Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active cyclaniliprole in the product ISK Cyclaniliprole 50 SL Insecticide

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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, Department of Environment (DoE), and State Departments of Primary Industries.

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

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

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

About this document

This is a Public Release Summary.

It indicates that the 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 approval of the active cyclaniliprole and registration of the product ISK Cyclaniliprole 50 SL Insecticide should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health, occupational health and safety, chemistry and manufacture,

residues in food, environmental safety, trade, and efficacy and target crop or animal safety. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on 12 December 2017 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
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604
Phone: +61 2 6210 4701
Fax: +61 2 6210 4721
Email: enquiries@apvma.gov.au

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 at www.apvma.gov.au.

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

1 INTRODUCTION

Ishihara Sangyo Kaisha, Ltd has applied to the APVMA for registration of the new product ISK Cyclaniliprole 50 SL Insecticide containing 50 g/L cyclaniliprole in a soluble concentrate formulation.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of ISK Cyclaniliprole 50 SL Insecticide, and approval of the new active constituent, cyclaniliprole.

ISK Cyclaniliprole 50 SL Insecticide is to be used for the control of codling moth in apples.

ISK Cyclaniliprole 50 SL Insecticide is the first product containing the active cyclaniliprole proposed for the Australian market.

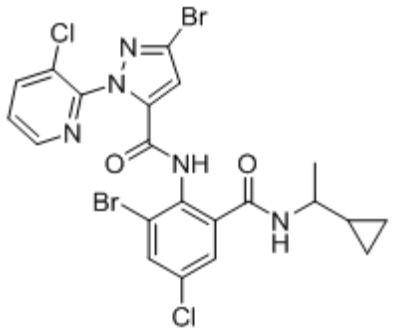
This submission has been assessed under a joint review/ workshare arrangement where registrations for the same formulations and uses have been submitted concurrently in Australia, Canada and USA.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

The active constituent cyclaniliprole will be manufactured overseas, and imported into Australia as the fully formulated end use product.

Cyclaniliprole is a white powder at room temperatures, with low volatility. It has very low solubility in water, aliphatic, and aromatic hydrocarbon solvents, while being moderately soluble in polar organic solvents. Cyclaniliprole gives an essentially neutral pH on dispersion in water. It is not explosive, flammable or oxidising, and is stable on storage.

COMMON NAME (ISO):	Cyclaniliprole
CHEMICAL NAME (IUPAC):	2',3-Dibromo-4'-chloro-1-(3-chloro-2-pyridyl)-6'-{[(1*RS*)-1-cyclopropylethyl]carbamoyl}pyrazole-5-carboxanilide
CAS REGISTRY NUMBER:	1031756-98-5
EMPIRICAL FORMULA:	$C_{21}H_{17}Br_2Cl_2N_5O_2$
MOLECULAR WEIGHT:	602.11
STRUCTURAL FORMULA:	
CHEMICAL FAMILY:	Diamide, pyridylpyrazole

Physico-chemical properties of cyclaniliprole active constituent

PHYSICAL FORM:	White powder
ODOUR:	No odour detected
MELTING POINT:	241 to 244°C for purified active
RELATIVE DENSITY AT 20°C:	1.60 for purified active
VAPOUR PRESSURE	2.4 x 10^{-6} Pa at 25°C for purified active
PH (1% W/V IN DISTILLED WATER)	5.9
DISSOCIATION CONSTANT (PKA):	8.6 for purified active
PARTITION COEFFICIENT	Pow = 557 (log Pow = 2.7) for purified active in purified water pH 5: Pow = 590 (log Pow = 2.8) pH 7: Pow = 275 (log Pow = 2.4) pH 9: Pow = 110 (log Pow = 2.0), all for purified active
SOLUBILITY IN WATER	0.15 mg/L (purified active in purified water) 0.12 mg/L (pH 5) 0.10 mg/L (pH 7) 0.18 mg/L (pH 9), all for purified active
SOLUBILITY IN SOLVENTS AT 20 °C (FOR TECHNICAL ACTIVE)	*n*-heptane: 0.0001 g/L xylene: 0.20 g/L 1,2-dichloroethane: 4.4 g/L Acetone: 10 g/L Methanol: 4.0 g/L *n*-octanol: 1.5 g/L ethyl acetate: 3.6 g/L
FLAMMABILITY	Not highly flammable for purified or technical active
EXPLOSIVE PROPERTIES	Not explosive under thermal, shock or frictional stimuli for purified or technical active
SELF-IGNITION TEMPERATURE	No self-ignition observed under the conditions of the test
OXIDISING PROPERTIES	Not oxidizing
STABILITY:	The available data show that technical cyclaniliprole is expected to be stable for at least two years when stored under normal conditions.

Purified active: typical purity ≥ 99%. Technical active: typical purity ≥ 95%.

The APVMA has evaluated the chemistry aspects of cyclaniliprole active constituent (identification, physico-chemical properties, stability, manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable.

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

APVMA ACTIVE CONSTITUENT STANDARD FOR CYCLANILIPROLE

CONSTITUENT	SPECIFICATION	LEVEL
Cyclaniliprole	Cyclaniliprole	935 g/kg minimum

Approval of cyclaniliprole is supported from a chemistry perspective.

2.2 Formulated product

The product ISK Cyclaniliprole 50 SL Insecticide will be manufactured overseas. It is a soluble concentrate formulation containing cyclaniliprole as the only active constituent. ISK Cyclaniliprole 50 SL Insecticide will be packaged in high density polyethylene (HDPE) containers ranging from 1–20 L. Suitable details of the product formulation, specifications for the ingredients, formulation and quality control processes, product specifications, stability data for the product when stored in the proposed packaging, analytical methods for the active constituent in the product, and details of the proposed containers, were provided and evaluated.

