabbit developmental study for both maternal (decreased body

weight gain and food consumption) and developmental toxicity (increased minor skeletal variations/abnormalities) and applying a default safety factor of 100 for potential interspecies and intraspecies variability.

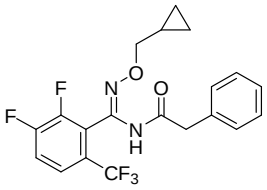
3.4 Conclusion

The APVMA is satisfied that the proposed use of Cyflamid 50 EW Fungicide, containing the active constituent Cyflufenamid, is not likely to be harmful to human beings when used according to the product label instructions.

4 RESIDUES ASSESSMENT

4.1 Introduction

Cyflamid 50 EW Fungicide contains the new active constituent cyflufenamid and is proposed for use on grapevines and cucurbits. As part of the residues assessment for cyflufenamid, plant and animal metabolism studies, supervised residue trials and trade aspects were considered.



Cyflufenamid (NF-149)

The active constituent of cyflufenamid contains 3 – 15 g/kg of the *E*-isomer.

4.2 Metabolism

The metabolism of cyflufenamid was investigated in wheat, apples, cucumber, confined rotational crops (leafy vegetable: lettuce, root vegetable: carrot, small grain: wheat) and lactating goats.

Plant Metabolism

For wheat, cyflufenamid labelled with ^{14}C in the fluorinated phenyl ring or in the cyclopropyl ring was applied twice foliarly at 25 – 100 g ai/ha. Applications were made between growth stages Z32-52 for the first application and between Z39-59 for the second. The major component of the total radioactive residues in all cereal plant parts was cyflufenamid at levels up to ~100% TRR in forage, 65% in mature straw and 7% in grain. The *E*-isomer was quantified in plant parts at up to 4% TRR in mature straw. Low concentrations of other metabolites were identified. Based on these results, a metabolic pathway was proposed for cyflufenamid in wheat involving oxidation at the benzyl moiety to form metabolites with a hydroxyl group (Figure 1).

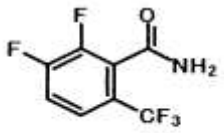
For apples, Cyflufenamid labelled with ^{14}C in the fluorinated phenyl ring was applied to apple trees at a rate of 270 g ai/ha approximately 13 weeks before harvest. Samples of leaves were taken 2 hours after application. Leaves and fruit were sampled at 3, 6 and 13 weeks after application. In apple fruit at harvest, the parent compound was found to form the major part of the total residue (66% TRR, 0.012 mg/kg). Low concentrations of other metabolites were identified. A proposed metabolic pathway for cyflufenamid in apples in shown below in Figure 2. The metabolism proceeds by hydroxylation at the 4- position of the phenylacetyl moiety followed by conjugation with glucose. Alternatively the cyclopropylmethyloxy moiety is removed followed by conjugation with glucose.

For cucumbers, Cyflufenamid (N-149) labelled with ^{14}C in the fluorinated phenyl ring was applied to cucumber plants at 50 g ai/ha (low application rate) and 200 g ai/ha (high application rate). Leaves and fruit

were collected at 0, 3, 7, 14 and 31 days after treatment (DAT) for the low application rate and 7 and 35 DAT for the high application rate. In cucumbers parent compound was recovered as 96% TRR in fruit immediately after application. By 14 DAT parent was still the major component of the TRR accounting for 55% TRR, while a number of other minor metabolites were also detected. A metabolic pathway was proposed for cyflufenamid in cucumber (figure 3) which involved oxidation at the 4 position of the phenyl ring and at the α position of the benzyl group and further formation of glycosides.

A confined crop rotation study was conducted for cyflufenamid. Compound labelled with ^{14}C in the fluorinated phenyl ring was applied to the surface of a sandy loam soil in plastic containers at an application rate of 50 g ai/ha (~3-4× maximum rate). The soil containers were kept outside for aging and seeded with representative crops (leafy vegetable: lettuce, root vegetable: carrot, small grain: wheat) at 30, 120 and 270 days after treatment. Crop samples were taken at immature harvest, earliest possible harvest and normal harvest.

No metabolites/fractions with levels >10% TRR and >0.01 mg/kg were found except for 149-F6 (33% TRR, 0.013 mg/kg) in final carrot foliage and a polar fraction (13% TRR, 0.011 mg/kg) in final wheat straw following day 120 sowing.



149-F6

Based on the results of the confined rotational crop study which involved application at ~3-4× maximum rate, quantifiable residues of cyflufenamid and its metabolites and unlikely to occur in rotated crops and rotational crop field trials were not required.

Animal Metabolism

^{14}C-Cyflufenamid, uniformly labelled in the fluorinated phenyl ring was orally administered to lactating goats. One goat was dosed at 1.2 mg/kg in the feed, a second was dosed at 13.3 mg/kg in the feed, a third goat served as a control. Each goat received its dose in the morning for 5 consecutive days. Milk was collected twice daily. After the first dose in the morning, the evening and following morning milk specimens were collected and combined (Day 1 milk). The goats were sacrificed within 24 hours of the last dose and samples of fat, kidney, liver and muscle were collected. The major radioactive residue in fat was parent (80% TRR), with low levels (<3% TRR) of 149-F, 149-F-4-OH-B, 149-(*E*)-FB and 149-F-α-OH-B. In the other tissue samples and milk, the main radioactive compound was 149-F1 (31 – 62% TRR), with lower levels of 149-F6 (3 – 30% TRR). Cyflufenamid (22% TRR) and 149-F (15% TRR) were additionally found in muscle and liver respectively. Based on these results a metabolic pathway was proposed for cyflufenamid in lactating goats (Figure 4). The main pathways include oxidation of NF-149 at the 3- and 4- positions of the unsubstituted phenyl ring, leading to 149-F-3-OH-B, 149-F-4-OH-B and 149-F-3-OH-4-OH-B. The cleavage of the amide bond forms 149-F and further cleavage of the oxime ether bond leads to 149-F1 and further to 149-F6, by oxidation.

