Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the new active Cyazofamid in the Product Ranman 400 SC Fungicide

APVMA Product Number 66411

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

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PREFACE

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

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Ageing, Office of Chemical Safety (OCS), Department of Environment, 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 website at http://apvma.gov.au/.

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 RANMAN 400 SC FUNGICIDE should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade, and efficacy and target crop or animal safety. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on 11 August 2015 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

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

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

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

Case Management and Administration Unit (CMAU)

Australian Pesticides and Veterinary Medicines Authority

PO Box 6182

Kingston ACT 2604

Phone: +61 2 6210 4701

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

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

Further information

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

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

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

1 INTRODUCTION

Applicant

Ishihara Sangyo Kaisha (ISK) Limited

Details of the Product

It is proposed to register Ranman 400 SC Fungicide, containing 400 g/L cyazofamid, as a suspension concentrate intended for use in the control of late blight in potatoes and white blister in broccoli. Ranman 400 SC Fungicide is intended to be used at the rate of 150–200 mL product/ha corresponding to 60–80 g ac/ha.

Both the active constituent cyazofamid, and the product Ranman 400 SC Fungicide, will be manufactured overseas. Ranman 400 SC Fungicide will be imported into Australia and will be available in 0.5, 1 and 5 L high density polyethylene (HDPE) containers.

Ranman 400 SC Fungicide (400 g/L cyazofamid) is currently registered overseas in a range of crops. In Canada, it is registered for use on cucurbits, potatoes, carrots, and spinach. In the USA it is registered for use on brassica leafy vegetables, fruiting vegetables, tuberous and corm vegetables, leafy greens, basil, grapes, hops and cucurbits. In the UK it is registered for use in potatoes. In Chile, the registered uses are in tomatoes, potatoes, lettuce, spinach, watermelon and rock melon. In Mexico the registered uses are in tomatoes, potatoes, melons, cucumber, pumpkin and zucchini.

This publication provides a summary of the data reviewed and an outline of regulatory considerations for the proposed registration of Ranman 400 SC Fungicide.

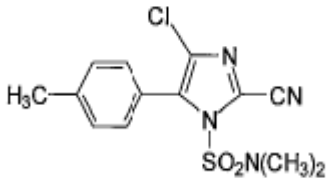
2 CHEMISTRY AND MANUFACTURE

2.1 Active Constituent

Manufacturing Site

The active constituent Cyazofamid will be manufactured at LG Life Science, Ltd. (Onsan plant) 580 Hwasan-ri, Onsan-eup, Ulju-gun, Ulsan City, Kyongam 689–896,Republic of Korea

Chemical Characteristics of Active Constituent

COMMON NAME (ISO):	Cyazofamid
IUPAC NAME:	4-chloro-2-cyano-N,N-dimethyl-5-p-tolylimidazole-1-sulfonamide
CAS NAME:	4-chloro-2-cyano-N,N-dimethyl-5-(4-methylphenyl)-1H-imidazole-sulfonamide
CAS REGISTRY NUMBER:	120116-88-3
MINIMUM PURITY:	935g/kg
MOLECULAR FORMULA:	$C_{13}H_{13}ClN_4O_2S$
MOLECULAR WEIGHT:	324.8 g/mol
STRUCTURE FAMILY:	
CHEMICAL FAMILY:	Sulphonamides and Imidazoles

APVMA Active Constituent Standard for Cyazofamid

CONSTITUENT	SPECIFICATION	LEVEL
Cyazofamid	Cyazofamid	not less than 935 g/kg

PHYSICO-CHEMICAL PROPERTIES OF ACTIVE CONSTITUENT

PHYSICAL FORM:	White to off-white powder
ODOUR:	Odourless
MELTING POINT:	152.7oC
BOILING POINT:	Decomposes before boiling
RELATIVE DENSITY:	1.446 g/cm3 at 20 oC
PH (1% SOLUTION):	4.9 at 20oC
SOLUBILITY IN WATER AT 20OC:	0.121 mg/L (pH 5) 0.107 mg/L (pH 7) 0.109 mg/L (pH 9)
SOLUBILITY IN VARIOUS SOLVENTS AT 20OC	Solvent — TGAI 9 g/L) at 21.2oC Acetone — 45.64 Ethyl acetate — 16.49 Methanol — Unstable Dichloromethane — 102.12 Toluene — 6.00 Hexane — Unstable n-Octonal — Unstable Acetonitrile — 30.59 2-propanol — Unstable
HYDROLYIS RATE AT 25OC	pH — [14C]IKF-916 (Bz) — [14C]IKF-916 (Im) 4 — 12.4 days — 12.3 days 5 — 13.3 days — 12.6 days 7 — 12.1 days — 12.3 days 9 — 11.8 days — 10.6 days
THERMALSTABILITY:	Stable (room temperature to melting point)
DISSOCIATION CONSTANT (pKa):	No pKa evident in the pH range of 2–12 (20 +/- 10C in 40% (v/v) ethanol/water)
OXIDISING PROPERTIES:	Not oxidising

2.2 Product

The product Ranman 400 SC Fungicide will be manufactured overseas and imported into Australia in 500mL to 5L high density polyethylene (HDPE) containers.

RANMAN 400 SC FUNGICIDE

DISTIGUISHING NAME:	Ranman 400 SC Fungicide
FORMULATION TYPE:	Soluble Concentrate (SC)
ACTIVE CONSITUENT CONCENTRATION:	Cyazofamid (400 g/L)

PHYSICAL AND CHEMICAL PROPERTIES OF THE PRODUCT

PHYSICAL FORM:	Beige liquid
ODOUR:	Musty latex paint odour
PH VALUE:	6.2
RELATIVE DENSITY:	1.154 g/L
SURFACE TENSION:	55.7mN/m
VISCOSITY AT 25OC	237at RPM 50
FLASH POINT:	None
OXIDISING PROPERTIES:	No exotherms>5^{o}C
FLAMMABILITY:	Not applicable
CORROSIVE HAZARD:	Not corrosive to HDPE containers
PACK SIZES:	500 mL, 1 L, 5 L
PACKAGING MATERIAL:	High density polyethylene (HDPE)
PRODUCT STABILITY:	The product should remain within specifications for at least 2 years when stored under normal conditions in HDPE packaging

2.3 Recommendations

Based on a review of the chemistry and manufacturing details provided by the applicant, registration of Ranman 400 SC Fungicide is supported.

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

Public Health Aspects & Toxicology

Ranman 400 SC Fungicide is a suspension concentrate formulation containing the new active constituent cyazofamid. The product is intended for control of late blight in potatoes and white blister in broccoli.

Cyazofamid is a member of the cyano-imidazole chemical class and is generally classified into the azole group. Cyazofamid is a fungicide and its mode of action is to inhibit all stages of fungal development, in particular, respiratory inhibition at Complex III in the mitochondria of Oomycete fungi.

Evaluation of the available metabolism and toxicokinetic data indicated that radiolabelled cyazofamid fed to rats was rapidly absorbed from the gastrointestinal tract with an estimated absorbed fraction of up to 75–78% of the administered dose. Toxicokinetic data indicated biphasic elimination from the blood with statistical analyses of all toxicokinetic parameters not revealing a difference between sexes. Cyazofamid was rapidly and widely distributed to tissues with the highest levels detected in liver, kidney and blood. There was no evidence of accumulation following single or repeat oral doses. In bile cannulated rats cyazofamid was completely metabolised when excreted in urine (30–55% of administered dose) and bile (12–39% of administered dose), with the remainder excreted in faeces almost completely as unchanged parent compound. The metabolic profile in excreta identified that cyazofamid was completely metabolised to CCBA (4-(4-chloro-2-cyanoimidazol-5-yl) benzoic acid) and glutathione conjugates (higher levels in females compared to males) in bile and urine. Excretion of cyazofamid and its metabolites was rapid with elimination almost complete by 24 to 48 hours post administration of single or repeat dose of cyazofamid.

Based on the findings of the acute toxicological studies evaluated, cyazofamid is of low acute oral, dermal and inhalational toxicity, and has slight eye irritation and slight skin irritation but is not considered to be a potential skin sensitiser in guinea pigs (Maximisation test).

In repeat dose studies in mice, rats and dogs treatment related and toxicologically significant effects were limited to a slight increase in histopathological changes in the ovaries of mice and decreased body weight gain and increased incidence of ocular cataracts in female rats following chronic oral dosing at the highest dose tested, with no treatment related and toxicologically significant findings in dogs.

Cyazofamid was negative in *in vitro* and short-term *in vivo* genotoxicity studies and carcinogenicity studies in mice and rats did not reveal any treatment related neoplastic findings from histopathological examinations. A marginal increase in lung adenocarcinomas and adrenal phenochromocytoma in male rats (outside historical controls) was not statistically significant compared to concurrent controls, was not seen in females administered higher doses, and negative control data for adrenal phenochromocytoma was itself outside historical controls. Thus overall the findings are not considered by The Office of Chemical Safety (OCS) to provide robust evidence of a treatment related carcinogenic effect.

There were no treatment related effects on reproductive or developmental parameters, with treatment related and toxicologically significant findings limited to pup toxicity (decreased body weight gain at weaning only) at the highest dose tested in a two-generation study in rats.