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

PRODUCT NAME:	ISK Cyclaniliprole 50 SL Insecticide
FORMULATION TYPE:	Soluble Concentrate (SL)
ACTIVE CONSTITUENT CONCENTRATION:	50 g/L Cyclaniliprole

Physical and chemical properties of product

PHYSICAL FORM:	Yellow transparent homogeneous liquid, free from visible suspended matter and sediment
ODOUR:	Chemical odour
PPH VALUE:	pH: 3.83 (undiluted); pH: 5.03 (1% in water)
SPECIFIC GRAVITY:	1.100 g/mL at 20 °C
SURFACE TENSION:	34.6 mN/m (undiluted, 25 °C)
KINEMATIC VISCOSITY:	8.05 cSt at 20 °C
FLASH POINT:	83.5 °C
OXIDISING PROPERTIES:	Not oxidizing
EXPLOSIVE PROPERTIES:	Not explosive
SELF-IGNITION TEMPERATURE:	272°C
CORROSIVE HAZARD:	Not corrosive to HDPE containers
PACK SIZES:	1 L – 20 L
PACKAGING MATERIAL:	HDPE
PRODUCT STABILITY:	The available data show that ISK Cyclaniliprole 50 SL Insecticide is expected to be stable for at least two years when stored under normal conditions.

2.3 Recommendations

Based on a review of the chemistry and manufacturing details provided by the applicant, registration of ISK Cyclaniliprole 50 SL Insecticide is supported from a chemistry perspective.

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

Public health aspects and toxicology

Cyclaniliprole is a new anthranilic diamide insecticide proposed for agricultural use. Similar to other diamide insecticides such as chlorantraniliprole and cyantraniliprole, cyclaniliprole is a ryanodine receptor modulator and known to impair nerve and muscle function which leads to rapid feeding cessation, regurgitation, lethargy and contractile paralysis of insects.

The proposed use of the new insecticide product ISK Cyclaniliprole 50 SL Insecticide, containing cyclaniliprole at 50 g/L in a soluble concentrate formulation, is for the control of codling moth in apples. The product will be used on apples no more than twice per crop and with a ten day minimum interval between applications.

Oral absorption of cyclaniliprole was up to 11% of the administered dose at 10 or 400 mg/kg bw in rats, and between 30-49% of the administered dose at 1 mg/kg bw in dogs. Elimination in rats was predominantly through faeces (88–92%), mainly as unchanged parent compound. Tissue distribution of cyclaniliprole was extensive, though residues were relatively low seven days after a single low dose. However, concentrations of radioactivity in tissues after 14-day repeated dosing to rats were generally 10–40 times those after a single dose, consistent with the observation that extensive accumulation of radioactivity was noted in plasma and whole blood after repeated dose administration (compared with single-dose administration).

In acute toxicity studies in rats, cyclaniliprole was of low acute oral (LD50 >2000 mg/kg bw), dermal (LD50 >2000 mg/kg bw) and inhalational (LC50 >4620 mg/m3) toxicity, was a non-irritant to the skin and eye in rabbits, and was not a skin sensitiser in guinea pigs (Maximization method) and mice (LLNA method).

Low systemic toxicity effects were observed with cyclaniliprole in all dietary studies in rats and mice. Across repeat-dose toxicity studies, dogs appeared to be the more sensitive species, with toxicologically significant changes in some liver-related clinical chemistry and organ weights noted at relatively low dose levels which were not similarly observed in rodents.

Cyclaniliprole was not genotoxic, carcinogenic or neurotoxic, and no evidence of reproductive toxicity, developmental toxicity or immunotoxic potential was identified in standard studies.

Based on the toxicological studies evaluated, the product ISK Cyclaniliprole 50 SL Insecticide was of low acute oral (LD50 >2000 mg/kg bw), dermal (LD50 >2000 mg/kg bw) and inhalational (LC50 >5050 mg/m3) toxicity in rats, was a slight eye irritant but not a skin irritant in rabbits, and was not a skin sensitiser in guinea pigs (Buehler test) or in mice (LLNA).

Work Health and Safety

The product ISK Cyclaniliprole 50 SL Insecticide will be professionally used by commercial operators, and farmers and their employees, as well as contract sprayers. Workers may be exposed to the product when opening containers, using the product, cleaning up spills, maintaining equipment and entering treated areas. The main routes of exposure to the product/spray will be dermal and inhalation, although ocular exposure is also possible.

An exposure assessment was conducted, and in conjunction with the hazard profile, used to determine whether the proposed use of the product would be an undue hazard to human health. 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 exposure.

The risk assessment concluded that exposure to the product, ISK CyclaniliproleTM 50 SL Insecticide, during mixing, loading and application by airblast was acceptable without the use of personal protective equipment, though a precautionary hazard statement notifying users of the slight eye irritation potential of the product is recommended. Based on the outcomes of the risk assessment, First Aid Instructions and Safety Directions have been recommended for inclusion on the product label.

Conclusion

Based on the outcomes of the human health risk assessment, approval of the active constituent cyclaniliprole and registration of ISK CyclaniliproleTM 50 SL Insecticide is supported.

3.2 Evaluation of toxicology

The data package included studies on toxicokinetics/metabolism, dermal absorption, acute toxicity (on both the active constituent and product), short-term, subchronic and chronic toxicity studies, carcinogenicity, reproduction and developmental studies, as well as studies on neurotoxicity, immunotoxicity and genotoxicity. The studies were conducted to a high standard and were generally GLP, QA and OECD guideline compliant. The studies were considered reliable to establish the toxicity profile of cyclaniliprole and the product ISK Cyclaniliprole 50 SL Insecticide.

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. However, from a conservative risk assessment perspective, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur.

Chemical class

Cyclaniliprole is a new anthranilic diamide insecticide. Similar to other diamide insecticides such as chlorantraniliprole and cyantraniliprole, cyclaniliprole is a ryanodine receptor modulator and known to impair nerve and muscle function, which leads to rapid feeding cessation, regurgitation, lethargy and contractile paralysis of insects.