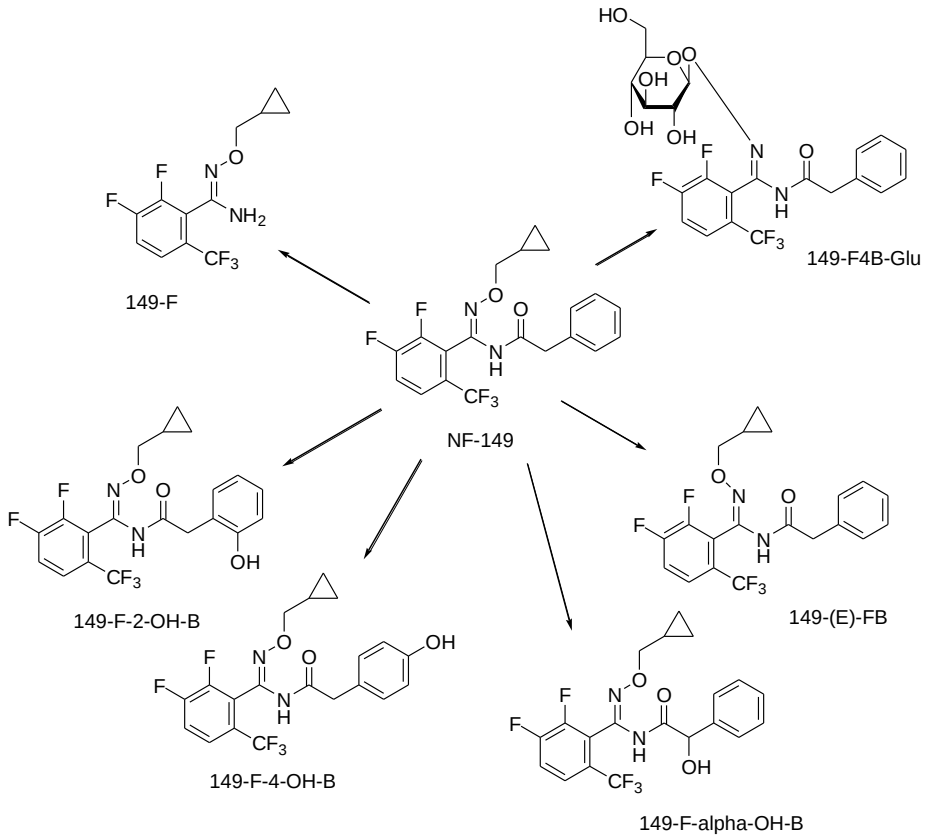


Figure 1: Proposed metabolic pathway for cyflufenamid (NF-149) in wheat

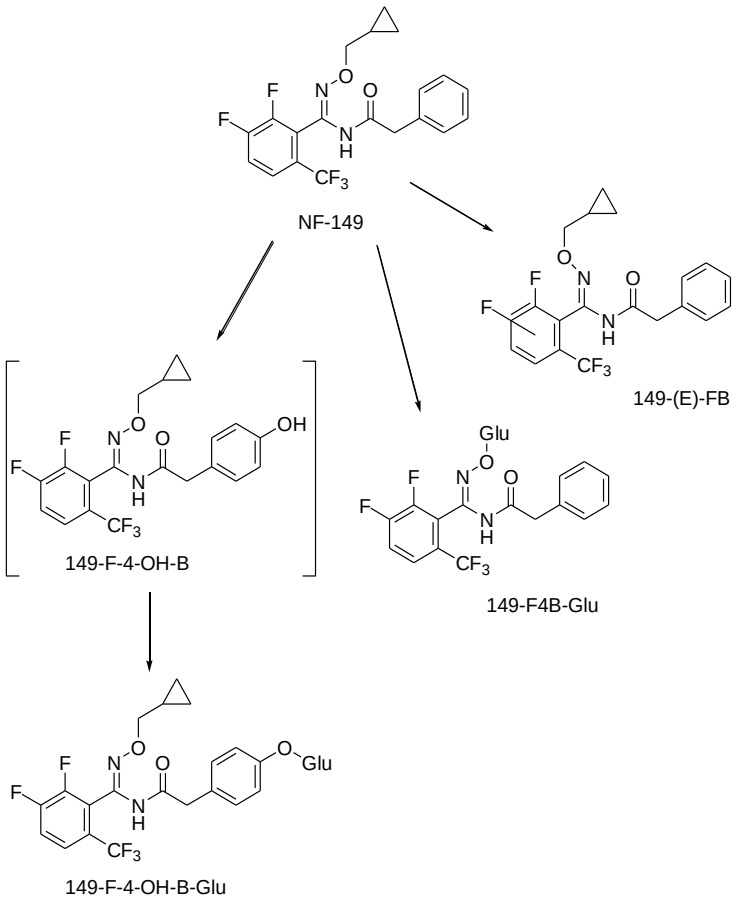


Figure 2: Proposed metabolic pathway for cyflufenamid in apples

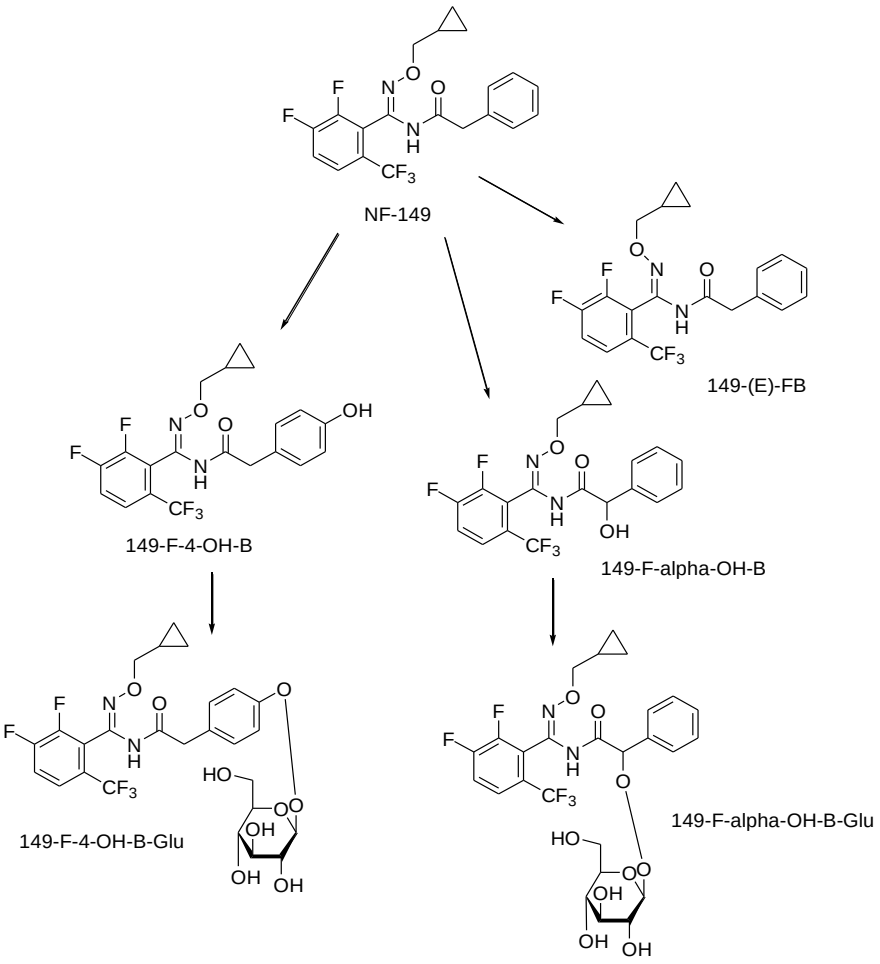


Figure 3: Proposed metabolic pathway for cyflufenamid in cucumber

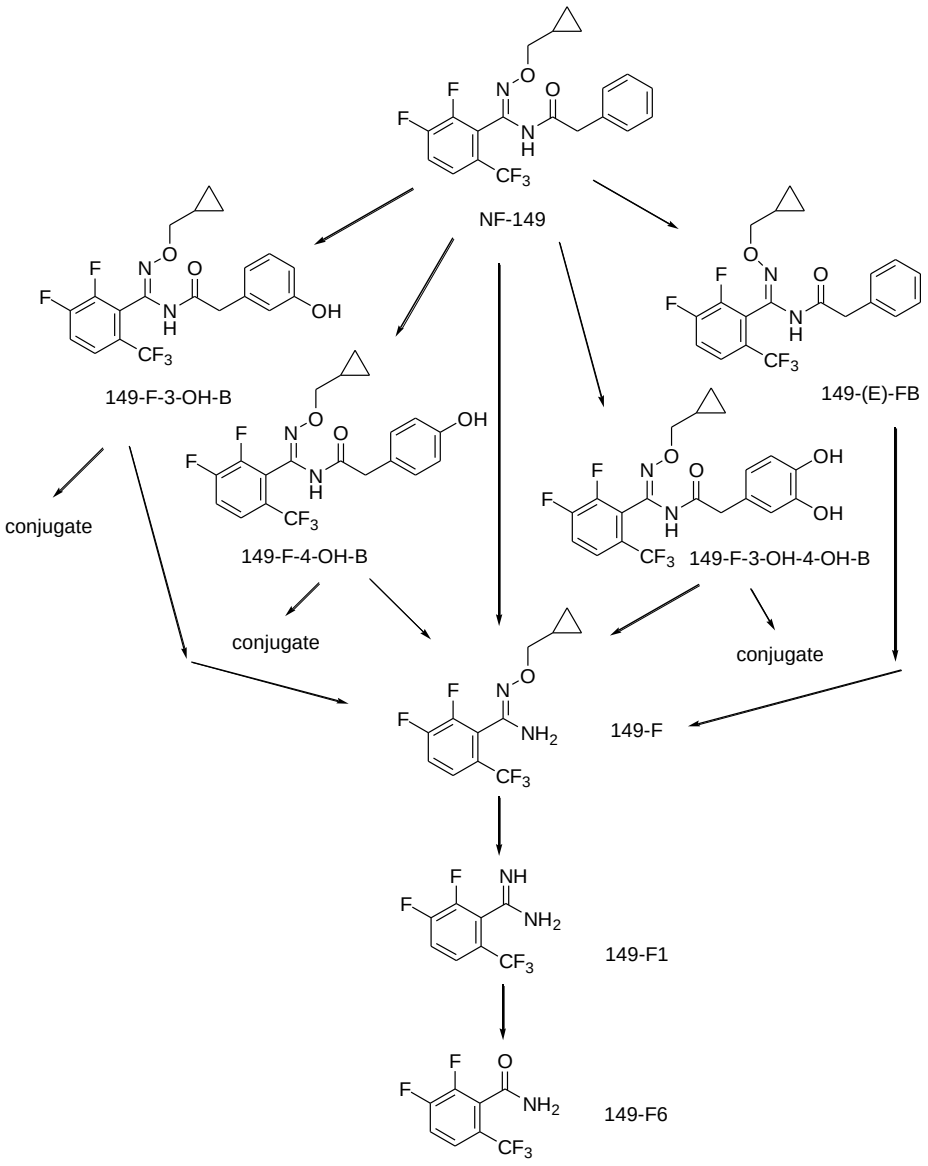


Figure 4: Proposed metabolic pathway of cyflufenamid (NF-149) in the lactating goat

4.3 Analytical methods

Determination of residues in plant commodities

Samples were extracted with acetonitrile solution containing 1% acetic acid. High fat samples (grape pomace and wine marc) were rehydrated prior to commencing extraction. Samples were cleaned up by dispersive solid phase extraction (dSPE). Analysis was performed by liquid chromatography with tandem mass spectrometry (LC/MS/MS). The LOQ for cyflufenamid was reported to be 0.01 mg/kg. A similar method was supplied for grape juice and wine. Recoveries obtained during method validation were within the acceptable range of 70 to 110%. Although recoveries of cyflufenamid from cucumber and zucchini at the LOQ (0.01 mg/kg) were low, acceptable procedural recoveries were obtained in the residues trials.

Determination of residues in animal commodities

Details of 2 methods were provided for the determination of cyflufenamid and metabolites in animal commodities:

The first method determined residues of parent (NF-149) and metabolites 149-F, 149-F1 and 149-F6. Muscle, liver and kidney samples were extracted with methanol. Clean-up of the extracts involves partition into ethyl acetate and solid phase extraction (on graphite carbon and C18 cartridges). The analytes were determined by liquid chromatography with tandem mass spectrometry (LC/MS/MS). The LOQ was 0.005 mg/kg for each analyte.

For fat, the analyte (parent only) was extracted with hexane. Clean-up of the extracts involves partition into acetonitrile and solid phase extraction (on C18 cartridge). The analyte was determined by LC/MS/MS with an LOQ of 0.005 mg/kg.

For milk, the analytes (parent and 149-F1) were extracted with methanol and cleaned up by partition into ethyl acetate and solid phase extraction (on C18 cartridge). The analytes were determined by LC/MS/MS with an LOQ of 0.005 mg/kg for each.

Recoveries of parent compound from fortified control samples of all matrices were within the acceptable range of 70 to 110%.

The second method was validated for the determination of NF-149 (cyflufenamid), its *trans* isomer 149-(*E*)-FB and its metabolite 149-F1 in animal tissues (muscle, liver, kidney and fat), milk and eggs.

The analytes were extracted with methanol followed by partitioning into ethyl acetate under acidic and basic conditions. A hexane partitioning clean-up step was performed followed by reconstitution in acetonitrile/0.1 M ammonium formate prior to quantitation by liquid chromatography with tandem mass spectrometric detection (LC-MS/MS). The method was validated at 0.01 and 0.1 mg/kg for each matrix. All recoveries of cyflufenamid lay within the acceptable range of 70 – 110%.

Residue Definition

Commodities of plant origin

As parent was the most significant component in the wheat, apple and cucumber metabolism studies, a residue definition of parent is recommended for commodities of plant origin.