In the reproduction study in rats an increase in litter and pup stillborn indices compared to concurrent controls was observed. However, the stillborn pup indices were within historical control ranges for all generations at the highest dose tested and are considered incidental to treatment and the increase in litter stillborn indices was not outside the range of historical controls for all generations (F2b within historical control range). Thus, OCS considers that overall the data do not provide robust evidence for a treatment related effect and, thus, are considered likely incidental and not treatment related.

In the developmental study in rats there was a higher incidence of bent ribs (3 foetuses in 3 litters i.e. 1 per litter) detected at 1000 mg/kg bw/d with a corresponding increased incidence in the total number of foetuses and litters examined. Historical control data were not provided by the applicant to assist in determining the toxicological significance of the findings. However, published historical control data in the same rat strain (Middle Atlantic Reproduction and Teratology Association (MARTA)) was considered acceptable for use and the incidence of bent ribs were found to be within the historical control range. Therefore the OCS considers that the finding at the limit dose of 1000 mg/kg bw/d was likely incidental and not toxicologically significant.

Supplementary toxicological data on four metabolites/impurities did not provide evidence of mutagenic potential in bacteria. DMSA (Dimethysulfamic Acid) and CCIM-AM (4-chloro-5-*p*-tolylimidazole-2-carboxamide) had low acute oral toxicity in rats, comparable to the active constituent cyazofamid. CCIM (4-chloro-5-*p*-tolylimidazole-2-carbonitrile) had moderate acute oral toxicity in rats and CTCA (4-chloro-5-*p*-tolylimidazole-2-carboxylic acid) had low to moderate acute oral toxicity in rats.

Based on the findings of the acute toxicological studies on Ranman 400 SC Fungicide, the product is of low acute oral, dermal and inhalational toxicity in rats. It neither is an irritant to the eyes and skin of rabbits, nor is it a potential skin sensitiser in guinea pigs (Buehler test).

Occupational Health and Safety

The product Ranman 400 SC Fungicide is proposed for use in the control of Late Blight (*Phytophthora infestans*) in potatoes, and White Blister (*Albugo candida*) in broccoli. 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. Dermal exposure may also during re-entry activities in treated crops.

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide was used to estimate exposure. Exposure to the product during mixing and loading and application by low and high pressure hand-wand and ground-boom were at an acceptable level for workers wearing a single layer of clothing and during mixing and loading and application by backpack for workers wearing a single layer of clothing and chemical resistant gloves.

There are no acute hazards of concern or re-entry risk associated with the product.

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

Conclusion

Based on an assessment of the toxicology and occupational health and safety, it was considered that there should be no adverse effects on human health from the use of Ranman 400 SC Fungicide when used in accordance with the label directions.

The toxicology database for cyazofamid is extensive, and comprehensive. The database includes toxicokinetics/metabolism and biliary excretion information in rats, acute, short-term, sub-chronic (two species), chronic (dogs), combined chronic/carcinogenicity (two rodent species), reproduction and developmental (two species) studies and *in vitro* and *in vivo* genotoxicity studies. Additionally, information on the acute oral toxicity and mutagenicity (Ames test) for four impurities/metabolites (mammalian and/or environmental) are also available.

The toxicological database was considered to be adequate for establishing a toxicological profile and sufficient for regulatory purposes.

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.

3.2 Chemical Class

Cyazofamid is a member of the cyanoimidazole chemical class and is generally classified into the azole group. The biochemical mode of action of cyazofamid is inhibition of all stages of fungal development. Cyazofamid has a novel mode of action acting specifically via respiratory inhibition at Complex III (inhibits Qi (ubiquinone-reducing sites)) in the mitochondria of Oomycetes fungi.

3.3 Toxicokinetics and Metabolism

The toxicokinetics studies in rats indicated that cyazofamid was rapidly absorbed from the gastrointestinal tract (45–78% absorbed fraction), and widely distributed to tissues (highest levels in liver, kidney and blood) with no evidence of accumulation. Cyazofamid was rapidly and extensively excreted as metabolites in urine (12–39%) and bile (30–55%) and the remainder as unchanged compound in faeces. Excretion was

essentially complete by 24–48 hours post dose. The metabolic profile in excreta identified CCBA (4-(4-chloro-2-cyanoimidazole-5-yl) benzoic acid) as the major metabolite in bile and urine in addition to lesser amounts of glutathione conjugates (higher levels in females compared to males). Statistical analyses of all toxicokinetic parameters did not reveal a difference between sexes. No dermal absorption data were available for cyazofamid.

Acute Toxicity

Cyazofamid was of low acute oral, acute dermal and acute inhalational toxicity in rats (LD_{50} > 5000 mg/kg bw, LD_{50} > 2000 mg/kg bw and LC_{50} > 5500 mg/m^3 respectively (no deaths)). It was a slight irritant to rabbit eyes and a slight irritant to rabbit skin. It was not considered likely to be a skin sensitiser in guinea pigs, based on the results of a maximisation test.

The formulated product Ranman 400 SC Fungicide low acute oral, acute dermal and acute inhalational toxicity in rats (LD_{50} > 5000 mg/kg bw, LD_{50} > 2000 mg/kg bw and LC_{50} > 5854 mg/m^3 respectively (no deaths)). It is not an eye or skin irritant in rabbits and is not a skin sensitiser in guinea pigs (Buehler test).

Systemic Effects

Cyazofamid is generally of a low order of toxicity in all tested species in short-term dermal and sub-chronic oral repeat dose studies in rats and dogs, with no treatment related and toxicologically significant findings up to the highest dose tested. The NOEL established in the short-term dermal study in rats was 1000 mg/kg bw/d. In sub-chronic oral studies in rats and dogs the NOELs established were 5000 ppm (295 mg/kg bw/d) for male rats and 20,000 ppm (1359 mg/kg bw/d) for female rats and 1000 mg/kg bw/d (male and female dogs), respectively.

In chronic oral studies in mice, rats and dogs treatment related and toxicologically significant effects were limited to an increase in histopathological changes in the ovaries (hematocysts) of mice and decreased body weight gain and increased incidence of ocular cataracts in female rats (of a similar intensity to that seen in control females) at the highest dose tested. The NOEL established for these effects was 700 ppm in female mice (124 mg/kg bw/d) and 20,000 ppm in female rats (856 mg/kg bw/d). There were no treatment related and toxicologically significant findings male mice and rats or in dogs.

Carcinogenicity

Cyazofamid was not carcinogenic in mice. In the 24–month rat dietary study increased neoplastic findings, outside historical controls, from examination of all treated animals were limited to an increase in lung adenocarcinomas in males at 17.1 mg/kg bw/d (4/50 males; 8.0%) and 171 mg/kg bw/d (3/50 males; 6%) that was greater than that seen in the concurrent control (1/50 males 2%) and incidences of adrenal phenochromocytoma outside historical controls at 171 mg/kg bw/d (17/50 males; 34%) compared to concurrent control (13/50 males; 26.0%). The increased incidences were not statistically significant compared to concurrent controls, a treatment related increase was not seen in females administered a higher dose (856 mg/kg bw/d), and negative control data for adrenal phenochromocytoma was itself outside the historical control range. Thus overall the findings are not considered by OCS to provide robust evidence of a treatment related carcinogenic effect.

Genotoxicity

Based on negative findings in a series of *in vitro* (Ames test and chromosome aberration test) and *in vivo* (Micronucleus test) genotoxicity studies, there is no evidence of potential of mutagenicity or genotoxicity for cyazofamid.

Reproductive and Developmental Toxicity

There were no treatment related effects on reproductive or developmental parameters, with treatment related and toxicologically significant findings limited to pup toxicity (decreased body weight gain at weaning only) at the highest dose tested in a two-generation study in rats. The NOEL in pups was established at 2,000 ppm (89.2 /133.9 mg/kg bw/d, m/f) based on lower pup weight at the end of lactation (Day 21 post birth) for all F1 and F2 generations observed at the highest dose tested. The NOEL in parental animals was 20,000 ppm (1338/2678 mg/kg bw/d, m/f) based on the absence of treatment related and toxicologically significant effects at the highest dose tested.

In the reproduction study in rats an increase in litter and pup stillborn indices compared to concurrent controls was observed. However, the stillborn pup indices were within historical control ranges for all generations at the highest dose tested and are considered incidental to treatment. The increase in litter stillborn indices was not outside the range of historical controls for all generations (F2b within historical control range). OCS considers that overall the data do not provide robust evidence for a treatment related effect and, thus, are considered likely incidental and not treatment related.

In the developmental study in rats there was a higher incidence of bent ribs (3 foetuses in 3 litters i.e. 1 per litter) detected at 1000 mg/kg bw/d with a corresponding increased incidence in the total number of foetuses and litters examined. Historical control data were not provided by the applicant to assist in determining the toxicological significance of the findings. However, published historical control data in the same rat strain (Middle Atlantic Reproduction and Teratology Association (MARTA)) was considered acceptable for use and the incidence of bent ribs were found to be within the historical control range. Therefore the OCS considers that the finding at the limit dose of 1000 mg/kg bw/d was likely incidental and not toxicologically significant.

Neurotoxicity

No neurotoxicity studies were submitted. Clinical observations of neurotoxicity endpoints (sensory reactivity to different stimuli/FOB) were not evaluated in repeat dose studies where required by relevant OECD Test Guidelines. However, the available toxicological database does not indicate a concern for neurotoxicity.