Toxicokinetics and metabolism

The oral absorption of cyclaniliprole was low in rats, with 8.96–10.67% of the administered dose absorbed at 10 mg/kg bw and 2.32–4.77% at 400 mg/kg bw. Both the rate and extent of exposure to radioactivity, as reflected by the parameters Cmax and AUCall respectively, increased with increasing dose. However, the increases in these parameters were less than the proportionate dose increase and were ~80% lower than expected from a linear relationship at 400 mg/kg bw for Cmax and AUCall. No notable differences in toxicokinetics parameters were noted between the different radiolabel forms utilised in the ADME study, with a plasma Cmax of ~2.47–2.70 µg/g at a Tmax between 24–72 hours. Terminal half-lives were not able to be determined as radioactivity concentrations did not decline sufficiently during the observation period.

With respect to distribution, concentrations of radioactivity in tissues were similar between sexes, with highest concentrations noted in plasma and whole blood at both low and high doses. Tissue accumulation after single oral doses were low (< 3% retention of radiolabelled material after 168 hours at 10 mg/kg bw, and < 1% at 400 mg/kg bw), though after repeated low doses, a significant amount of radiolabelled material (~31% administered dose) was retained in tissues and present at study termination 168 hours after the final dose.

Cyclaniliprole was not metabolised to a large extent. In bile and urine, three metabolites were identified, each at < 1% of the administered dose, with all other metabolites accounting for < 1% of the administered dose.

Elimination of cyclaniliprole was relatively rapid (>85% in excreta eliminated by 48 hours after single doses) and primarily by the faecal route (88–92% of the administered dose), with most of the faecal elimination identified as unabsorbed parent compound (~77–86%). Urinary excretion accounted for < 1% of the administered dose. Similarly rapid elimination and excretion patterns were noted in the repeat low-dose (10 mg/kg bw) oral dosing study.

Preliminary ADME data in dogs suggested that absorption, assessed as the sum of total radioactivity measured in bile, urine, liver and carcass, ranged from 30.5–48.9% after single oral doses of 1 mg/kg bw. Excretion was not complete at 48 hours, and biliary and urinary pathways were not major routes of elimination in the dog.

Dermal absorption

Dermal absorption studies (in vitro human, in vitro rat, and in vivo rat) were conducted using a similar formulation containing 50 g/L cyclaniliprole. Applying the ‘triple pack’ calculation principles, and extrapolating dilution ratio information from the in vitro dermal absorption studies, the estimated maximum human dermal absorption factor is approximately 0.5% for the undiluted formulation, 0.8% for an intermediate end-use dilution (1:1000 dilution) and 1.5% for an end-use product dilution (1:5000 dilution).

Acute toxicity

In acute toxicity studies in rats, cyclaniliprole was of low acute oral (LD50 >2000 mg/kg bw), dermal (LD50 >2000 mg/kg bw) and inhalational (LC50 >4620 mg/m3) toxicity, was a non-irritant to the skin and eye in rabbits, and was not a skin sensitiser in guinea pigs (Maximization method) and mice (LLNA method).

In acute toxicity studies in rats, the product ISK Cyclaniliprole 50 SL Insecticide was of low acute oral (LD50 >2000 mg/kg bw), dermal (LD50 >2000 mg/kg bw) and inhalational (LC50 >5050 mg/m3) toxicity, was a slight eye irritant but not a skin irritant in rabbits, and was not a skin sensitiser in guinea pigs (Buehler test) or in mice (LLNA).

Systemic toxicity

Repeat dose toxicity studies including reproduction and developmental studies were generally unremarkable in rodents, with no toxicologically relevant effects seen at the highest administered doses, with the exception of the 13-week rat dietary study where increased heart and ovary weights were observed in females at the highest dose of 1594 mg/kg bw/d (20000 ppm), and in the 2-year rat dietary study where follicular cell hypertrophy in the thyroid was detected in males at the highest dose of 834 mg/kg bw/d (20000 ppm).

Dogs appeared to be the more sensitive species compared to rodents, with relatively low NOAELs identified (~4 mg/kg bw/d) based on toxicologically significant changes in liver weights and clinical chemistry (notably ALP and albumin levels) at higher dose levels.

No treatment related adverse effects were seen in a short-term dermal study in the rat at the limit dose.

Genotoxicity and carcinogenicity

Cyclaniliprole was negative in an array of Guideline-compliant genotoxicity studies, including a reverse gene mutation assay, an in vitro chromosome aberration assay, an in vitro gene mutation assay, and an in vivo micronucleus assay. Hence, cyclaniliprole showed neither mutagenic nor genotoxic potential.

No increased incidence was seen in any tumour type in male or female mice in a 78-week dietary study or in male or female rats in a 2 year dietary study.

Reproductive and developmental toxicity

There was no evidence of reproductive or developmental toxicity in the two-generation reproduction study in rats, or in the developmental studies in rats and rabbits.

Neurotoxicity

No evidence of an acute neurotoxic effect was observed in functional observation battery or motor activity assessment in the acute and repeat dose neurotoxicity studies at or up to the limit dose.

Toxicity of metabolites

The cyclaniliprole metabolite NK-1375 was negative in a bacterial reverse mutation assay.

3.3 Public health standards

Poisons scheduling

On 23 June 2016, the Delegate to the Secretary of the Department of Health published a final scheduling decision to create a new Appendix B listing for cyclaniliprole in the Standard for the Uniform Scheduling of Medicines and Poisons, with an implementation date of 1 October 2016.

NOAEL/ADI

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

The toxicological database for cyclaniliprole included several long-term oral toxicity and carcinogenicity studies in the mouse and rat, as well as a 12-month study in beagle dogs, and was considered comprehensive. Across the cyclaniliprole studies, there was evidence that dogs were the more sensitive species to treatment-related effects, with the lowest NOAEL identified at 4.07/4.20 mg/kg bw/d (M/F respectively; 150 ppm) in the 1-year dog dietary study based on increased liver weights and changes in ALP and albumin at higher doses. However, there were no other indications of serious toxicological effects requiring the application of additional safety factors.

On this basis, the ADI for cyclaniliprole is established at 0.041 mg/kg bw/d based on the NOAEL of 4.07 mg/kg bw/d from the 1-year dog dietary study and applying a 100 fold safety factor (consisting of a 10-fold safety factor for both intra- and inter-species variation).

Acute Reference Dose (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.