Commodities of animal origin

In the goat metabolism study the major residue in fat was parent, which was also present at significant levels in muscle. 149-F1 is present at significant levels in milk, liver, kidney and muscle. Parent is not a suitable marker in milk, kidney and liver. However, detectable residues are not expected to occur in animal commodities as a result of the proposed use.

The recommended residue definition for commodities of animal origin is cyflufenamid.

4.4 Residue Trials

Grapes

Six Australian residue trials on grapes are supported by 9 trials from the EU and 12 from the USA. The Australian and USA trials include information on the concentration of residues during processing.

In Australian trials matching GAP, residues in grapes at 28 – 32 days after the last of 2 applications at 2 g ai/100 L (1.1×) were 0.01 and 0.03 mg/kg. At 0 and 14 DALA at 2 g ai/100 L residues were 0.04 and <0.01 mg/kg respectively.

In European trials, residues in grapes at 21 days after the last of 2 application at 2.7 g ai/100 L (~1.5×) were <0.01 (4), 0.02, 0.03 (2), 0.04 and 0.07 mg/kg.

In US trials, residues in grapes at 3 days after the last of 4 applications at 25 g ai/ha (for a spray volume of 1000 L/ha the proposed use would correspond to 17.5 g ai/ha) were 0.01, 0.03 (3), 0.04 (6), 0.07 and 0.08 mg/kg.

An MRL of 0.1 mg/kg is recommended for cyflufenamid on FB 0269 Grapes in conjunction with a 35 day (5 week) harvest withholding period.

Cucurbits

Fourteen Australian trials on cucurbits (melon, cucumber and zucchini) are supported by 38 European trials and 17 from the USA.

The proposed use pattern for cucurbits is for up to 2 applications at 12.5 g ai/ha for field grown cucurbits or 1.25 g ai/100 L for protected crops in conjunction with a 1 day withholding period. In the Australian trials residues in field grown rock melon at 1 day after the last of 2 applications at 12.5 g ai/ha were <0.01 (4) and

0.03 mg/kg. In the Australian trials residues in field grown cucumber at 1 day after the last of 2 applications at 12.5 g ai/ha were <0.01 and 0.01 mg/kg. Residues in protected cucumber at 1 day after the last of 2 applications at 1.25 g ai/100 L were 0.02 and 0.05 mg/kg. In the Australian trials residues in field grown zucchini at 1 day after the last of 2 applications at 12.5 g ai/ha were 0.01, 0.03, 0.04 and 0.06 mg/kg. Taken together residues in the Australian trials matching GAP were <0.01 (5), 0.01 (2), 0.02, 0.03 (2), 0.04, 0.05 and 0.06 mg/kg.

In European field and protected trials on melons, calculated whole fruit residues at 1 day after the last of 2 applications at 15 – 17 g ai/ha (~1.2 - 1.4×) were <0.01 (8), 0.01 (9), 0.02 (4) and 0.03 mg/kg. In European protected trials on cucumbers, residues at 1 day after the last of 2 applications at 14 – 17 g ai/ha (~1.1 - 1.4×) were <0.01 (3), 0.01 (2) and 0.02 (3) mg/kg. In European field trials on courgettes (zucchini), residues at 1 day after the last of 2 applications at 14 – 17 g ai/ha (~1.1 - 1.4×) were <0.01 (2), 0.01, 0.02 (4) and 0.04 mg/kg.

In US field trials, residues in cucurbits at 0 days after the last of 4 applications at 12.5 g ai/ha were: Cucumber: <0.01, 0.01 (3), 0.02 and 0.03 mg/kg. Cantaloupe: <0.01, 0.01 (2), 0.02 and 0.03 (2) mg/kg. Summer squash: <0.01, 0.02 (2), 0.03 and 0.04 mg/kg.