Other studies

CCIM (an impurity, a major metabolite of cyazofamid in some plant commodities, and mainly an intermittent compound in rat metabolism studies) appeared more acutely toxic than cyazofamid, showing moderate acute oral toxicity (LD_{50} 324 / 440 mg/kg bw in rats). Low acute oral toxicity was observed for other metabolites CCIM-AM, CTCA (4-chloro-5-*p*-tolylimidazole-2-carboxylic acid) and DMSA (Dimethysulfamic Acid) (LD_{50} > 3000, 2947 / 1863 and 3238 / 2948 mg/kg bw respectively).

All metabolites tested, CCIM, CCIM-AM, CTCA and DMSA, showed no mutagenicity potential by the Ames test.

3.4 Public Health Standards

Poisons Scheduling

On 27 June 2013, the delegate to the Secretary to the Department of Health and Ageing made a delegate only decision on cyazofamid that it be included in Schedule 5 of the Standard for the Uniform Scheduling of Medicines and Poisons with no cut-off, along with an implementation date of 1 September 2013.

NOEL/ADI

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

Rodents appeared to be the most sensitive species for cyazofamid following chronic oral exposure. In an 18 month carcinogenicity study in mice an increased incidence of hematocysts in the ovaries was observed at the highest dose tested of 7000 ppm (1203 mg/kg bw/d). There were no treatment related and toxicologically significant findings in males up to the highest dose tested of 7000 ppm (984.9 mg/kg bw/d). In a 24 month carcinogenicity study in rats decreased body weight gain and a statistically significant increase in the incidence of ocular cataracts in females at 20,000 ppm (856 mg/kg bw/d) compared to controls. There were no treatment related and toxicologically significant effects in males up to the highest dose tested of 5000 ppm (171 mg/kg bw/d). The toxicological database for cyazofamid included a long-term oral study in dogs and carcinogenicity studies in the mouse and rat, and was considered complete and adequate and does not indicate a potential concern for reproductive or developmental effects, or carcinogenicity.

The lowest NOEL following chronic oral dosing was 124 mg/kg bw/d in mice based on the increased incidence of hematocysts in the ovaries observed in an 18 month carcinogenicity study. This NOEL is considered to be protective of systemic effects in other species following repeat dose oral exposure.

A 100–fold safety factor, consisting of factors of 10 for intra-species and interspecies variation, was considered appropriate for establishing an ADI for cyazofamid based on the NOEL of 124 mg/kg bw/d from the 18–month carcinogenicity study in mice.

Hence, an ADI limit of 1.24 mg/kg bw/d is recommended based on the NOEL of 124 mg/kg bw/d from the 18–month carcinogenicity study in mice, using a 100–fold safety factor.

ARfD

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

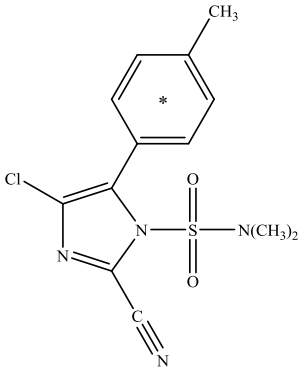
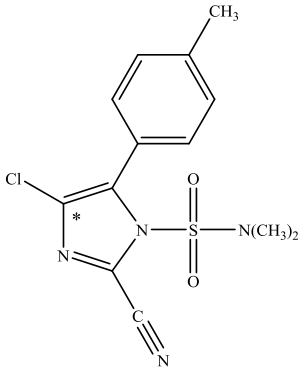
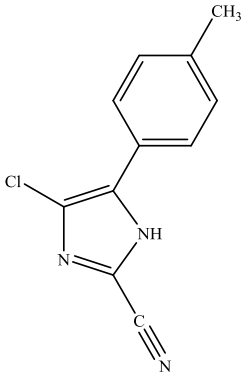
An ARfD has not been established for cyazofamid and is not considered necessary based on the low acute toxicity profile in addition to the absence of acute effects in developmental, reproductive and genotoxicity studies. The OCS considers cyazofamid is unlikely to present an acute hazard to humans after single dose administration.

4 RESIDUES ASSESSMENT

Ranman 400 SC Fungicide is a suspension concentrate formulation containing the new active constituent cyazofamid. The product is intended for control of late blight in potatoes and white blister in broccoli. As part of the residues assessment for cyazofamid, plant and animal metabolism studies, supervised residue trials, processing studies, and trade aspects were considered.

4.1 Metabolism

Metabolism data for 14C-labelled cyazofamid in potatoes, tomatoes, grapes, rotational crops (lettuce, wheat and carrot), rats, lactating goats and laying hens were provided.

COMPONENT	CHEMICAL NAME	STRUCTURE	
Parent	4-Chloro-2-cyano-*N,N*-dimethyl-5-(4-methylphenyl)-1*H*-imidazole-1-sulfonamide	 ^{14}C-Phenyl-cyazofamid	 ^{14}C-Imidazolyl-cyazofamid
CCIM	4-Chloro-5-(4-methylphenyl)-1*H*-imidazole-2-carbonitrile		

Key metabolic pathways in potatoes, grapes, tomatoes, and rotational crops include:

- Hydrolysis of the sulfonamide functionality;
- Hydrolysis of the nitrile group to an amide functionality;
- Oxidation of the methyl group of the phenyl ring to a hydroxymethyl, and further oxidation to a carboxylic acid;
- Photo-induced migration of the sulfonamide functional group to the phenyl ring and to the 4–position on the imidazole ring; and

- Conjugation with glucose and other sugars in the hydroxymethyl phenyl position, and the imidazole nitrogen.
- Incorporation of the molecule in natural products.

In tubers from the potato metabolism study, no identified component exceeded 0.01 mg eq./kg, while in the other edible matrices tested (tomatoes and grapes), the components which exceeded 0.01 mg eq./kg after treatment with 4 or 5 × 100 g ac/ha applications (similar to the proposed GAPs in potatoes and broccoli,) were parent, polar compounds (sugars and simple organic acids), CCIM, and CCIM conjugates. In all edible matrices as well as in foliage, parent compound was the largest identified component.

In the field residue studies for potatoes, with very few exceptions, no residues of either parent compound or CCIM were detected in tubers. In the residue trials in brassica vegetables and spinach, residues of parent compound were much higher than those of CCIM.

In the rotational crop study, after treatment of bare soil with 5 × 100 g ai/ha applications, only very low levels (<0.01 mg/kg) of parent and the metabolites CCIM, CCIM-AM (4-chloro-5-*p*-tolylimidazole-2-carboxamide)and CCBA (4-(4-chloro-2-cyanoimidazole-5-yl) benzoic acid)were identified in carrot tops and wheat straw and forage, along with a number of simple sugars in the polar fraction.

CCIM was found as a metabolite in rats. It was determined to have a higher acute toxicity than parent compound. Given that CCIM was found at levels above 0.01 mg/kg in a number of edible matrices in the metabolism studies and considering its higher acute toxicity compared with parent, it is proposed that a residue definition of the sum of parent and CCIM be established for the purposes of dietary risk assessment in plant commodities. Levels of CCIM in the field residue studies were much lower than those of parent. A residue definition of parent only is proposed for cyazofamid in plant commodities, for compliance with MRLs. For dietary risk assessment purposes, the proposed definition is the sum of cyazofamid and 4-chloro-5-(4-methylphenyl)-1H-imidazole-2-carbonitrile, expressed as cyazofamid.

The key reactions occurring in the metabolism of cyazofamid in lactating goats and laying hens are:

- Oxidation of the methyl group on the benzene ring to a carboxylic acid;
- Hydrolysis of the cyano group to an amide;
- Cleavage of the sulfonamide functionality from the molecule; and
- Cysteine conjugation of the imidazole moiety.

The first and third listed reactions are particularly significant in goats, leading to CCBA being the most significant component of the radioactivity in most goat tissues. Rearrangement of the sulfonamide moiety from the imidazole to the phenyl ring was tentatively identified as minor pathway in hens only.

In goat tissues and milk, parent, and the metabolites CCBA-AM, CCBA (and conjugates), CCIM-AM, and CCIM were detected. The highest levels observed in any matrix were <0.001, 0.021, 0.104, 0.019, and 0.004 mg eq./kg respectively. CCBA was observed at 0.005 mg eq./kg in kidney only. In hen tissues (liver and kidney) parent and the metabolites CHCN (and conjugates), CCBA, and CCIM were observed at maximum levels of 0.0004, 0.0134, 0.0064, and 0.0013 mg eq./kg respectively.

The only proposed use patterns for cyazofamid at this time are in potatoes and broccoli. Neither is a significant animal feed, although potato culls can be fed at up to 10% of the diet for cattle and pigs, while dried potato can be fed at up to 5% of the diet for cattle. Detectable residues of cyazofamid are not expected to be found in potatoes or potato products, or in turn, in the feed of mammalian livestock or poultry. Scaling the residues observed in goats and hens for the expected maximum feeding level (0.01 mg/kg, the limit of quantitation) indicates that detectable residues of cyazofamid are not expected to be found in mammalian or poultry meat, offal, or in milk or eggs.

Therefore, even though parent compound and CCIM are not the most significant residue components found in milk, eggs and tissues in the goat and hen metabolism studies, given that the residues in animal feed are expected to be essentially nil based on the proposed use patterns, no residues of cyazofamid parent compound or any of the metabolites are expected to be detected in meat, offal, eggs, or milk. A residue definition of parent only is proposed for cyazofamid in animal commodities, for compliance with MRLs. For dietary risk assessment purposes, the proposed definition is the sum of cyazofamid and 4-chloro-5-(4-methylphenyl)-1H-imidazole-2-carbonitrile, expressed as cyazofamid.