Since cyclaniliprole was of low toxicity across the single dose toxicity studies and did not demonstrate evidence of a genotoxic, neurotoxic or reproductive/developmental toxicity potential, an ARfD was not established in this case.

4 RESIDUES ASSESSMENT

As part of the residues assessment for cyclaniliprole, plant and animal metabolism studies, supervised residue trials, processing studies, and trade aspects were considered.

4.1 Metabolism and Residue Definition

Metabolism studies in apples, lettuce, potatoes, confined rotational crops (carrots, lettuce and wheat), rats, lactating goats and laying hens were provided.

Relatively little metabolism of cyclaniliprole occurs in plants, whether the compound is applied directly or to preceding crops. The most significant metabolic pathways are cleavage of the cyclopropyl amide moiety to yield 3-bromo-5-chloro-2-[3-bromo-1-(3-chloro-2-pyridyl)pyrazole-5-carbamoyl]benzamide (YT-1284) and internal ring condensation of the pyridyl and amide moieties to yield 3-bromo-2-((2-bromo-4*H*-pyrazolo[1,5-*d*]pyrido[3,2-*b*]-[1,4]oxazin-4-ylidene)amino)-5-chloro-*N*-(1-cyclopropylethyl)benzamide (NK-1375).

In all plant matrices, parent was the major component of the residue, at 39.6–90.0% of the Total Radioactive Residue (TRR). The only other component which exceeded 10% of the TRR and/or 0.01 mg eq./kg was the metabolite NK-1375, at up to 24.7% of the TRR. In the field residue studies for cyclaniliprole in apples, parent compound and NK-1375 were tested for. Residues of parent compound were almost always higher than those of NK-1375, while NK-1375 was often <LOQ.

Metabolism of cyclaniliprole in rats, goats and hens is similar, with the major pathway being hydrolysis of the phenyl amide moiety to give 3-bromo-5-chloro-2-[3-bromo-1-(3-chloro-2-pyridyl)pyrazole-5-carbamoyl]benzamide (YT-1284), with subsequent further hydrolysis to 3-bromo-5-chloro-2-[3-bromo-1-(3-chloro-2-pyridyl)pyrazole-5-carbamoyl]benzoic acid (NSY-27) and ring condensation to give 8-bromo-2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloroquinazolin-4(3*H*)-one (NSY-28). In rats, an additional pathway of internal ring condensation of the pyridyl and amide moieties to yield 3-bromo-2-((2-bromo-4*H*-pyrazolo[1,5-*d*]pyrido[3,2-*b*]-[1,4]oxazin-4-ylidene)amino)-5-chloro-*N*-(1-cyclopropylethyl)benzamide (NK-1375) is observed.

In edible matrices of lactating goats and laying hens, parent compound was a significant residue component, at 4.4–79.5% of TRR (0.006–0.750 mg eq./kg). Other significant components were the metabolites YT-1284, at 2.1–30.4% of TRR (0.008–0.246 mg eq./kg), NSY-28, at 5.2–63.2% of TRR (0.003–1.049 mg eq./kg), and NSY-27, at <0.3–6.2% of TRR (0.001–0.070 mg eq./kg).

In the cattle feeding study, residues of parent compound and the metabolites NK-1375, YT-1284, NSY-27 and NSY-28 were tested for. In whole milk, residues were mostly <LOQ, with the exception of parent compound, which was observed at low levels of up to 0.016 mg/kg only at the highest feeding level of 2.0 ppm. In tissues, at the two lower feeding levels of 0.2 and 0.6 ppm, only parent compound was detected, while residues of the metabolites were all <LOQ. At the 2.0 ppm feeding level, residues of up 0.141 mg/kg of parent compound were observed (in liver), while of the metabolites, only NSY-28 was detected, at up to 0.032 mg/kg, again in liver.

Given that parent compound is the most commonly found residue in both plants and animals, and is usually the largest component, a residue definition of parent compound only is proposed for compliance with MRLs for both plant and animal commodities. For dietary risk assessment, a residue definition of the sum of cyclaniliprole and 3-bromo-2-((2-bromo-4*H*-pyrazolo[1,5-*d*]pyrido[3,2-*b*]-[1,4]oxazin-4-ylidene)amino)-5-chloro-*N*-(1-cyclopropylethyl)benzamide (NK-1375), expressed as cyclaniliprole, is proposed for plant commodities. For dietary risk assessment in animal commodities, a residue definition of the sum of cyclaniliprole and 8-bromo-2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloroquinazolin-4(3*H*)-one (NSY-28), expressed as cyclaniliprole, is proposed.

4.2 Residue analytical methods

Determination of cyclaniliprole residues in plant commodities

An LC-MS/MS method was developed and validated for determination of cyclaniliprole and the metabolite NK-1375 in plant matrices. Samples were extracted with acetonitrile or acetonitrile/water, then cleaned up by solid phase extraction prior to LC-MS/MS analysis. A limit of quantitation (LOQ) of 0.01 mg/kg was validated for both analytes.

Determination of cyclaniliprole residues in animal commodities

An LC-MS/MS method was developed and validated for determination of cyclaniliprole and the metabolites NK-1375, YT-1284, NSY-27 and NSY-28 in animal tissues and milk. Samples were extracted with acetonitrile and cleaned up by partition with hexane, followed by solid phase extraction. An LOQ of 0.01 mg/kg was validated for all analytes.

Stability of residues

A storage stability study was conducted for both cyclaniliprole and the metabolite NK-1375 (fortified separately) in plant matrices. Samples were fortified at 0.10 ppm and stored frozen for up to 18 months. Matrices texted included wine, grapes, potato, rapeseed, lettuce, broccoli, and dry beans, covering high water content, acidic, oily and dry matrices. Over the 18-month storage period, corrected recoveries for parent compound and NK-1375 ranged from 78–109%, indicating that residues of cyclaniliprole and the metabolite NK-1375 are stable in a wide range of plant matrices over at least 18 months of frozen storage.