An MRL of 0.1 mg/kg is recommended for cyflufenamid on VC 0045 Fruiting vegetables, cucurbits in conjunction with a 1 day withholding period.

4.5 Processing studies

The Australian and USA grape trials include information on the concentration of residues during processing. The processing trials indicated that cyflufenamid residues do not concentrate in wine or juice, so it is not necessary to establish separate MRLs for these commodities. Residues did concentrate on processing to raisins by a factor of 3.6×. Based on a HR of 0.08 mg/kg in grapes, the highest predicted residue in raisins is 0.29 mg/kg. An MRL of 0.5 mg/kg is recommended for cyflufenamid on DF 0269 Dried grapes.

Residues in grape pomace at 32 – 84 days after the last of 2 applications at 2 g ai/100 L were <0.01 (2), 0.03, 0.04 (2) and 0.06 mg/kg. (The highest residue was observed in pomace from grapes sampled 77 days after the last application). The moisture content of the HR sample was 76%, giving a dry weight HR of 0.25 mg/kg (0.06 ÷ 0.24). An MRL of 0.5 mg/kg is recommended for cyflufenamid on AB 0269 Grape pomace, dry.

4.6 Animal commodity MRLs

Animal transfer studies for cyflufenamid have not been provided. Of commodities from the proposed uses only grape pomace is used as an animal feed in Australia. Grape pomace may form 20% of the diet for beef and dairy cattle, and 20% of the diet for turkeys. The highest residue in grape pomace in the Australian trials was 0.06 mg/kg. The moisture content of the pomace sample was reported to be 76%, giving a dry weight residue of 0.25 mg/kg. At 20% of the diet, the livestock dietary exposure for both cattle and poultry would be below the 0.1 ppm threshold for the requirement of a feeding study (0.25 × 0.2 = 0.05 ppm).

Based on the goat metabolism study, the likelihood of detectable residues occurring in animal commodities as a result of the proposed use is low (estimated <0.0005 mg/kg in fat). It is appropriate to establish animal commodity MRLs at the respective LOQs for the analytical method. The following MRLs are recommended:

MO 0105 Edible offal (mammalian)	*0.01 mg/kg
MM 0095 Meat [mammalian][in the fat]	*0.01 mg/kg
ML 0106 Milks	*0.01 mg/kg
PE 0112 Eggs	*0.01 mg/kg
PO 0111 Poultry, Edible offal of	*0.01 mg/kg
PM 0110 Poultry meat [in the fat]	*0.01 mg/kg

4.7 Estimated dietary intake

The chronic dietary exposure to cyflufenamid 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[2] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for cyflufenamid is equivalent to <1% 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 were all less than 5% of the acute reference dose. It is concluded that the acute dietary exposure is acceptable.

4.8 Bioaccumulation potential

The K_{ow} log P of cyflufenamid is 4.70 suggesting significant fat solubility. However, in the goat metabolism study feeding at 1.2 ppm gave a TRR in fat of 0.014 mg/kg. Bioaccumulation potential cannot be confirmed in the absence of a feeding study.

[2] Guidelines for predicting dietary intake of pesticide residues, WHO, 1997.

4.9 Spray drift

The draft label includes a restraint that the product should not be applied by air. The product should also not be applied with smaller than MEDIUM spray droplets according to ASAE S572 definition for standard nozzles.

In the goat metabolism study supplied with the application, dosing with cyflufenamid at 1.2 ppm gave highest residues of the 149-F1 metabolite of 0.034 mg/kg in liver. For residues of 149-F1 to be at the LOQ (0.01 mg/kg) the maximum feeding level is 0.353 ppm. Assuming pasture consists of 1500 kg DM/ha this corresponds to a maximum permitted drift of 0.530 g ai/ha.

For ground application to cucurbits at a maximum rate of 12.5 g ai/ha, the standard scenario (High ground boom, medium droplet) indicates drift will drop to 0.530 g ai/ha (0.0424× field rate) by 3 – 4 metres downwind from the application area. A no-spray zone is not required for application to cucurbits for protection of international trade.

For ground application to grapevines at a maximum rate of 17.5 g ai/ha (assuming a spray volume of 1000 L/ha), the standard scenario (Airblast – vineyard) indicates drift will drop to 0.530 g ai/ha (0.0303× field rate) by 3 -4 metres downwind from the application area. A no-spray zone is not required for application to grapevines for protection of international trade.

4.10 Recommendations

Upon granting of the application, the following amendments will be made to the MRL Standard. MRLs in Tables 1 and 3 will be recommended for inclusion in the Food Standards Code:

Table 6: MRL Standard - Table 1

COMPOUND		FOOD	MRL (mg/kg)
ADD:			
CYFLUFENAMID			
DF	0269	Dried grapes (currants, raisins, sultanas)	0.5
MO	0105	Edible offal (mammalian)	*0.01
PE	0112	Eggs	*0.01
VC	0045	Fruiting vegetables, Cucurbits	0.1
FB	0269	Grapes	0.1
MM	0095	Meat [mammalian][in the fat]	*0.01
ML	0106	Milks	*0.01
PO	0111	Poultry, Edible offal of	*0.01
PM	0110	Poultry meat [in the fat]	*0.01

*MRL set at the limit of quantification

Table 7: MRL Standard - Table 3

COMPOUND	RESIDUE
ADD:	
Cyflufenamid	Cyflufenamid

Table 8: MRL Standard - Table 4

	COMPOUND	Animal Feed Commodity	MRL (mg/kg)
ADD:			
Cyflufenamid			
1.	AB 0269	Grape pomace, dry	0.5

HARVEST WITHHOLDING PERIODS:

Grapes: Do not harvest for 35 days after application.

Cucurbits: Do not harvest for 1 day after application.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Cucurbits are not considered to be major export commodities according to Part 5B of MORAG so will not be considered further.

Grapes and wine (including dried grapes) are considered to be major export commodities along with animal commodities derived from livestock that have been fed feeds (i.e. grape pomace) containing residues arising from the proposed use.

5.2 Destination and Value of Exports

Australian exports of wine were worth $1,957 million during 2010-2011. The largest export markets by value are summarised below.

Table 9: Australian exports of wine, 2010 to 2011(Australian Commodity Statistics 2011)

Destination	Value ($ million)
United States	477.8
United Kingdom	451.6
Canada	198.3
China	181.4
New Zealand	56.0
Germany	51.9
Hong Kong	51.4
Singapore	44.3
Netherlands	43.0
Japan	41.1

Australian exports of fresh grapes between August 2010 and September 2011 were worth $79.5 million. The largest export markets by value are summarised below:

Table 10: Australian exports of fresh grapes, August 2010 to September 2011(Australian Bureau of Statistics)

Destination	Value ($ million)
Hong Kong	27.1
Indonesia	12.7
Thailand	9.9
Vietnam	7.1
Singapore	6.0
Malaysia	3.6
United Arab Emirates	2.9
New Zealand	2.1
Russia	1.8
Bangladesh	1.3

Australian exports of dried vine fruit were worth $6 million during 2010 – 2011 (Australian Commodity Statistics 2011). Information on the export markets for dried vine fruit is not readily available.

The significant export markets for animal commodities are defined in Part 5B of MoRaG.