Analytical methods

Determination of cyazofamid residues in plant commodities

The analytical method for plant commodities involved extraction with acetone/acetonitrile, clean-up by liquid/liquid partition with hexane, followed by partition into dichloromethane and further clean-up by solid phase extraction. Residues of parent and CCIM were eluted separately from the column before analysis by HPLC-UV. This method was validated for analysis of potatoes and tomatoes, giving mean recoveries in the range of 77–98% for cyazofamid and CCIM at fortifications from 0.01–2.0 mg/kg. The method LOQ (Limit of Quantitation) was 0.01 mg/kg for each analyte.

A modified version of the above method was used for determination of cyazofamid and CCIM in the local residue trials. Samples were extracted with acetonitrile/acetone and in most cases an aliquot of the extract was diluted and analysed by LC-MS/MS, the clean-up steps not being required in most cases. Some of the potato sample extracts were cleaned up using the partition steps described above before analysis by LC-MS/MS, but the solid phase extraction was not included. Good recoveries (in the range 70–120%) were achieved, along with an LOQ of 0.01 mg/kg for each analyte.

Determination of residues of cyazofamid in animal tissues

An HPLC method with UV detection was validated for determination of cyazofamid parent compound in milk, and bovine and chicken muscle. Milk samples were extracted by homogenisation with acetonitrile or acetonitrile/acetic acid, followed by centrifuging and clean-up of the supernatant by solid phase extraction. Muscle samples were extracted using acetonitrile, followed by partition with hexane, then with dichloromethane, and a final clean-up using solid phase extraction. The method limit of detection was 0.005 mg/kg, while the limit of quantitation was 0.01 mg/kg.

A second method involving acetonitrile extraction, followed by clean-up by partition with hexane, and LC-MS/MS analysis of the resultant extracts was presented. This gave generally acceptable mean range of

recoveries and fortification concentrations for parent and several metabolites including CCIM from bovine milk, muscle, liver, fat and kidney, with an LOQ of 0.01 mg/kg.

The methods are suitable for the proposed purposes and are acceptable.

Residue definition

The following residue definition is recommended for cyazofamid for the purposes of dietary exposure assessment and for compliance and monitoring:

COMPOUND	RESIDUE DEFINITION
Cyazofamid	For compliance in plant and animal commodities: cyazofamid
	For dietary risk assessment in plant and animal commodities: the sum of cyazofamid and 4-chloro-5-(4-methyphenyl)-1H-imidazole-2-carbonitrile, expressed as cyazofamid

Storage stability

The storage stability trial for residues in potatoes showed good stability of cyazofamid residues up to 6 months of frozen storage, and fair stability between 6 and 36 months, while residues of CCIM showed good stability up 24 months and poor stability from 24 until 36 months. The storage stability data for broccoli showed variable stability over 26 months. This may have been due to poor experimental technique, as spinach, mustard greens and cabbage showed excellent stability of cyazofamid and CCIM residues on storage for up to 32 months.

4.2 Residue trials

Potato

The proposed GAP for cyazofamid in potatoes is 6 × 80 g ac/ha foliar applications with a 7–day harvest withholding period.

A large package of residue trials conducted in Australia, Europe and the USA for potatoes was supplied. Residues resulting from the proposed GAP in the combined dataset were: <0.005 (10), and <0.01 (41) mg/kg. Additionally, residues of cyazofamid in potatoes collected 7 days after 6 × 160 g ai/ha applications (i.e. 2× GAP) were <0.005 (10) mg/kg.

An MRL of *0.01 mg/kg is proposed for cyazofamid in potatoes, in conjunction with a 7–day harvest withholding period.

Broccoli

The proposed GAP for cyazofamid in broccoli is 6 × 80 g ac/ha foliar applications with a nil harvest withholding period.

Six trials each in Australia and in the USA for broccoli were provided. The combined residue data set for cyazofamid in broccoli from the trials matching GAP is 0.11, 0.17, 0.19, 0.26, 0.27, 0.39, 0.41 (2), 0.43, 0.47, 0.71, and 0.91 mg/kg, with an STMR of 0.40 mg/kg and an HR of 0.91 mg/kg.

Residues of cyazofamid in broccoli after treatment at 2× GAP were 0.18, 0.28, 0.56, 0.82, and 1.3 (2) mg/kg.

An MRL of 2 mg/kg is proposed for cyazofamid in broccoli, with a nil harvest withholding period. It is noted that the 2× trial results are also all below the proposed MRL.

For consideration of residues for the purposes of dietary risk assessment, the total residues in broccoli after application at GAP were 0.11, 0.17, 0.19, 0.27, 0.28, 0.40, 0.42 (2), 0.44, 0.48, 0.72, and 0.92 mg/kg (STMR = 0.41 mg/kg; HR = 0.92 mg/kg).

4.3 Crop rotation

A confined crop rotation metabolism study showed that after 5 × 100 g ac/ha applications, which approximates the proposed seasonal GAP for potatoes and broccoli, residues of cyazofamid and related metabolites in lettuce, wheat and carrots planted at intervals of 31, 119 and 360 days after the last application were all below 0.003 mg/kg, while only polar metabolites such as simple sugars exceeded levels of 0.01 mg/kg. Residues of cyazofamid parent compound or related toxicologically significant metabolites are therefore very unlikely to be detected in crops planted in rotation with a treated potato or broccoli crop. Plant-back intervals are therefore not required for cyazofamid.

4.4 Animal commodity MRLs

Neither potatoes nor broccoli are significant animal feeds. Potato culls can comprise up to 10% of the diet of beef cattle, dairy cattle and pigs, while dried potato pulp can comprise up to 5% of the diet of beef and dairy cattle. The residues trials show that detectable residues of cyazofamid are not likely to be found in either potatoes or potato products. Therefore, quantifiable levels of cyazofamid are unlikely to be present in the diets of cattle, sheep, pigs or poultry.

Mammalian livestock

In the lactating goat metabolism study, after feeding at a target level of 10 ppm, the maximum total radioactive residues of cyazofamid in milk, liver, kidney, muscle, and fat were 0.012, 0.16, 0.136, 0.007, and 0.012 mg eq./kg respectively. Scaling these values to the maximum feeding level for cyazofamid (0.01 mg/kg, the LOQ) indicates that detectable residues of cyazofamid or metabolites will not be found in the milk or tissues of mammalian livestock. It is therefore proposed to establish MRLs for cyazofamid in meat (mammalian), edible offal, mammalian, and milk at the limit of quantitation (*0.01 mg/kg).

Poultry

In the hen metabolism study, no residues at all were detected in muscle, fat, skin or eggs after feeding at a target level of 10 ppm, while the total radioactive residues in liver reached a maximum of 0.0878 mg eq./kg, and those in kidney reached a maximum of 0.0578 mg eq./kg. Scaling these values to the maximum feeding

level for cyazofamid (0.01 mg/kg, the LOQ) indicates that detectable residues of cyazofamid or metabolites will not be found in eggs or tissues of laying hens. It is therefore proposed to establish MRLs for cyazofamid in poultry meat, poultry, edible offal of, and eggs at the limit of quantitation (*0.01 mg/kg).

4.5 Spray drift

The proposed label instructions for Ranman 400 SC Fungicide include a restraint against applying the product aerially. Modelling of the spray drift resulting from ground applications was conducted. The average spray drift over a distance 2–300 metres downwind from the application area is calculated at a level which is not expected to result in detectable residues of cyazofamid in the meat, milk or offal of grazing animals. Therefore, no buffer zones are required for Ranman400 SC Fungicide.

4.6 Bioaccumulation potential

The octanol-water partition coefficient (log10KOW) of cyazofamid was measured at of 3.2, suggesting moderate fat solubility and potential for bioaccumulation. Although in the goat metabolism study, residues of individual compounds and the total residue were generally higher in fat matrices than in muscle, given that detectable residues of cyazofamid are unlikely to be found in meat, offal milk or eggs as result of the currently proposed use patterns, and in the absence of livestock feeding studies, it is not proposed to include an ‘in the fat’ designation for the mammalian and poultry meat MRLs at this time.

4.7 Risk Assessment Conclusions

Estimated dietary intake

The chronic dietary intake risk for cyazofamid has been assessed. The ADI (Acceptable Daily Intake) for cyazofamid is 1.2 mg/kg bw/day, based upon a NOEL (No Observable Effect Limit) of 124 mg/kg bw/day and a 100–fold safety factor. The NEDI (National Estimated Daily Intake) 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 cyazofamid, is equivalent to <1% of the ADI. DIAMOND Modelling[3] of chronic dietary exposure is also performed on new chemicals. The DIAMOND model estimated the chronic dietary exposure of cyazofamid as <1% of the ADI for the general population.

An acute reference dose (ARfD) has not been established for cyazofamid and therefore an estimate of short-term dietary intake is not required.

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

[3]. DIAMOND: The Diamond Modelling Of Nutritional Data is a computer dietary modelling program based upon statistical software that is used by FSANZ

It is concluded that the dietary exposure to cyazofamid is low and the risk from residues in food is acceptable when Ranman 400 SC Fungicide is used according to label directions.