4.3 Residue trials

Apples

The proposed GAP for cyclaniliprole in apples is 2 dilute foliar spray applications with a minimum re-treatment interval of 10 days at a spray concentration of 4 g a.i./100 L, with a harvest withholding period of 28 days.

Residue data in apples from trials conducted in Australia were used to propose an MRL.

In the Australian trials, at a 28-day harvest interval after 2 × 4 g a.i./100 L dilute applications (1× GAP), residues of cyclaniliprole parent compound in apples were <0.01, 0.021, 0.025, 0.036, 0.038, and 0.050 mg/kg (STMR = 0.031 mg/kg).

In the same series of trials, after treatment at 2× GAP, parent compound residues at a 28-day harvest interval were <0.01, 0.040, 0.051, 0.082, 0.11, and 0.12 mg/kg.

No residues of the metabolite NK-1375 were detected (LOD = 0.005 mg/kg) in any of the samples from the Australian trials, therefore total residues of parent plus NK-1375 are regarded as being the same as those of parent only.

An MRL of 0.1 mg/kg is proposed for cyclaniliprole in apples, in conjunction with a 28-day harvest withholding period.

The only processed commodity of commercial importance in which residues of cyclaniliprole and the metabolite NK-1375 concentrate is apple pomace, a by-product of juice and cider manufacture that can be fed to livestock. Using a factor of 8 (derived from a processing study) for dry apple pomace, and the STMR and HR values of 0.031 and 0.05 mg/kg from the Australian 1× dataset, STMR-P and HR-P values of 0.25 and 0.40 mg/kg respectively are calculated.

Based on these figures, an MRL of 0.7 mg/kg is proposed for cyclaniliprole in apple pomace, dry.

4.4 Rotational cropping

Currently, cyclaniliprole is only proposed for use in apples, which are not a rotational crop. It will be necessary to consider MRLs for rotational crop residues in the future, if use of cyclaniliprole in non-permanent crops, or in situations where animal feeds may be produced, is proposed.

4.5 Animal commodities

The only livestock feed of significance for the proposed use pattern is apple pomace. Apple pomace can be fed to beef and dairy cattle at up to 20% and 10% of the diet respectively. As apple pomace is a bulked and blended commodity, with fruit from many different orchards typically being combined for juice manufacture, the STMR-P (0.25 mg/kg for dry apple pomace) is the appropriate residue value to use in calculating the livestock dietary burden. For beef and dairy cattle, the dietary burdens will be 0.05 and 0.025 mg/kg respectively.

A lactating cattle feeding study was supplied with the application. Cyclaniliprole was administered twice daily in the diet to lactating Friesian dairy cows for 28-31 consecutive days at levels nominally equivalent to 0.2, 0.6 and 2 mg/kg diet dry wt./day. Cyclaniliprole and the metabolites NK-1375, NSY-27, NSY-28 and YT-1284 were determined in milk throughout the treatment period and in edible tissues at sacrifice. Three animals were maintained in the high dose group for up to two weeks after cessation of treatment as part of a depuration study.

At 0.2 ppm feeding level, the level closest to the calculated mammalian livestock dietary burden, residues of parent compound and the metabolites NK-1375, YT-1284, NSY-27, and NSY-28 in milk and all tissues other than kidney were <LOQ (0.01 mg/kg). In kidney, a residue of 0.011 mg/kg of parent compound only was observed.

The depuration phase of the study enabled the calculation of half-lives of 5.4, 4.3, 4.5, 3.2 and 3.3 days for total cyclaniliprole residues in liver, kidney, subcutaneous fat, perirenal fat, and omental fat respectively using exponential fitting of the decline data. For milk and muscle, all residues of cyclaniliprole and related metabolites were <LOQ by 2 days after cessation of feeding, indicating a short half-lives of ≤2 days.

As the calculated dietary burdens of cyclaniliprole for beef and dairy cattle are 0.05 and 0.025 mg/kg respectively, quantifiable residues of parent compound and the four metabolites are not expected to be found in the milk, meat or offal of livestock fed treated apple pomace. Therefore, MRLs of *0.01 mg/kg are proposed for mammalian milk, meat and offal.

Apple pomace is not commonly fed to poultry. Given that the dietary burden for cyclaniliprole in poultry is nil, it is proposed to establish MRLs at the LOQ (0.01 mg/kg) in eggs, poultry edible offal, and poultry meat.

4.6 Spray drift

It is proposed to include a 20-metre buffer zone on the product label to mitigate risks to international trade associated with residues in grazing animals.

4.7 Bioaccumulation potential

The $\log_{10}K_{OW}$ (octanol-water partition coefficient) for cyclaniliprole was found to be 2.8, 2.4 and 2.0 at pH of 5, 7, and 9 respectively, at 40°C. In the cattle feeding study, quantifiable residues of cyclaniliprole were found in cream (0.037–0.144 mg/kg after 28 days feeding at 2.0 ppm), while residues in skim milk were all <LOQ. In muscle, residues of cyclaniliprole reached <LOQ-0.032 mg/kg after 28 days feeding at 2.0 ppm, while in subcutaneous fat, cyclaniliprole residues were 0.015–0.119 mg/kg.

Although residues of cyclaniliprole were higher in fatty matrices such as cream and subcutaneous fat than in skim milk and muscle, as the octanol-water partition coefficient is less than 3 at pH values of 5–9, the bioaccumulation potential of cyclaniliprole is expected to be low.

4.8 Risk assessment conclusions

Estimated dietary intake

The chronic dietary exposure to cyclaniliprole is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived primarily from the 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 cyclaniliprole is equivalent to <1% of the ADI. It is concluded that the chronic dietary exposure to cyclaniliprole is acceptable.

NESTIs have not been calculated for cyclaniliprole, as it has been determined that an Acute Reference Dose (ARfD) is not required due to low acute toxicity, and no evidence of genotoxic, neurotoxic or reproductive/developmental toxicity after a single dose.

2 WHO (2008). Consultations and workshops: Dietary Exposure Assessment of Chemicals in Food: Report of a joint FAO/WHO Consultation, Annapolis, Maryland, USA, 2–6 May 2005.