5.3 Proposed Australian use-pattern

Cyflamid 50 EW Fungicide (50 g/L cyflufenamid)

Crop	Pest	Rate	Critical Comments
Grapevines	Powdery mildew (*Erysiphe necator*)	*Dilute spraying:* 35 mL/100 L water (1.75 g ai/100 L) *Concentrate spraying:* Refer to mixing /application section	Apply before first sign of disease or when conditions (varietal and climatic) are conducive to disease development as part of a disease management program. Apply sprays at 10 to 21 day intervals. Use the shorter intervals under conditions favouring disease infection, and at the start of the season (first leaf separated from shoot tip EL7) when there has been a heavy carry-over of powdery mildew infection. Do not apply later than EL31 [berries pea size] when grapes are to be used to make wine for export. For resistance management: Do not apply Cyflamid 50 EW as consecutive sprays or apply more than 2 sprays per season. Application should be made in sufficient water to obtain thorough coverage of the crop. *Dilute spraying:* apply by dilute spraying equipment. The required dilute spray volume will change and the sprayer setup and operation may also need to be changed, as the crop grows. *Concentrate spraying:* apply the same total amount of product to the target crop whether applying this product by dilute or concentrate spraying methods. Do not apply at concentrations greater than 3 X (i.e. concentrated volumes that require rates greater than 105 mL/100 L).
Cucurbits	Powedery mildew (*Podosphaera xanthii*)	250 mL/ha (12.5 g ai/ha) or *Glasshouse:* 25 mL/100 L (1.25 g ai/100L)	Apply before the first sign of disease or when conditions are conducive to disease development as part of a disease management program. Apply sprays at 7 to 10 day intervals. Use the shorter intervals under conditions favouring disease infection. For resistance management: Do not apply Cyflamid 50 EW as consecutive sprays or apply more than 2 sprays per crop. *Glasshouse*: To ensure thorough spray coverage of the target crop, apply to the point of run-off. The required dilute spray volume will change and the sprayer setup and operation may also need to be changed, as the crop grows.

Withholding periods:
Grapes: Do not harvest for 35 days after application.
Cucurbits: Do not harvest for 1 day after application.

5.4 Overseas registration and approved label instructions

The applicant indicated that cyflufenamid products are registered in Japan, Korea, USA and the EU and are under development in various markets, for control of fungal diseases in cereals, various fruits, vegetables and non-crop uses.

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. Cyflufenamid has not been considered by Codex.

The following overseas residue MRLs/ tolerances have been established:

Country/status	Commodity	Tolerance, mg/kg
EU (Sum of cyflufenamid (Z-isomer) and its *E*-isomer)*	Table grapes	0.15
	Wine grapes	0.15
	Cucumbers	0.04
	Gerkins	*0.02
	Courgettes (Summer squash, marrow (patisson))	0.05
	Cucurbits – edible peel, others	*0.02
	Melons (Kiwano)	0.04
	Pumpkins (Winter squash)	*0.02
	Watermelons	*0.02
	Cucurbits – inedible peel, others	*0.02
Japan	Cucumber (including gherkin)	0.3
	Pumpkin (including squash)	0.3
	Oriental pickling melon (vegetable)	0.2
	Water melon	0.02
	Melons	0.02
	Other cucurbitaceous vegetables	0.5
Korea	Grape	0.5
	Fruiting vegetables, cucurbits	0.5
USA	Fruit, small vine climbing, except fuzzy kiwifruit, subgroup 13-07F	0.15
	Grape, raisin	0.3
	Vegetable, cucurbit, group 9	0.07

*Based on metabolism studies and EU residue trials the *E*-isomer is not a major component of the residue.

Animal commodities

The following overseas animal commodity MRLs /tolerances have been established:

Country	Commodity	Tolerance, mg/kg (expiry date)
EU (Sum of cyflufenamid (Z-isomer) and its E-isomer)	Bovine meat	*0.03
	Bovine fat	*0.03
	Bovine liver	*0.03
	Bovine kidney	*0.03
	Bovine edible offal	*0.03
	Milk	*0.03

5.6 Potential risk to trade

Export of treated produce containing finite (measurable) residues of cyflufenamid may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country or (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country.

The draft label included the following recommendation for grapes for export:

Grapes (Export): Do not apply last spray after crop stage EL31 [berries pea-size].

In the Australian residue trials provided in support of this application, quantifiable residues did not occur in wine when the last application was made at this growth stage at up to 2× the proposed concentration. The risk to Australian trade in wine is considered to be low.

In the Australian trials for application at 2 g ai/100 L (1×) up to growth stage EL-31, residues in grapes were <0.01, 0.01 (2), 0.02 and 0.04 mg/kg. Therefore low residues of cyflufenamid may be expected in grapes for export. Although residues will be below the MRLs established in the USA and EU, there is a potential risk to trade as not all the export markets for fresh grapes have established appropriate MRLs. Given residues increased 3.6× on processing to raisins, there will also be a similar risk to trade in dried grapes.

The draft label included the following export advice:

Growers should note that suitable MRLs or import tolerances may not be established in all markets for produce treated with Cyflamid 50 EW. Additionally some export markets have established MRLs different to those in Australia. If growing fruit for export, (either fresh, dried or for wine production) please check with supplier. If growing wine grapes, contact the Australian Wine Research Institute www.awri.com.au for the latest information on MRLs and overseas import tolerances BEFORE using Cyflamid 50 EW.

All recommendations made for grapes for export have been incorporated into the “Export of Treated Produce” section of the relevant label particulars.

The overall risk to export trade in animal commodities is considered to be low as detectable residues of cyflufenamid are not expected to occur.

The relevant industry groups should be given the opportunity to comment 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

The product Cyflamid 50EW Fungicide is intended for professional use only. 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 and diluted spray will be dermal and inhalational, 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. For repeated use, exposure to the product when mixing and loading, application to cucurbits by boom spray and hand-wand spraying, and application to grapes by airblast sprayer behind a tractor, were acceptable without the use of personal protective equipment. However, based on the product acute hazard of moderate skin irritation, it is recommended that when mixing, loading and applying the product cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves are worn.

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

6.2 Health Hazards

Cyflufenamid (CAS: 180409-60-3) is not listed on Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2011). With the available toxicology information, OCS classifies cyflufenamid as a non-hazardous substance according to the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004). Thus, no human health risk phrases have been assigned to this new active constituent.

Based on the product toxicology information and concentrations of cyflufenamid in the product, Cyflamid 50 EW Fungicide is classified as a hazardous substance in accordance with the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004) with the following human health risk phrase assigned:

R38 Irritating to skin

6.3 Formulation, packaging, transport, storage and retailing

The active constituent cyflufenamid will be manufactured overseas. The product Cyflamid 50 EW Fungicide will be manufactured overseas and imported into Australia in 1, 2.5, 5, 10 or 20 L non-fluorinated high-density polyethylene (HDPE) containers with self-adhesive labels.

6.4 Use pattern

Cyflamid 50 EW Fungicide is an emulsion, oil in water, containing 50 g/L cyflufenamid and is intended for use in cucurbits and grapes as a protectant fungicide against powdery mildew. It is intended for professional use only.

The proposed use rates are 35 mL product/100 L water with spray volumes of up to 1500 L water on grapes (equivalent to 160–560 mL product/ha), and 250 mL product/ha with spray volumes of between 300–1300 L water/ha on cucurbits. Application to grapes should be no more than twice per season, while application to cucurbits is limited to two sprays per crop. The product is to be applied to cucurbits by boom spray and hand-wand spraying and to grapes by airblast sprayer behind a tractor.

6.5 Exposure during use

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 and diluted spray will be dermal and inhalational, although ocular exposure is also possible during application of the dilute spray.

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used to estimate potential worker exposure. The toxic endpoint of concern and identified NOEL 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 potential interspecies and intraspecies variation and the seriousness of the critical health effect of concern.

The MOE's associated with repeated use of the product when mixing and loading, application to cucurbits by boom spray and hand-wand spraying, and application to grapes by airblast sprayer behind tractor, are acceptable (i.e. >100) without the use of personal protective equipment. However, based on the product acute hazard of moderate skin irritation, it is recommended that when mixing, loading and applying the product cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves are worn.

6.6 Exposure during re-entry

Workers may be exposed to Cyflamid 50 EW Fungicide when re-entering treated areas. In the absence of worker exposure studies, the post-application exposure has been calculated using the Occupational Post-Application Risk Assessment Calculator Version 1 (8/9/00) EPA Policy 003.1.

The cucurbit vegetable or vine/trellis re-entry scenarios were used to estimate re-entry exposure, with high exposure potentials or very high exposure potentials selected to simulate a worst-case for workers. The high exposure potential lists activities such as grape girdling and cane turning for grape crops, and hand harvesting, leaf thinning and turning for cucurbits.