Recommendations

The following amendments to the MRL Standard are recommended in relation to the proposed use of Ranman 400 SC Fungicide:

Table 1: MRL for plant and animal commodities –

COMPOUND	FOOD	MRL (mg/kg)
ADD: CYAZOFAMID		
VB 0400	Broccoli	2
MO 0105	Edible offal (mammalian)	*0.01
MM 0095	Meat (mammalian)	*0.01
PE 0112	Eggs	*0.01
ML 0106	Milks	*0.01
VR 0589	Potato	*0.01
PO 0111	Poultry, edible offal of	*0.01
PM 0110	Poultry meat	*0.01

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

[3]. DIAMOND: The Diamond Modelling of Nutritional Data is a computer dietary modelling program based upon statistical software that is used by FSANZ.

*MRL set at the limit of quantitation.

Table 2: Residues Definition

COMPOUND	RESIDUE DEFINITION
ADD:	
CYAZOFAMID	For compliance in plant and animal commodities: cyazofamid For dietary risk assessment in plant and animal commodities: the sum of cyazofamid and 4-chloro-5-(4-methyphenyl)-1H-imidazole-2-carbonitrile, expressed as cyazofamid

The following withholding periods are required in conjunction with the above MRLs:

Harvest withholding periods:

Potatoes	Do not harvest for 7 days after the last application.
Broccoli	Not required when used as directed.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported and main destinations

Potatoes and broccoli are not considered to be significant export commodities. Meat and dairy products are major export commodities, however detectable residues of cyazofamid are not expected to be found.

5.2 Overseas registration status

The residues aspects of cyazofamid have not been considered by the Joint Meeting on Pesticide Residues (JMPR).

The following relevant Australian and overseas MRLs have been established or proposed:

Cyazofamid plant commodity MRLs

COUNTRY	RESIDUE DEFINITION	COMMODITY	MRL (mg/kg)
Australia (proposed)	For compliance: cyazofamid For dietary risk assessment: the sum of cyazofamid and 4-chloro-5-(4-methyphenyl)-1*H*-imidazole-2-carbonitrile, expressed as cyazofamid	Potato	*0.01
		Broccoli	2
EU	Cyazofamid	Potato	*0.01
		Broccoli	*0.01
USA	Sum of cyazofamid and 4-chloro-5-(4-methylphenyl)-1*H*-imidazole-2-carbonitrile (CCIM), expressed as cyazofamid	Brassica, head and stem, subgroup 5A	1.2
		Vegetable, tuberous and corm, subgroup 1C	0.02
Canada	Sum of cyazofamid and 4-chloro-5-(4-methylphenyl)-1*H*-imidazole-2-carbonitrile (CCIM)	Potato	0.02
		Broccoli	0.02
Japan	Cyazofamid	Potato	0.05
		Broccoli	1

The following Australian and overseas animal commodity MRLs/tolerances have been proposed:

Cyazofamid animal commodity MRLs

COUNTRY	RESIDUE DEFINITION	COMMODITY	MRL (mg/kg)
Australia (proposed)	For compliance: cyazofamid For dietary risk assessment: the sum of cyazofamid and 4-chloro-5-(4-methyphenyl)-1*H*-imidazole-2-carbonitrile, expressed as cyazofamid	Edible offal (mammalian)	*0.01
		Eggs	*0.01
		Meat (mammalian)	*0.01
		Milks	*0.01
		Poultry, edible offal of	*0.01
		Poultry meat	*0.01
EU	Cyazofamid	Mammalian meat	*0.01
		Mammalian fat	*0.01
		Mammalian offal	*0.01
		Milk	*0.01
		Poultry meat	*0.01
		Poultry fat	*0.01
		Poultry offal	*0.01
		Eggs	*0.01
Canada	Sum of cyazofamid and 4-chloro-5-(4-methylphenyl)-1*H*-imidazole-2-carbonitrile (CCIM)	Mammalian meat	0.02
		Mammalian fat	0.02
		Mammalian offal	0.02
		Milk	0.02

5.3 Potential Risk to Trade

The risk to trade is expected to be low, as finite residues of cyazofamid are not expected to be found in potatoes, mammalian or poultry meat or offal, eggs, or milk. Finite residues of cyazofamid may occur in broccoli, however broccoli is not a significant export commodity.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

The active constituent cyazofamid will be manufactured overseas. The product Ranman 400 SC Fungicide will be manufactured overseas and imported into Australia in sizes of 0.5, 1 and 5 L HDPE bottles.

6.1 Use pattern

Ranman 400 SC Fungicide is proposed for use in the control of Late Blight (*Phytophthora infestans*) in potatoes, and White Blister (*Albugo Candida*) in broccoli, both induced by the fungus class of Oomycetes. The product is a suspension concentrate formulation containing 400 g/L cyazofamid. The product is intended for professional use.

The product is to be applied to all crops at a use rate of 150–200 mL/ha (60–80 g ac/ha), in 250 to 600 L water per ha for potatoes, or 250–800 L per ha for broccoli. The product may be applied at 7 to 10 day intervals with a maximum 3 consecutive sprays and up to 10 times in a growing season of potato (August—October) and broccoli (April—July). The product label indicates that workers may apply the product using ground-boom, and handheld spray (vehicle mounted hand-wand or backpack).

6.2 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 intra-species variation.

The MOE’s for the general public associated with short-term repeat use of the product when mixing and loading, application by back pack without any recommended protective clothing are acceptable (i.e. >100). The MOE’s for workers associated with long-term repeat use of the mixing and loading, application by low and high pressure hand-wand and ground boom are acceptable (i.e. >100) with a single layer of clothing without the use of additional personal protective equipment. The MOE’s for workers associated with long-term repeat use of the mixing and loading, application by back pack are acceptable (i.e. >100) with a single layer of clothing and the use of chemical resistant gloves.

There are no acute hazards of concern associated with the product.

6.3 Exposure during re-entry

Workers may be exposed to Ranman 400 SC Fungicide when re-entering treated crop 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.

Based on MOEs much greater than the acceptable level (100) on day 0 post-application for high exposure activities in potato and broccoli crops there is no re-entry risk associated with this product and a nil re-entry statement has been recommended.

6.4 Recommendations for safe use

Users should follow the First Aid Instructions and Safety Directions on the product label.

6.5 Conclusion

The registration of Ranman 400 SC Fungicide containing 400 g/L cyazofamid for the control of Late Blight (*Phytophthora infestans*) in potatoes, and White Blister (*Albugo candida*) in broccoli is supported.

Ranman 400 SC 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

Ishihara Sangyo Kaisha (ISK) Limited has applied for the registration of the new product Ranman 400 SC Fungicide containing 400 g/L of the new active constituent (ac) cyazofamid for the control of late blight in potatoes and white blister in broccoli. The product is a suspension concentrate for use in the control of diseases caused by oomycete fungi.

Cyazofamid has limited systemic activity so it is used as a protectant fungicide. The biochemical mode of action of cyazofamid is inhibition of all stages of fungal development.

The product is proposed to be applied at the application rate of 150–200 mL/ha by ground application corresponding to 60–80 g ac/ha with a maximum number of 6 seasonal applications; a maximum of 3 consecutive sprays with a minimum retreatment interval of 7 days followed by a fungicide of another chemical group. Environmental fate and effects studies were provided in support of the application. These were considered sufficient to undertake a standard environmental risk assessment.

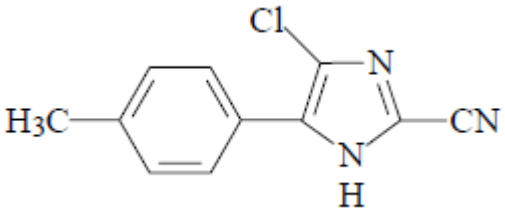
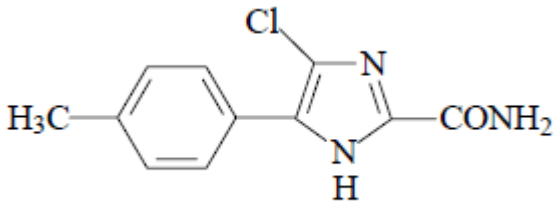
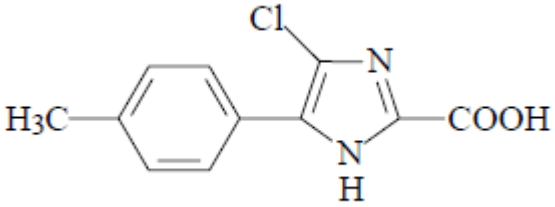
7.2 Environmental Fate

Abiotic Degradation

Hydrolysis

In hydrolysis studies conducted using sterile buffer solutions at 25°C the hydrolytic half-life of cyazofamid was found to range from 10.6 to 13.3 d at various pHs (4, 5, 7 and 9). Hydrolysis of cyazofamid was found to be most rapid at pH 9 and under elevated water temperatures. CCIM (4-chloro-5-*p*-tolylimidazole-2-carbonitrile) at pH 4-9 and CCIM-AM (4-chloro-5-*p*-tolylimidazole-2-carboxamide) at pH 9 were the only major hydrolysis products formed. CCIM, CCIM-AM and CTCA (4-chloro-5-*p*-tolylimidazole-2-carboxylic acid) are each hydrolytically stable. Refer to Table 1 for identity of environmental degadants.