Recommendations

The following amendments to the MRL Standard are recommended in relation to the proposed use of ISK Cyclaniliprole 50 SL Insecticide:

Table 1- Proposed amendments to MRL Standard Table 1-MRLs of agricultural and veterinary chemicals and associated substances in food commodities

COMPOUND		FOOD	MRL (mg/kg)
ADD:			
Cyclaniliprole			
FP	0226	Apple	0.1
MO	0105	Edible offal (mammalian)	*0.01
PE	0112	Eggs	*0.01
MM	0095	Meat (mammalian)	*0.01
ML	0106	Milks	*0.01
PO	0111	Poultry, edible offal of	*0.01
PM	0110	Poultry meats	*0.01

Table 2- Proposed amendments to MRL Standard Table 3-Residue definitions (and marker residues)

COMPOUND	RESIDUE
ADD:	
Cyclaniliprole	For enforcement for commodities of plant and animal origin: cyclaniliprole
	Commodities of plant origin for dietary exposure assessment: sum of cyclaniliprole and 3-bromo-2-((2-bromo-4*H*-pyrazolo[1,5-*d*]pyrido[3,2-*b*]-[1,4]oxazin-4-ylidene)amino)-5-chloro-*N*-(1-cyclopropylethyl)benzamide (NK-1375), expressed as cyclaniliprole
	Commodities of animal origin for dietary exposure assessment: sum of cyclaniliprole and 8-bromo-2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloroquinazolin-4(3*H*)-one (NSY-28), expressed as cyclaniliprole

Table 3- Proposed amendments to MRL Standard – Table 4 MRLs for pesticides in animal feed commodities

COMPOUND		ANIMAL FEED COMMODITY	MRL (mg/kg)
ADD:			
Cyclaniliprole			
AB	0226	Apple pomace, dry	0.7

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

HARVEST WITHHOLDING PERIOD:

APPLES: DO NOT HARVEST FOR 28 DAYS AFTER APPLICATION

GRAZING WITHHOLDING PERIOD:

DO NOT ALLOW LIVESTOCK TO GRAZE TREATED ORCHARDS OR CUT FOR STOCK FOOD.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported and main destinations

Apples are considered to be major export commodities[3], as are commodities of animal origin, such as meat, offal and dairy products, which may be derived from livestock fed feeds produced from treated apples.

According to Apple and Pear Australia Ltd, Australian pome fruit is exported to the United Kingdom, Asia, New Zealand and Canada[4].

The significant export markets for Australian beef, sheep, pig meat and offal are listed in the APVMA Regulatory Guidelines—Data Guidelines: Agricultural—Overseas trade (Part 5B)[3]. Total exports of dairy products in 2014–15 were worth $2.46 billion, with key export destinations including Japan, Singapore, China, Indonesia, Malaysia, Thailand, the Philippines, Korea, and Russia. Total exports of beef and veal were worth $8.86 billion in 2014–15, with the major destinations including Japan, the USA, Korea, China, Taiwan, the EU, the Middle East, and Russia. Total exports of lamb and mutton were worth $2.47 billion in 2014–15, with the key destinations including the USA, China, the Middle East, the European Union, and Japan[5].

5.2 Overseas registration status

Codex MRLs are not yet established for cyclaniliprole. It is however noted that cyclaniliprole was considered by the JMPR at the 2017 meeting. Cyclaniliprole MRLs for apple at 0.3 mg/kg have been established by the US[6] and Canada[7].

5.3 Potential risk to trade

The applicant has proposed including the following trade risk mitigation statement on the label, which is considered appropriate and acceptable:

Export of treated produce: *Growers should note that suitable MRLs or import tolerances do not exist in all markets for produce treated with ISK Cyclaniliprole 50 SL Insecticide. In some situations export requirements may be met by limiting application numbers and/or imposing a longer withholding period than specified above. If you are growing produce for export, please check with ISK Biosciences Oceania Pty Ltd or your industry body for the latest information on any potential trade issues and their management before using ISK Cyclaniliprole 50 SL Insecticide.*

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[3] APVMA Regulatory Guidelines—Data Guidelines: Agricultural—Overseas trade (Part 5B)

[4] http://apal.org.au/statistics/#apei

[5] Agricultural Commodity Statistics 2015, Australian Bureau of Agricultural and Resource Economics and Sciences, Department of Agriculture and Water Resources, December 2015 (http://data.daff.gov.au/data/warehouse/agcstd9abcc002/agcstd9abcc0022015/ACS_2015_1.0.0.pdf)

[6] US: https://www.ecfr.gov/cgi-bin/text-idx?SID=587ed0829d5d1c653bbfe2391838ffef&mc=true&node=se40.26.180_1694&rgn=div8

[7] Canada: http://pr-rp.hc-sc.gc.ca/mrl-lrm/index-eng.php

For the purpose of compliance with MRLs, the proposed Australian residue definition for cyclaniliprole is parent compound only, for both plant and animal commodities.

There is a potential for finite residues in apples as a result of the proposed use of ISK Cyclaniliprole 50 SL Insecticide. There is a potential risk to trade, to overseas markets that have established or proposed standards for cyclaniliprole. The US and Canadian MRLs at 0.3 mg/kg are higher than the proposed Australian MRL (0.1 mg/kg)

The risk to Australian trade in animal commodities is considered to be low, as finite residues of cyclaniliprole are not expected to be found, and MRLs at the LOQ (*0.01 mg/kg) are proposed for milk, eggs, and mammalian and poultry meat and offal. Both the USA and Canada are proposing MRLs at the LOQ for mammalian animal commodities, while they are not proposing to establish poultry MRLs due to the calculated zero dietary burden for poultry.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Health hazards

The active constituent cyclaniliprole (CAS: 1031756-98-5) is not listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2016).

With the available toxicology information, cyclaniliprole is not considered a hazardous substance according to the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

Based on the results of the acute oral, acute dermal, acute inhalation as well as the skin and eye irritation studies and the skin sensitization study with the product, the minimum requirements for classification of ISK Cyclaniliprole 50 SL Insecticide with risk phrases according to the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004) are not met.