The following re-entry statements are recommended.

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.

For glasshouses or other enclosed areas, do not allow re-entry until spray has dried or dissipated, and enclosed area has been thoroughly ventilated.

6.7 Recommendations for safe use

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

6.8 Conclusion

The registration of Cyflamid 50 EW Fungicide containing 50 g/L cyflufenamid for use in cucurbits and grapes as a protectant fungicide against powdery mildew is supported. Cyflamid 50 EW 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 Material Safety Data Sheet.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

Nippon Soda Co Ltd has applied for the approval of a new active constituent, cyflufenamid and new formulated product, Cyflamid 50EW Fungicide, an oil in water emulsion containing 50 g/L cyflufenamid. Cyflufenamid belongs to the amidoximes class of fungicides and the mode of action at this stage has not been established. The proposed use in Australia is for control of powdery mildew in grapevines and cucurbits.

7.2 Environmental Fate

Hydrolysis

Cyflufenamid is hydrolytically stable at environmentally relevant pH levels. Hydrolysis may be faster under more alkaline conditions, but even at pH 9 (20^{o}C), the hydrolysis half-life was calculated to be >600 days.

Photolysis/Photodegradation

Based on one photodegradation study on soil surfaces, photolysis is not expected to be a major degradation route in the environment (DT50 176 days, midsummer sun, 40^{o}N).

Biodegradation

Aerobic Soil Metabolism

Several aerobic soil degradation studies were provided to address both the rate and route of degradation. Degradation of the parent compound in aerobic soils tended to follow a bi-phasic pattern with faster initial degradation. While the majority of these results support a fast initial degradation period, there remain some results that suggest cyflufenamid can persist under aerobic conditions. In one study two soils were tested. In one of the soils, cyflufenamid again showed limited persistence in the initial phase. However, in the second soil, degradation was very slow and the half-life exceeded 1 year. This result was unusual considering the range of other results, and the soil was re-tested under several different conditions. In all tests, the half-life of cyflufenamid was much faster and ranged from 3.5-23 days. Despite this, no clear explanation could be found as to why the rate was so slow in the earlier study. Disregarding the initial findings in the Terling soil, the DT50 range from both laboratory and field studies was 2.1 days to 121 days. The 50th and 90th percentile DT50s were 14 days and 38 days respectively, indicating cyflufenamid is unlikely to persist in soil.

This potential variability in metabolism in soil is also found in field studies. In Europe, four sites were tested and at three of these, the half-life was <30 days or less. However, in the fourth soil, it was 91 days.

The majority of the results support a conclusion that initially, cyflufenamid will degrade/dissipate faster with a slower second phase of degradation/dissipation. It is not expected to degrade readily under anaerobic conditions and photolysis is not expected to be major degradation process for cyflufenamid.

Of the major metabolites considered, the shortest half-lives were associated with 149-F and 149-F11. These two metabolites represent the first stage of biodegradation of cyflufenamid as the parent compound is oxidised to 149-F11, then hydrolysed to 149-F. This metabolite undergoes deamination to 149-F6. This metabolite is much more persistent (half-lives >1 year) as it slowly reduces to 149-F1, which also has longer half-lives exceeding 4 months.

Cyflufenamid is resistant to degradation in soils where anaerobic conditions are present, with one study showing a DT50 >>1 year.

When exposed to water systems, the half-life in the water column is expected to be short (up to a few days) as the substance predominantly moves to sediment. In sediment, the half-life is likely to vary depending on the conditions of the sediment (reducing or not). Based on two water/sediment systems tested, DT50 values from the whole system ranged from around 51 days to 128 days. The metabolite found at the highest levels was 149-F11, accounting for up to 20% of initially applied radioactivity with 149-F also being found at >10% AR. Degradation was biphasic in the water column, but tended to follow first order kinetics when considered for the whole system.

There was no test provided on water/sediment systems under anaerobic conditions. However, one of the anaerobic soil studies employed a test system that enabled consideration of both water and sediment compartments and cyflufenamid was shown to persist under such conditions.

Cyflufenamid is not readily biodegradable.

Mobility

The vapour pressure of cyflufenamid is low (<0.0001 Pa), making this substance only very slightly volatile.

In standard batch adsorption tests, cyflufenamid was tested in four different soils with %OC ranging from 0.8-2.4%. Koc (organic carbon coefficient) values ranged from 1000-2350. In three of the soils, cyflufenamid can be considered to have low mobility (Koc 500-2000 L/kg) while it has slight mobility in the fourth soil (Koc 2000-5000 L/kg). One metabolite (149-F) had Kdes (apparent desorption coefficient) values lower than initial Kads (adsorption coefficient) for three of four tested soils indicating a low affinity for the soils, and a high potential to desorb. Generally though, for cyflufenamid and its metabolites, the Kdes following the first desorption step was higher than the Kads, although often these values were not substantially higher. This indicates that adsorption is not fully reversible, but a moderate degree of desorption can be expected.

In a field leaching study using a sandy soil where it was concluded there was a very low potential for cyflufenamid or its degradation products to leach to groundwater. In field dissipation studies, there was limited movement of cyflufenamid or its main metabolites through the soil profile. In European studies, no quantifiable residues for parent or metabolites was found below 10 cm. In USA studies, parent compound was restricted to the top 15 cm layer, and movement to lower soil depths than this for metabolites was not considered significant.

Bioaccumulation

In one bioconcentration study, bioconcentration factors (BCF) were highest in non-edible tissues (~600) and whole fish BCFs ranged from 436-449. These results indicate cyflufenamid is moderately concentrating, however, depuration was rapid with only 1-2% of residues remaining after a 14 day depuration period.

7.3 Environmental Effects

Avian

Cyflufenamid is practically non-toxic to birds based on acute and dietary exposure. When tested for chronic/reproductive effects, mallard duck was the most sensitive species. The study NOEC was 300 mg/kg diet based on adverse effects on chick bodyweights at 14 days. No other reproductive parameter measured in this study was effected at the highest test level of 1000 mg/kg diet.

Fish

Cyflufenamid, when tested as the active constituent, is moderately toxic to fish (acute), and moderately toxic to fish based on one early life stage (fish weight). Metabolites were much less toxic than the parent compound being slightly to practically non-toxic to fish. When tested as the formulation, toxicity appeared enhanced to fish based on acute exposure.

Aquatic Invertebrates

Cyflufenamid was moderately toxic to the freshwater invertebrate, Daphnia magna under acute exposure, and moderately toxic in chronic toxicity tests. However, it was highly toxic to the two saltwater invertebrates tested (Eastern oyster and mysid shrimp). Metabolites were much less toxic than the parent compound being slightly to practically non-toxic to aquatic invertebrates (Daphnia). When tested as the formulation, toxicity appeared enhanced to aquatic invertebrates (Daphnia) based on acute exposure.

The parent compound was at worst slightly chronically toxic to the sediment dwelling midge.

Algae, Diatoms and Aquatic Plants

Test results were available for parent toxicity to four algal species and one aquatic macrophyte. When tested as the active constituent, cyflufenamid failed to show adverse effects sufficient to calculate EC50 values. The major metabolites were generally practically non-toxic to algae, although one (149-F) was slightly toxic. However, when tested as the formulation, toxicity to algae appeared to be enhanced, and if the toxicity observed was attributed to the parent compound it was considered very highly toxic to algae.

Terrestrial Invertebrates

Cyflufenamid was shown to not be toxic to bees, soil dwelling organisms or non-target arthropods. In the case of bees, oral and contact LD50s exceeded 100 µg/bee when tested as the active constituent.

While dose response testing was not available for non-target arthropods, there were a number of laboratory and extended laboratory tests available assessing mortality and reproduction parameters to standard test species. These results indicated cyflufenamid would not be harmful to such organisms in the field.