Table 1 Environmental metabolites

CODE	IDENTITY
CCIM	 4-chloro-5-*p*-tolylimidazole-2-carbonitrile $C_{11}H_8ClN_3$ 235.6 g/mol
CCIM-AM	 4-chloro-5-*p*-tolylimidazole-2-carboxamide $C_{11}H_{10}ClN_3O$ 235.6 g/mol
CTCA	 4-chloro-5-*p*-tolylimidazole-2-carboxylic acid $C_{11}H_9ClN_2O_2$ 236.7 g/mol

Aqueous photolysis

The aqueous photolysis half-lives of cyazofamid ranged from 28 to 34 minutes. The photolytic half-lives of the degradants CCIM, CCTS (6-(4-chloro-2-cyanoimidazol-5-yl)-*N*,*N*-dimethyl-*m*-toluensulfonamide) and HTID (5-hydroxy-5-*p*-tolyl-2,4-imidazolidinedion) ranged from, respectively, 20.7 to 25.6, 2.1 to 2.3 and 41.6 to 46.1 d. In water systems, cyazofamid is expected to undergo ready photolytic transformation by sunlight (as well as concomitant hydrolysis) with the photolytic route expected to be a primary route of degradation in the aquatic environment.

Soil photolysis

The mean half-life (DT_{50}) of cyazofamid under the conditions employed for this study was determined to be 104 hours for the dark control and 98.5 hours for the light-exposed samples. In a second soil photolysis study, radiolabelled cyazofamid on soil was exposed to the equivalent of 12 days of continuous illumination equivalent to 28 days outdoor sunlight exposure. The major degradants were CCIM (max. 39%) and CCBA (max. 37.6%). In the light exposed samples there was 51.3 to 68% of the cyazofamid remaining after 12 days. In the dark controls, the range was markedly higher, 91.1 to 97.6%. CCIM was the main degradation product identified (maximum levels of 5.7 to 7.7% in both the irradiated and dark controls). The half-lives were calculated to be 630 and 330 experimental hours of continuous irradiation for the benzene and imidazole labelled cyazofamid, respectively. These values correspond to 62 and 32 solar days.

Biodegradation

Aerobic soil metabolism

The aerobic soil metabolism of cyazofamid is quite rapid with DT_{50} = 2.5–5.5 days in a range of soils tested.

The aerobic soil metabolism of radiolabelled cyazofamid was studied on a loamy sand soil at a fortification level of 0.1 ppm (~80 g cyazofamid/ha) at 20°C. Un-extractable soil residues made up almost 50% of the applied radioactivity after 59 days. Soil cyazofamid DT_{50} values were 4 and 5 days.

In a second aerobic soil degradation study with cyazofamid added to a sandy loam, a sandy soil and a loamy sand soil at approximately 0.1 ppm at 10 and 20°C. DT_{50} values for cyazofamid ranged from 3.4 to 5.5 d for the three soils incubated at 20°C.

A third aerobic soil metabolism using a Californian sandy loam and a North Dakotan sandy clay loam soil was conducted to investigate the nature of the bound residues observed in the previous studies. The soil was dosed at a targeted rate of 0.147 ppm (~112 g cyazofamid/ha). Samples were maintained for 366 days. Un-extracted residues in the California soil reached a maximum of 27.4% at 28 days then declined to 11.1 % AR at 366 days. In the North Dakota soil the unextracted residues increased to 58.9% AR at 28 days then remained between 57.9 and 63.2% for the rest of the incubation period. Both soils were further characterised by partitioning into humic, fulvic and humin components. These results are taken as indicative of the bound residues not being cyazofamid or its metabolites. The cyazofamid DT_{50} in the sandy loam soil was determined to be 4.0 days. In the North Dakotan sandy clay loam soil, the DT_{50} was 2.5 days.

The aerobic degradation of CCIM, CCIM-AM and CTCA was studied at 20°C with a sandy loam, a loamy sand and a sandy soil and also at 10°C for the sandy soil. CCIM DT_{50} values, based on a double exponential function, ranged from 0.9 to 3.6 days for both radiolabels at 20°C and 6.2 and 7.7 days at 10°C.

In a study conducted with the same sandy loam soil, a sandy soil and a loamy sand soils used in the study of the aerobic degradation of CCIM, the aerobic degradation of CCIM-AM was studied over a period of 112 days at 20°C (and 10°C for the sandy soil). CCIM-AM DT_{50} values ranged from 7.0 to 16.2 days at 20°C and 7.2 to 10.4 days at 10°C. CTCA had estimated DT_{50} values of 153 to 612 days.

Anaerobic soil metabolism

Cyazofamid in aquatic soil under partial anaerobic conditions is expected to degrade quite rapidly (DT_{50}s ~ 4.7–6.8 days) with degradation products remaining in the sediment phase. DT_{50}s for CCIM, CCIM-AM and CTCA were, respectively, 5.4 days, 41.1 days and 331 days. The degradation pathway is the same metabolic pathway as was found in aerobic soil. Extractability of residues is expected to decrease over time with the majority eventually covalently bound to the soil in the humin, fulvic acid and humic acid fractions and most probably not available for uptake or leaching.

Aerobic aqueous metabolism

The rate and pattern of degradation of [^{14}C]cyazofamid were determined in two aerobic water/sediment mixtures at a fortification level of approximately 0.1 ppm. Over the 100 days of the study, the water column remained relatively aerobic while the sediment had a more anaerobic nature. Major metabolites formed were CCIM, CCIM-AM and CTCA. CCIM was the only metabolite seen in the aqueous phases at levels exceeding 10% of the applied ^{14}C. Levels of cyazofamid DT_{50} values in the water phase ranged from 3.7 to 7.9 days. Cyazofamid DT_{50}s for the water/sediment systems ranged from 10.0 to 18.4 days.

Field dissipation

Field dissipation studies with cyazofamid were conducted in the US States of Georgia, California, Washington and New York. Eight applications, each of 100 g cyazofamid/ha and with a seven day interval between applications, were made to bare soils with a 400 SC formulated product. The field studies ran from 470 to 582 days, depending on the location. Soil samples were taken to depths of 122 cm. Cyazofamid residues were observed to degrade readily in the field dissipation trials with DT_{50} values of 1.3 to 7.35 days.Significant residues of cyazofamid were not found below the 15 cm soil depth. Resides of CCIM, CCIM-MA and CTCA were detected in all the trials along with CCBA (albeit at low concentrations). All these degradates were present in the soils shortly after the first application and sometimes persisted through the study. There was no substantial movement of the degradation products below 30 cm depth.

Mobility

The adsorption and desorption properties of [^{14}C]cyazofamid were investigated to assess potential mobility in six soils (sandy loams, sandy clay loam, a loamy sand and a sand with organic carbon contents of 0.47 to 3.37%) using batch equilibrium methodology. Cyazofamid has slight to low mobility (Koc 657–2900).

The adsorption and desorption properties of [^{14}C]CCIM were also investigated to assess potential mobility in soils. CCIM K_F adsorption values are indicative of CCIM having low to medium soil mobility. CCIM-AM adsorption values are indicative of slight soil mobility. CTCA values indicate low soil mobility.

In column leaching studies using radiolabeled cyazofamid and loamy sands, sandy loam and a sandy soil, it was found that the leachate contains <1% of the applied radiolabel while there was 82.9 to 97.6% of the applied dose retained on the column. The majority of radioactivity was detected in the top 5 cm section of the column. Cyazofamid made up the major part of the radiolabeled material followed by CCIM, CCIM-AM and CTCA in decreasing order. Thus these results are consistent with the low soil mobility of cyazofamid and its metabolites.

Bioconcentration

Cyazofamid is considered not to have potential for bio-concentration since BCF (Bio-concentration Factor) values in fish were 186 and 286 for the whole body. The study's results identify the build-up of radioactive residues in the fish, especially the non-edible tissues, over approximately the first 6 days of uptake followed by a depuration effect on days 8 and 9 of the uptake phase. The depuration results clearly identify removal of the radiolabeled material from edible and non-edible tissues.

Degradation in air

The calculated half-life of 0.26 days (based on reaction with hydroxyl radicals) predicts cyazofamid will not be persistent in the atmosphere.

7.3 Environmental Effects

Birds

Cyazofamid is practically non-toxic to both bobwhite quail and mallard duck via the acute oral exposure route. Five day dietary toxicity studies in which bobwhite quail and mallard ducks were exposed to cyazofamid via their diet identified no cyazofamid treatment related deaths. The 5 day dietary toxicity was practically non-toxic with LC_{50}s >5000 mg ac/kg feed for both bobwhite quail and mallard duck. A feeding/reproduction study with the Japanese quail identified no dose responsive adverse effects on either adults or reproductive success. The 20.5 week NOEC (No Observable Effect Concentration) was determined to be 1000 mg ac/kg feed (highest dose tested). Reproduction studies for both mallard duck and bobwhite quail gave NOECs of 5000 and 1000 mg ac/kg feed (highest doses tested), respectively, indicating cyazofamid is not expected to have reproductive effects on birds.

Aquatic Organisms

Effects on Fish

In three acute fish toxicity studies using carp, rainbow trout and bluegill sunfish exposed to cyazofamid for 96 hours under flow through conditions, the toxicity (i.e. LC_{50}) exceeded the solubility limit of cyazofamid in water (0.11 mg ac/L) on all occasions.