6.2 Formulation, packaging, transport, storage and retailing

The active constituent cyclaniliprole and the formulated product ISK Cyclaniliprole 50 SL Insecticide will be manufactured overseas. ISK Cyclaniliprole 50 SL Insecticide will be available in 1–20 L pack sizes in HDPE containers.

6.3 Use pattern

ISK Cyclaniliprole 50 SL Insecticide is proposed to be used for the control of codling moth in apples. Prior to application, the product is to be mixed with water in a spray tank under constant agitation. The concentration of the diluted solution is 60–80 mL/100 L water. The recommended application rate is 1500–2000 L diluted spray/ha. The draft label indicates that concentrate spraying using solutions 3–4 times more concentrated may be used; however the same quantity of cyclaniliprole per hectare should be applied. Application is likely to be via an airblast-type applicator.

The draft label states that no more than 2 applications/crop should be made for codling moth control, with a 10 day minimum interval between treatments. It is possible that a contract sprayer may make multiple applications a year. The draft label also indicates that only one generation of codling moth should be treated with the product before rotation to an insecticide with a different mode of action.

6.4 Exposure during use

The product ISK Cyclaniliprole 50 SL Insecticide will be used in commercial situations by farmers, their employees, as well as contract sprayers. Workers may be exposed to the product when opening containers, using the product, cleaning up spills, maintaining equipment and entering treated areas. The main routes of exposure to the product/spray will be dermal and inhalation, although ocular exposure is also possible.

An exposure assessment was conducted, and in conjunction with the hazard profile, used to determine whether the proposed use of the product would be an undue health hazard to humans. 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 exposure.

The toxic endpoint of concern and identified NOAEL for risk assessment is derived from a repeat dose study in animals, and in this instance a margin of exposure (MOE) of 100 or above is considered acceptable. The MOE takes into account both potential inter-species extrapolation and intra-species variability. Based on the risk assessment, the proposed use of the product for apples is acceptable without the need for PPE, though a precautionary hazard statement notifying users of the slight eye irritation potential of the product is recommended.

6.5 Exposure during re-entry

The re-entry risks associated with conducting activities where the product has been applied are expected to be by the dermal route. The MOEs determined for re-entry activities associated with use of ISK Cyclaniliprole 50 SL Insecticide are considered acceptable (MOE >> 300) on day zero after application. Therefore, a NIL re-entry statement is appropriate for this product.

6.6 Recommendations for safe use

Based on the risk assessment, ISK Cyclaniliprole 50 SL Insecticide is supported for professional use; and where users follow the First Aid Instructions and Safety Directions on the product label.

6.7 Conclusion

The approval of the active constituent cyclaniliprole and registration of ISK Cyclaniliprole 50 SL Insecticide, containing 50 g/L cyclaniliprole for the control of codling moth in apples is supported.

ISK Cyclaniliprole 50 SL Insecticide can be used safely if handled in accordance with the instructions on the product label.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

The following environmental fate and ecotoxicity information relate to the new active constituent, cyclaniliprole, and for test results relating to the end-use product.

7.2 Environmental fate and behaviour

Hydrolysis

Cyclaniliprole is hydrolytically stable under environmentally relevant pH values (pH 4, 7 and 9).

Photolysis/photodegradation

Based on laboratory data, aqueous photolysis may provide an important removal route for cyclaniliprole in in clear water with the half-life being <1.5 days. NK-1375 and NU-536 were major photodegradates forming up to 40 % and 15 % of applied radioactivity, respectively.

Fate and behaviour in soil

The range of DT50s for the parent compound indicated longer persistence under laboratory conditions than those found in the field, but cyclaniliprole was persistent in all situations. Laboratory aerobic soil half-lives of radiolabelled cyclaniliprole at 20^{o}C ranged from 1409 days to 1728 days (5 soils) and in four of these soils at 35^{o}C, ranged from 548-681 days. No metabolite was found to be >2% applied radioactivity.

Field dissipation results were available for 4 different sites in North America. The maximum field half-life was 1247 days Single First Order (SFO). The range of field half-lives was 381 days to 1247 days and the geometric mean field half-life was 694 days.

No metabolite exceeded 5% applied parent, and separate degradation experiments on metabolites were not performed.

Fate and behaviour in water

In aerobic water/sediment systems, the half-life of cyclaniliprole in the water column was 37 days. No major metabolites were formed. Cyclaniliprole dissipated from the water column by partitioning to sediment rather than breaking down. The two sediment systems tested were sandy silt loam and sand, and the total system half-lives were 694 days and 495 days respectively.

Similar results were found in the same systems but incubated under anaerobic conditions. The water column DT50 ranged from 32.9 days to 44.9 days with no major metabolites found in either sediment or water. In the total systems, the DT50s were 854 days (sandy silt loam) and 794 days (sand).

Mobility

In standard batch adsorption tests, cyclaniliprole was tested in five different soils with %OC ranging from 0.5–7.0%. There was a clear relationship of increasing soil sorption with increasing organic carbon, and there was no apparent concentration dependence on sorption. Koc values ranged from 247 L/kg to 1131 L/kg. The desorption constant following the first desorption step was higher than the adsorption constant, indicating that adsorption is not fully reversible.

Estimation of adsorption of the photodegradate NK-1375 was determined by HPLC against several reference substances. The Log10Koc of NK-1375 at pH 4, 7 and 9 was 4.4 and is considered immobile in soil.

In field studies, there was limited movement of cyclaniliprole through the soil profile although in one study, residues were found as deep at 105 cm in a sandy soil.

Bioaccumulation

Cyclaniliprole is not expected to bioaccumulate in food chains. Bioconcentration testing in fish showed highest bioconcentration factor (BCF) values in the non-edible fraction ranging from 72.5 to 152.

7.3 Environmental effects

Terrestrial vertebrates

Avian

Cyclaniliprole is slightly toxic to birds with acute oral or short term dietary exposure (acute oral LD50 > 1914 mg ac/kg bw for both bobwhite quail and canary; 5–day dietary LC50 > 5000 ppm for both bobwhite quail and mallard duck). Reproduction studies indicated NOECs of 100 ppm and 40 ppm for bobwhite quail and mallard duck, respectively.