Acute toxicity tests for earthworms showed cyflufenamid and its major metabolites to only be very slightly toxic, with the exception of 149-F that was slightly toxic to earthworms. For reproductive toxicity testing, cyflufenamid had a study NOEC of 1000 g ac/ha (applied as a surface spray) while the two main metabolites tested had NOECs >1 mg/kg dw soil.

Microorganisms

Exposure of cyflufenamid to soil microorganisms showed no significant adverse effects on the soil nitrogen cycle or soil respiration at levels up to 0.29 mg ac/kg dw soil. The major metabolites tested at soil concentrations considered indicative of five times the application rate also showed no significant effects on soil nitrogen or carbon cycles.

Terrestrial Plants

Vegetative vigour and seedling emergence studies showed no deleterious effects at 100 g ac/ha.

7.4 Environmental Risk Assessment

Cyflufenamid is to be applied at application rates of 12.5 g ac/ha to cucurbits and up to a maximum expected 30 g ac/ha in vineyards, with up to two applications in a season. The risk assessment, which was performed using standard methodology, showed an acceptable risk to all environmental organisms considered, with no further mitigation such as inclusion of downwind spray buffer zones required.

7.5 Conclusions

The APVMA is satisfied that the proposed use of the new product CYFLAMID 50EW FUNGICIDE, containing the active constituent cyflufenamid, would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment if used according to the product label directions.

8 EFFICACY AND SAFETY ASSESSMENT

The applicant, Nippon Soda Co., Ltd, seeks registration of the proposed new product, CYFLAMID 50 EW FUNGICIDE, for the control of powdery mildew (*Podosphaera xanthii*) of cucurbits and powdery mildew (*Erysiphe necator*) of grapevines. The product is an oil in water emulsion containing 50 g/L of the new active constituent cyflufenamid.

8.1 Proposed use pattern

CYFLAMID 50 EW Fungicide is intended to be used at a rate of 250mL product/ha in cucurbits and 35mL product/100L water (dilute application rate) in grapevines. In grapes, CYFLAMID 50 EW Fungicide is to be used as a protectant spray before disease is apparent and then after a 10-21 day interval. In cucurbits, CYFLAMID 50 EW Fungicide is to be used as a protectant spray before disease is apparent and then after a 7-10 day interval. Use is proposed in all Australian states and territories.

8.2 Summary of Evaluation of Efficacy and Crop Safety

Cyflamid 50EW Fungicide was evaluated in 18 field studies for the control of powdery mildew. There were nine grapevine trials and nine cucurbit trials, each of which had a suitable trial design (randomised complete block, three or four replicates, and data were correctly analysed by ANOVA). Every Australian field trial was based on suitable varieties, susceptible to powdery mildew. Of the grapevine trials, there were seven with Chardonnay, two with Cabernet Sauvignon and one with Riesling. Of the nine Australian cucurbit trials, there was one with cucumber, two with honey dew melon, one with pumpkin, one with rockmelon, two with watermelon, and two with zucchini. Climatic conditions for two of the cucurbit trials were not suitable, being located in a dry region over a hot season so the disease pressure was very low. However, the other seven cucurbit trials had adequate disease pressure to demonstrate a good fungicidal response.

The scale of the trials was adequate. The grapevine trial blocks consisted of one or two panels, each containing three or four vines. The cucurbit trial block size ranged from (1.5 m – 3 m) x (5 m – 12 m); i.e. from 7.5 m2 to 36 m2.

All grapevine trials supported control of powdery mildew with 1.75 g a.i/100 L Cyflamid 50EW Fungicide (35mL/100L). The two Tasmanian studies showed that the lowest effective spray concentration for control of powdery mildew was 1.0 g a.i/100 L. Two Healesville (Vic) studies and one Lenswood (SA) trials showed the lowest effective spray concentration to be 1.5 g a.i/100 L. Two Pemberton (WA) trials showed the lowest effective spray concentration to be 1.75 g a.i/100 L.

All cucurbit trials supported control of powdery mildew with 12.5 g a.i/100 L. For one Queensland (cucumber) trial the lowest effective spray concentration was 2.5 g a.i/100 L. Two Queensland studies (pumpkin and honey dew melon) showed the lowest effective spray concentration to be 5 g a.i/100 L. Two Tasmanian (zucchini), one Queensland and one WA study (watermelon) showed the lowest effective spray concentration to be 10 g a.i/100 L.

Every trial evaluated Cyflamid 50EW Fungicide phytotoxicity by monitoring plants sprayed with 20 or 30 g a.i./100 L. No adverse effects were found in any of the reported trials.

The supporting data from efficacy trials demonstrate that Cyflamid 50EW Fungicide is an effective control agent of powdery mildew in grapevines and cucurbits. There were no instances of crop phytotoxicity or damage found with its use. The efficacy reviewer concluded that the Australian field data justify the label claims and directions for use for Cyflamid 50EW Fungicide.

9 LABELLING REQUIREMENTS

RELEVANT LABEL PARTICULARS (RLPs) Cyflamid® 50 EW Fungicide

Signal heading	CAUTION KEEP OUT OF REACH OF CHILDREN READ SAFETY DIRECTIONS BEFORE OPENING OR USING
Product name	Cyflamid® 50 EW Fungicide
Active constituent/s	50 g/L CYFLUFENAMID
Mode of action	GROUP U6 FUNGICIDE
Statement of claims	A fungicide for the control of powdery mildew in grapevines and cucurbits as per the Directions for Use Table
Restricted chemical	n/a
Net contents	1 L, 2.5 L, 5 L, 10 L, 20L
Name & address	AgNova Technologies Pty, Suite 3, 935 Station St, Box Hill North, Vic 3129
Directions for Use	DIRECTIONS FOR USE
Restraints	DO NOT apply by air as uneven coverage is likely to result. DO NOT apply when wind speed is less than 3 or more than 20 km/hr at the application site. DO NOT apply with smaller than MEDIUM spray droplets according to ASAE S572 definition for standard nozzles. 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 humidity; 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.)

Directions for Use

CROPS	DISEASE	RATE	WHP	CRITICAL COMMENTS
Grapevines	Powdery mildew (*Erysiphe necator)*	*Dilute spraying*: 35 mL/100 L water Concentrate spraying: Refer to the Mixing/ Application section	5 weeks	Apply as part of a protectant spray program before first sign of disease or when conditions (varietal and climatic) are conducive to disease development as part of a disease management program. Apply sprays at 10 to 21 day intervals. Use the shorter intervals under conditions favouring disease infection, and at the start of the season (first leaf separated from shoot tip EL7) when there has been a heavy carry-over of powdery mildew infection, or during periods of rapid vine growth. Do not apply more than 2 Cyflamid 50 EW Fungicide sprays per season, and follow the CropLife Australia resistance management guidelines.

					Apply in sufficient water volume to obtain thorough coverage of the crop. Apply by dilute or concentrate spraying equipment. Apply the same total amount of product to the target crop whether applying by dilute or concentrate spraying method. Do not apply at concentrations greater than 3 X (i.e. concentrated volumes that require rates greater than 105 mL/100 L) The required dilute spray volume will change and the sprayer setup and operation may also need to be changed, as the crop grows.
	Cucurbits	Powdery mildew (*Podosphaera xanthii*)	250 mL/ha or	1 day	Apply before first sign of disease or when conditions are conducive to disease development as part of a disease management program. Apply sprays at 7 to 10 day intervals. Use the shorter intervals under conditions favouring disease infection. For resistance management: Do not apply Cyflamid 50 EW Fungicide as consecutive sprays or apply more than 2 sprays per crop.
			Glasshouse: 25 mL/100 L		*Glasshouse*: To ensure thorough spray coverage of the target crop, apply to the point of run-off. The required dilute spray volume will change and the sprayer setup and operation may also need to be changed, as the crop grows.