The toxicity of four cyazofamid degradation products (CCIM, CCIM-AM, CTCA and DMSA) to rainbow trout was investigated in static exposure studies. The 96 h LC_{50s} were determined to be 2.65, >7.9, >94 and >100 mg/L for CCIM, CCIM-AM, CTCA and DMSA, respectively, indicating the toxicity of the metabolites ranged from moderately to practically non-toxic to fish. In a 28 day juvenile growth test rainbow trout were exposed to cyazofamid under flow through conditions. The NOEC was established as 0.11 mg ac/L, indicating cyazofamid is not expected to have chronic effects on fish at its limit of water solubility.

Effects on aquatic invertebrates

The acute toxicity study of cyazofamid on *Daphnia magna* (48 h EC_{50} >0.11 mg ac/L) indicates that cyazofamid is not toxic to daphnids up to its limit of water solubility. Reduced dry weight was observed in on *Daphnia magna* after chronic exposure at 0.035 mg ac/L (21 d NOEC = 0.020 mg ac/L based on dry weight. Acute toxicity tests performed on the metabolites CCIM, CCIM-AM CTCA and DMSA indicate high to practically no toxicity; 48 h EC_{50} values were 0.42, >4, and 100 mg/L, repectively.

Effects on algae and aquatic plants

Cyazofamid did not adversely affect the growth rate of green algae at its limit of water solubility (96 h ErC_{50} >0.1 mg ac/L) Similarly the metabolites CCIM, CCIM-AM and CTCA are toxic to practically non-toxic to green algae (*Selenastrum capricumutum* with 72 h ErC_{50} 1.34, >0.4 to >100 mg/L). Cyazofamid is considered to be very toxic to marine diatoms based on the 72 h ErC_{50} =0.096 mg ac/L. The 7 d ErC_{50} >1.2 mg ac/L indicates that cyazofamid is not toxic to duckweed up to its limit of solubility.

Effects on sediment dwelling organisms

Cyazofamid had no adverse impact on *Chironomous riparius* at its limit of solubility (23 d NOEC = 0.1 mg ac/L). The metabolite CTCA is practically non-toxic to *Chironomous riparius* (48 h EC_{50} >100 mg/L).

Terrestrial Organisms

Effects on bees

Cyazofamid is practically non-toxic to honey bees for both acute oral and contact toxicity (LD_{50} >100 µg/bee).

Effects on non-target terrestrial arthropods

Both soil dwelling and above ground terrestrial arthropods including *parasitoid wasps*, predatory mite, lacewings and rove beetles are insensitive to cyazofamid at the tested rates ranging from 80 to 800 g ac/ha.

Effects on earthworms

Cyazofamid and its metabolites CCIM-AM, CTCA and DMSA are practically non-toxic to earthworms with 14 d acute toxicity of >1000 mg/kg soil. However, the metabolite CCIM is considered to be moderately toxic to earthworms with an acute 14 d LC_{50} = 56 mg as/kg soil. No chronic effects of the metabolite CTCA on earthworms were observed at the highest dose tested (28 d NOEC = 1.0 mg as/kg soil).

Soil Micro-organisms

No significant effects were observed on soil micro-organisms at the soil concentration of 0.27 mg ac/kg soil for an exposure period of 28 days.

Effects on terrestrial plants

Seedling emergence and vegetative vigour of crops tested were not affected up to the application rate of 1.75 kg ac/ha.

7.4 Risk assessment

The date submitted data were considered in determining the potential risk to aquatic and terrestrial organisms especially from spray drift and run-off from ground application. The potential for direct overspray on water bodies is limited by the method of application. The risk to aquatic systems from spray drift with multiple applications was assessed and concluded that the acute and chronic risks of spray drift can be considered acceptable for ground application for the protection of the aquatic and sediment systems for the proposed use on potatoes and broccoli.

The risk resulting from the run-off following multiple applications in environmental water bodies was assessed using a contemporary screening model. The results showed acceptable acute and chronic risks to aquatic and sediment systems.

Risks for the exposure of the product to terrestrial organisms were assessed based on the available endpoints and proposed application rate of the product. The environmental risk assessment has concluded that the risks from the proposed use of the product will be acceptable to terrestrial organisms including birds, small mammals, honey bees, earthworms, soil microorganisms, beneficial non-target arthropods and non-target plants.

Consequently, the APVMA is satisfied that the use of the product in the proposed manner would not be likely to have an unintended effect that is harmful to animals, plants, or things, or to the environment and that the label contains adequate instruction with respect to environmental safety.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed product Use Pattern

It is proposed that Ranman 400SC Fungicide (400g/L cyazofamid as a suspension concentrate) be used for the control of Late blight in potato crops and White blister disease in broccoli crops both induced by the fungal class of Oomycetes. Cyazofamid has limited systemic activity so it is used as a protectant fungicide only.

The product is to be applied to all crops at a use rate of 150–200 mL/ha (60–80 g ac/ha), in 250 to 600 L water per ha for potatoes, or 250–800 L per ha for broccoli. The product may be applied at 7 to 10 day intervals with a maximum 3 consecutive sprays and up to 10 times in a growing season of potato (August—October) and broccoli (April—July). The product label indicates that workers may apply the product using ground-boom, and handheld spray (vehicle mounted hand-wand or backpack).

8.2 Summary of Evaluation of Efficacy and Crop Safety

The results of 23 trials on the efficacy and crop safety of Ranman 400 SC Fungicide were presented. Eleven of these were conducted on crops in Australia. Six of the Australian trials were on Late blight in potatoes, and 5 trials were on White blister in broccoli. All trials were randomised complete block design with 4 replicates and an untreated control. Rates tested ranged from 50 mL/ha (20 g ac/ha) to 200 mL/ha (80 g ac/ha). The rate of 400mL/ha (160 g ac/ha) was also tested to demonstrate crop safety. Disease pressure ranged from low to high. The number of applications varied from 4 to 7, applied at 6–14 day intervals.

All Australian trials assessed efficacy and crop safety. Efficacy was measured as incidence (% infected), and severity (% area infected). Assessments of efficacy and safety were carried at varying intervals. Details of experimental conditions (including site/weather conditions) were given in all trials. Statistical analysis (ANOVA (Analysis of variance) and Fischer's LSD (Least Significant Difference) test) was carried out on results in all trials. In all trials, trial design, experimental conditions, application rates and methods used were appropriate.

The twelve trials carried out overseas were all on potatoes. Ten of these trials assessed efficacy. Most trials tested efficacy at one rate (80 g ac/ha) only. A rate of 160 g ac/ha was used in two trials to determine crop safety. All trials were randomised block design with 4 replicates and most had an untreated control. Most applications were at 7–10 day intervals. The trials assessed efficacy and crop safety. Details of experimental conditions were given in most trials.

It is concluded from the trial results presented, that treatment with Ranman 400 SC Fungicide (400 g cyazofamid ac/L), applied at a rate of 60–80 g ac/ha (150–200mL/ha) at 7–10 day intervals, will be effective in controlling Late blight (*Phytophthora infestans*) disease in potatoes and White blister (*Albugo candida*) disease in broccoli.

Crop Safety

No phytotoxic effects were observed at any rate or any application. Trial results showed that cyazofamid is safe to use on potato and broccoli crops at rates up to 160 g ac/ha.

The information and data presented indicate that Ranman 400 SC Fungicide is safe to use on broccoli and potatoes when used as directed.

Resistance Management

Cyazofamid is a member of the cyano-imidazole chemical class of fungicides. Cyazofamid has a novel mode of action, acting specifically via respiratory inhibition at Complex III (inhibits Qi (ubiquinone-reducing sites)) in the mitochondria of Oomycetes fungi.

The Fungicide Resistance Action Committee (a specialist technical group of CropLife International) has designated cyazofamid as a Group 21 fungicide. The proposed use pattern is not currently subject to a CropLife anti-resistance management strategy.

8.3 Conclusion

The claims on the proposed label that Ranman 400 SC Fungicide provides acceptable control of Late blight in potato crops and White blister disease in broccoli crops when used as directed is supported by the results from the Australian and overseas trials.

Acceptable crop safety is expected when the product is used as directed. The Directions for Use are appropriate and consistent with fungicide use in commercial agriculture in Australia.

The application by Ishihara Sangyo Kaisha (ISK) Limited for the registration of Ranman 400 SC Fungicide is supported on efficacy and crop safety grounds when used in accordance with label instructions.

9 LABELLING REQUIREMENTS

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

Ranman® 400 SC Fungicide

ACTIVE CONSTITUENT: 400 g/L CYAZOFAMID

GROUP	21	FUNGICIDE

For the control of various fungal diseases in certain crops as specified in the DIRECTIONS FOR USE table

CONTENTS: (500 mL, 1 L, 5 L)

ISK Biosciences Oceania Pty Ltd

Distributed in Australia by:
UPL Australia Limited
ABN 76 066 391 384
Suite 416, Level 4, 14 Lexington Drive
Norwest Business Park,
Bella Vista NSW 2153
TELEPHONE (02) 8824 7277
FACSIMILE (02) 8814 6469

® **Registered trademark of Ishihara Sangyo Kaisha, Ltd**

DIRECTIONS FOR USE
RESTRAINTS
DO NOT apply with aircraft.
DO NOT apply through any type of irrigation equipment.

SPRAY DRIFT RESTRAINTS
DO NOT apply with spray droplets smaller than a MEDIUM spray droplet size category according to nozzle manufacturer specifications that refer to the ASAE S572 Standard or the British Crop Production Council Guideline.
DO NOT apply when wind speed is less than 3 or more than 20 kilometres per hour as measured at the application site.
DO NOT apply during surface temperature inversion conditions at the application site.

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

MANDATORY NO-SPRAY ZONES: Not required when used as directed.

Crop	Disease	Rate	WHP	Critical Comments
Potatoes	Late blight *(Phytophthora infestans)*	150 – 200 mL/ha (60-80 g a.i./ha)	7 days	When conditions favour disease development apply consecutive sprays of Ranman 400 SC at 7 to 10 day intervals. DO NOT wait for disease to appear. Use the shorter interval when disease pressure is severe. Ensure thorough coverage of plants. The total number of Ranman 400 SC applications per season should not exceed 6. When applying Ranman 400 SC consecutively, apply a maximum of 3 consecutive sprays, then switch to a fungicide of another chemical group. Apply Ranman 400 SC in 250 L to 600 L water per hectare.
Broccoli	White Blister (*Albugo candida*)	150 – 200 mL/ha (60-80 g a.i./ha)	0 days	When conditions favour disease development apply consecutive sprays of Ranman 400 SC at 7 to 10 day intervals. DO NOT wait for disease to appear. Use the shorter interval when disease pressure is severe. Ensure thorough coverage of plants. The total number of Ranman 400 SC applications per season should not exceed 6. When applying Ranman 400 SC consecutively, apply a maximum of 3 consecutive sprays, then switch to a fungicide of another chemical group. Apply Ranman 400 SC in 250 L to 800 L water per hectare.

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

WITHHOLDING PERIODS:
Potatoes: DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION
Broccoli: NOT REQUIRED WHEN USED AS DIRECTED

GENERAL INSTRUCTIONS

Fungicide Resistance Warning

GROUP	21	FUNGICIDE

For fungicide resistance management Ranman 400 SC Fungicide is a Group 21 fungicide. Some naturally occurring individual fungi resistant to the product and other Group 21 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 the product or other Group 21 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, UPL Australia Limited accepts no liability for any losses that may result from the failure of this product to control resistant fungi.

Export of treated produce
Growers should note that suitable MRLs or import tolerances do not exist in all markets for produce treated with Ranman 400 SC Fungicide. In some situations export requirements may be met by limiting application number and/or imposing a longer withholding period than specified above. If you are growing produce for

export, please check with UPL Australia Limited for the latest information on any potential trade issues and their management before using Ranman 400 SC Fungicide.

Mixing
Fill minimum 50% of the required water into the spray tank, and agitate when adding the required amount of Ranman 400 SC fungicide. Finally add the rest of the required water volume. Keep the spray solution agitated until all product is applied. Never prepare more spray solution than required.

Compatibility
For information on the compatibility of Ranman 400 SC Fungicide with other products, contact your local UPL Australia Limited representative.

PROTECTION OF LIVESTOCK
DO NOT graze or feed treated crops to animals.

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

PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS
DO NOT apply under weather conditions, or from spraying equipment that may cause drift onto nearby plants/crops, cropping lands or pastures.

STORAGE AND DISPOSAL
Store in the closed, original container in a cool, well-ventilated area. Do NOT store for prolonged periods in direct sunlight. Triple or (preferably) pressure rinse containers before disposal. Add rinsings to the 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
When preparing the product for use and using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing). In addition if applying by spraying equipment carried on the back of the user, when preparing the product for use wear elbow length chemical resistant gloves. Wash hands after use. After each day’s use wash gloves and contaminated clothing.

FIRST AID
If poisoning occurs contact a doctor or Poisons Information Centre. Phone Australia 131 126; New Zealand 0800 764 766.

MATERIAL SAFETY DATA SHEET
Additional information is listed in the Material Safety Data Sheet which can be obtained from the supplier representative or visit www.uplonline/uplaustralia.com.au .

CONDITIONS OF SALE
ISK Biosciences Oceania Pty Ltd and UPL Australia Limited accept responsibility for the consistent quality of the product; however since the use and application of the product is beyond control, the companies accept no responsibility whatsoever for any loss, damage or other result following the use of the product whether used in accordance with directions or not; other than those mandatorily imposed by statutes, the liability is limited to the replacement of the goods and is conditional upon a claim made in writing and, where necessary, a sufficient part of the goods being returned for proper examination by the company within thirty days of sale.

APVMA Approval Number: 66411/53590 Bar code, label code to be inserted
BN DOM

ABBREVIATIONS

ac	active constituent
ACN	Acetonitrile
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ANOVA	Analysis of variance
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
BCF	Bio-concentration Factor
BrdU	Bromodeoxyuridine
bw	bodyweight
^{o}C	Degrees Centigrade
^{14}C	Carbon 14
Cd-1	Cluster of differentiation 1
d	day
cm	Centimetre
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EL_{50}	Effective Loading rate lethal to 50% of the test population
EI	Export Interval

EGI	Export Grazing Interval
ER_{50}	Effect (sub-lethal) rate that cause 50% of maximal defined response in test population
ESI	Export Slaughter Interval
EUP	End Use Product
Fo	original parent generation
FOB	Functional Observational Battery
F1	First Generation
F2	Second generation
F2b	Second generation backcross
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPMT	Guinea Pig Maximisation Test
GVP	Good Veterinary Practice
h	hour
ha	hectare
HCl	Hydrogen chloride
Hct	Heamatocrit
HDPE	High Density Polyethylene
Hg	Haemoglobin
HR	Highest residue
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
IARC	International Agency for Research on Cancer
id	intradermal
im	intramuscular
pH	Potential of hydrogen.

ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOAEL	Lowest Observable Adverse Effect Level
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
LR50	Lethal rate required to kill half (50%) of the test population
$MgSO_4$	Magnesium Sulphate
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NaCl	Sodium Chloride
NOEC/NOEL	No Observable Effect Concentration/Level
OC	Organic Carbon

OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
STMR	Supervised Trials Medium Residues
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Ames Test	A biological assay to determine the mutagenic potential of chemical compounds
ANOVA	Analysis of Variance (ANOVA) is a statistical model used to test differences between group means.
Bio-concentration Factor (BCF)	The concentration of a contaminant in an organism compared to the surrounding ambient environment
Back Cross	Crossing a hybrid with one of its parents (or a genetically similar individual) to produce offspring with genetic identities which are closer to that of the parent
Clara Cells	The Clara cells are a group of cells, sometimes called "non-ciliated bronchiolar secretory cells", found in the bronchiolar epithelium of mammals including man, and in the upper airways of some species such as mice. One of their main functions is to protect the bronchiolar epithelium
Carcinogenicity	The ability to cause cancer
CD1 Mice	A laboratory strain of outbred mice used extensively in toxicological and chemical carcinogenicity bioassys
Central Tendency	In statistics, a central tendency is a central or typical value for probability distribution
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Chronic	Of long duration
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Eukaryote	Any organism having as its fundamental structural unit a cell type that contains a nucleus and other organelles enclosed within membranes.
Fluvic Acid	A component of humic soil substances and are a light yellow to light brown colour; soluble in water under all pH conditions
Fischer's LSD	Statistical method to calculate the smallest significant difference between two means
Formulation	A combination of both active and inactive constituents to form the end use product
Functional Observational Battery (FOB)	A neuro-behavioural assessment tool designed to detect gross functional deficits in young adult rats resulting from exposure to
Formulation	A combination of both active and inactive constituents to form the end use product

Filial 1 (F1)	The first filial generation of offspring of distinctly different parental types that have a combination of characteristics from both parents.
Genotoxicity	The ability to damage genetic material
Guinea Pig Maximisation Test (GPMT)	Is an in vivo test to screen for substances that cause human skin sensitisation (i.e. allergens)
Hematocyst	A blood-containing cyst that develops abnormally in a body structure
Humin	Insoluble organic component of soil humic substances and black in colour. Humins comprise approximately 50% of the organic matter in soil.
Humic Acid	The major extractable component of soil humic substances and are dark-brown to black in colour. They are insoluble in water under acidic conditions (<pH 2) but soluble at higher pH values.
Humic Substances	The major organic components of soil that are produced by bio-degradation of dead organic matter. Relatively high molecular weight substances formed by secondary synthesis reactions.
Hydrophobic	repels water
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Mean	In statistics, mean refers to the mean or average that is used to derive the central tendency of the data in question. It is determined by adding all the data points in a population and then dividing the total number by the number of points.
Metabolism	The chemical processes that maintain living organisms
Micronucleus Test	A test used in toxicological screening to determine a chemicals ability to induce numerical or structural chromosomal damage
Oomycetes Fungi	Fungus-like, eukaryotic micro-organisms. Formerly classified as fungi due to their filamentous bodies, nutrition by absorption and reproduction via spores, they are more closely related to algae and green plants.
pH	A figure expressing the acidity or alkalinity of a solution on a logarithmic scale on which 7 is neutral, lower values are more acid and higher values more alkaline. The pH is equal $-\log_{10}[H^+]$ where $[H^+]$ is the hydrogen ion concentration in moles per litre
Phenochromocytoma	A rare tumour of adrenal gland tissue. It results in the release of too much epinephrine and norepinephrine, hormones that control heart rate, metabolisms and blood pressure.
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body

Toxicology	The study of the nature and effects of poisons

REFERENCES

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

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