"Not to be used…"	NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL UNLESS AUTHORISED UNDER APPRORIATE LEGISLATION.
Other limitations	n/a
Withholding Period/s	GRAPES (DOMESTIC): DO NOT HARVEST FOR 5 WEEKS AFTER APPLICATION GRAPES (FOR WINE INTENDED FOR EXPORT): CONTACT NIPPON SODA CO LTD, OR CONSULT YOUR WINERY OR THE AUSTRALIAN WINE RESEARCH INSTITUTE (AWRI) FOR THE RECOMMENDED WITHHOLDING PERIOD. CUCURBITS: DO NOT HARVEST FOR 1 DAY AFTER APPLICATION
Trade Advice	EXPORT OF TREATED PRODUCE Growers should note that MRLs or import tolerances do not exist in all markets for fruit treated with Cyflamid 50 EW Fungicide. Fruit: If growing fruit for export (either fresh or dried) consult your peak industry body or Nippon Soda Co. Ltd for the latest information on MRLs and import tolerances. Wine: Cyflamid 50 EW Fungicide should not be applied later than EL31 [berries pea-size] when grapes are to be used to make wine for export. Contact your winery or the Australian Wine Research Institute (AWRI) at www.awri.com.au for the updated information on MRLs and overseas import tolerances BEFORE using Cyflamid 50 EW Fungicide.
General instructions	**GENERAL INSTRUCTIONS** MIXING/APPLICATION

	Add the required quantity of Cyflamid 50 EW fungicide to a partly filled spray tank and agitate. Complete filling while agitating. Ensure the spray mixture is properly agitated before restarting after stoppage. Grapevines *Dilute Spraying* Use a sprayer designed to apply high volumes of water 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 runoff. Avoid excessive run-off. The required water volume may be determined by applying different test volumes, using different settings on the sprayer, from industry guidelines or expert advice. Add the amount of product specified in the Directions for Use table for each 100 L of water. Spray to the point of run-off. The required dilute spray volume will change and the sprayer setup and operation may also need to be changed as the crop grows. *Concentrate Spraying* Use a sprayer designed and set up for concentrate spraying (that is a sprayer which applies water volumes less than those required to reach the point of 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 water 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 Dilute spray volume as determined above: For example 1500 L/ha Your chosen concentrate spray volume: For example 500 L/ha The concentration factor in this example is: 3 X (i.e.1500 L ÷ 500 L = 3) If the dilute label rate is 35 mL/100 L, then the concentrate rate becomes 3 x 35, that is 105 mL/100 L of concentrate spray. The chosen spray volume, amount of product /100 L of water, and the sprayer set up and operation may need to be changed as the crop grows. Do not use a concentration rate higher that that specified in the Critical Comments Use a spray volume of at least 200 L/ha. For further information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow industry Best Practices.
Resistance warning	FUNGICIDE RESISTANCE WARNING — GROUP U6 FUNGICIDE Cyflamid 50 EW Fungicide is a member of the amidoxime group of fungicides. For fungicide resistance management, the product is a Group U6 fungicide. Some naturally occurring individual fungi resistant to Cyflamid 50 EW Fungicide and other Group U6 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 Cyflamid 50 EW Fungicide or other Group U6 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, Nippon Soda Co., Ltd accepts no liability for any losses that may result from the failure of Cyflamid 50 EW Fungicide to control resistant fungi. Refer to Directions for Use table and published CropLife Resistance Management Strategies www.croplifeaustralia.org.au
Precautions	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 elbow-length chemical resistant gloves. Clothing must be laundered after each day's use. For glasshouses and other enclosed areas, do not allow re-entry until spray has dried or dissipated, and enclosed area has been thoroughly ventilated.
Protections	PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS DO NOT apply under weather conditions, or from spraying equipment, that may cause spray to drift onto nearby susceptible plants/crops, cropping lands or pastures.

	PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT Very toxic to aquatic life. DO NOT contaminate wetlands or water courses with this product or used containers.
Storage & disposal	Store in the closed, original container in a cool, well-ventilated area. Do not store for prolonged periods in direct sunlight. Triple rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and deliver empty packaging to an approved waste management facility. If an approved waste management facility is not available bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots, in compliance with relevant Local, State or Territory government regulations. DO NOT burn empty containers or product.
Safety Directions	Will irritate the skin. May irritate the eyes. Avoid contact with eyes and skin. When opening the container, preparing spray and using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length chemical resistant gloves. If product on skin, immediately wash area with soap and water. 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. Phone Australia 13 11 26

The following is for APVMA use only:

APVMA approval no.	APVMA No: 66036/52568

ABBREVIATIONS

ac	active constituent
ACCS	Advisory Committee on Chemicals Scheduling
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ANOVA	Analysis of Variance
ARfD	Acute Reference Dose
BCF	Bioconcentration Factor
bw	bodyweight
^{o}C	Degrees Celcius
^{14}C	Carbon-14
Codex	Codex Alimentarius Commission
CXLs	Codex Maximum Residue Limits
d	day
DALA	Days after last application
DAT	Days After Treatment
DM	Dry Matter
DNA	Deoxyribonucleic acid
DSEWPaC	Department of Sustainability Environment Water Population and Communities
dSPE	Dispersive solid phase extraction
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted

EI	Export Interval
EGI	Export Grazing Interval
ESI	Export Slaughter Interval
EUP	End Use Product
EW	Emulsion, oil in water
FOB	Functional observation battery
g	gram
GAP	Good Agricultural Practice
GI	Gastro-intestinal
GLP	Good Laboratory Practice
h	hour
ha	hectare
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HSIS	Hazardous Substances Information System
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
Kads	Adsorption constant
Kdes	Apparent desorption coefficient
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms

LC/MS/	Liquid Chromotography with tandem mass spectrometry
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MOA	Mode of Action
MOE	Margin of Ezposure
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
MTD	Maximum tolerated dose
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
NOHSC	National Occupational Health and Safety
OC	Organic Carbon
OCS	Office of Chemical Safety
OM	Organic Matter
Pa	Pascal
po	oral
ppb	parts per billion
pH	Hydrogen ion concentration
PHED	Pesticide Handler Exposure Database
PPE	Personal Protective Equipment

ppm	parts per million
PRS	Public Release Summary
Q-value	Quotient-value
RBC	Red Blood Cell Count
RSD	Relative Standard Deviation
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SWA	Safe Work Australia
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
TRR	Total Radioactive Residues
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
UDS	Urine drug screen
vmd	volume median diameter
WG	Water Dispersible Granule
WHO	World Health Organisation
WHP	Withholding Period

GLOSSARY

Acceptable daily intake	The daily intake of a chemical which, during an entire lifetime, appears to be without appreciable risk to the health of the consumer on the basis of all the known facts at the time. The ADI is expressed in milligrams of the chemical per kilogram of body weight per day (mg/kg/day). It is derived from the no-observed-effect level (NOEL) observed in the most sensitive animal species, utilising an appropriate safety factor.
Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Acute reference dose	The ARfD of a chemical is an estimate of the amount of a substance in food and/or drinking water, normally expressed on a body-weight basis that can be ingested in a period of 24 hours or less, without appreciable risk to the consumer, on the basis of all known facts at the time of the evaluation.
Carcinogenicity	The ability to cause cancer
CAS registry	A database of the Chemical Abstracts Service (CAS) in which numbers are randomly assigned to compounds and are unique for each compound.
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
Evaluation	A written assessment of study reports or other data examined in the course of an appraisal by the APVMA for the granting or refusing of an application or other consideration
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Maximum residue limit	The maximum concentration of a chemical residue that is legally permitted in or on a food or feed commodity when that chemical is applied according to good agricultural practice (GAP) or good practice in the use of veterinary drugs (GPVD)
Metabolism	The chemical processes that maintain living organisms
New active constituent	An active constituent that has not previously been approved for use in an agricultural /veterinary chemical product in Australia
Photodegradation	Breakdown of chemicals due to the action of light

Photolysis	Breakdown of chemicals due to the action of light
Product	A formulation containing one or more active constituents, and possibly non-active constituent(s), which is intended for application, with or without dilution prior to use, and which is labelled with directions for use
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.

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