Aquatic organisms

Effects on fish

Based on the results of acute toxicity studies conducted with the active constituent, cyclaniliprole showed no toxicity to fish up to its water solubility (0.15 mg/L). Acute tests are available for four species and no mortalities for any species were recorded.

An early life stage toxicity study with cyclaniliprole to fathead minnow showed no evidence of test item related abnormalities at any tested level. There was no effect on growth or reproduction parameters. The LOEC and NOEC were >0.212 mg ac/L, the highest level tested.

Effects on aquatic invertebrates

Cyclaniliprole is very highly toxic to aquatic invertebrates. The 48 h EC50 to Daphnia magna was 0.0773 mg ac/L while the 96 h EC50 (shell deposition) to the eastern oyster was 0.023 mg ac/L. Acute testing with the mysid shrimp or midge did not result in 50% mortality or effects at the highest tested rates of 0.2 mg ac/L and 0.053 mg ac/L respectively.

Metabolite acute toxicity to Daphnia magna was less than the parent compound. No immobilisation was observed at the highest test rates of 0.0543 mg/L and 24.4 mg/L for photodegradates NK-1375 and NU-536 respectively. The EC50 for TJ-537 was >0.355 mg/L (highest tested rate), but at this rate, mortality was 45%.

A 21 day chronic toxicity study of cyclaniliprole to Daphnia magna indicated a NOEC of 0.01 mg ac/L based upon treatment-related effects on adult survival.

A 28 day whole sediment test was undertaken with midge larvae (Chironomus dilutus) with exposure through spiked sediment. The EC50 was calculated to be 0.15 mg/kg (emergence success) and the NOEC was 0.122 mg/kg (development rate).

Effects on algae and aquatic plants

Tests were undertaken on four standard algae species and the aquatic macrophyte, Lemna gibba. In all cases, no effects were observed at the highest tested rates, which approximated the water solubility of cyclaniliprole. ErC50 values ranged from >0.099 mg/L to >0.195 mg/L (corresponding study NOECs ranged from 0.099 mg/L to 0.195 mg/L, the highest tested rates).

Terrestrial organisms

Effects on bees

Cyclaniliprole was highly toxic to honey bees. Based on product tests, the oral and contact LD50s were 0.194 µg/bee and 0.486 µg/bee respectively. Potential effects on bees were assessed further through several semi-field (tunnel) tests and full field tests. There were no effects on adult, pupae survival, foraging activity, colony strength, conditions of the colony performance and brood development in any study with some possible treatment related effects on adult survival in one test. In terms of overall mortality, this was insufficient to impact the hive during the course of the study. Rates tested were lower than those proposed in Australia. However, there were sufficient measurements of residues in nectar and pollen to allow extrapolation to the Australian use pattern.

Effects on non-target terrestrial arthropods

The end-use product was tested on the standard beneficial insects, the parasitoid (Aphidius rhopalosiphi) and the predatory mite (Typhlodromus pyri) in glass plate tier 1 laboratory dose/response tests. The LR50s were 0.507 g ac/ha and 105 g ac/ha respectively. Given the high hazard to Aphidius rhopalosiphi, this species was tested under extended laboratory conditions. Effects diminished with time after application with a 0 d LR50 = 4.3 g ac/ha, 14 d LR50 = 24.1 g ac/ha and 28-56 d LR50 >80 g ac/ha. The reproduction 14 d

and 28 d ER50s were 12.7 g ac/ha and 47.7 g ac/ha respectively. Extended laboratory tests were also carried out on additional species including the ladybird (Coccinella septempuctata) and rove beetle (Aleochara bilineata). No effects on reproduction were found after 28 days and 14 days respectively. The 0 d LR50 for ladybird was 28.1 g ac/ha, but was >80 g ac/ha after 14 days. The 0 d LR50 for rove beetle was 84.3 g ac/ha, but was >80 g ac/ha after 14 days.

A 28 d test to the collembolan (Folsomia candida) resulted in an EC50–6.76 mg/kg dw and a NOEC = 2.5 mg/kg dw while a 14 d test on the soil predatory mite (Hypoaspis aculeifer) resulted in an LC50 and EC50 >1000 mg/kg dw and a NOECreproduction = 555 mg/kg dw.

Effects on earthworms

Acute toxicity tests for earthworms showed cyclaniliprole to not be toxic up to the level tested with a 14 d LC50 >46.3 mg/kg dw dw. For reproductive toxicity testing, cyclaniliprole was not toxic with a NOEC = 1000 mg/kg dw.

Soil micro-organisms

Exposure of cyclaniliprole to soil microorganisms showed no significant adverse effects on the soil nitrogen cycle or soil respiration at levels up to 0.53 mg ac/kg dw soil, the highest tested rate.

Terrestrial plants

Testing on the Australian end-use product was undertaken using standard tier II terrestrial vegetation test methods. Both the vegetative vigour and seedling emergence studies were undertaken as limit tests at a rate of 1000 g ac/ha. There were no adverse effects (>25% compared with control) for any species, so the ER25 for both vegetative vigour and seedling emergence is >1000 g ac/ha.

7.4 Risk assessment

Cyclaniliprole is to be applied at a maximum application rate of 80 g ac/ha with up to 2 applications 10–14 days apart. The environmental risk assessment has determined that the risk to birds, mammals, terrestrial plants, earthworms and other non-target soil macro-organisms was found to be acceptable and no adverse effects on soil nitrogen and carbon metabolism is expected from the proposed uses. The risk to aquatic organisms was demonstrated to be manageable based on the proposed use pattern subject to additional label statements and appropriate downwind mandatory no-spray zones of 30 metres from aquatic areas.

A risk to bees identified in tier 1 testing and several semi-field and field tests were undertaken to refine the risk assessment. While these were performed at levels lower than rates being sought in Australia, residue measurements in pollen and nectar were considered sufficient to adequately demonstrate that, subject to appropriate labelling, the risk to pollinators is considered acceptable.

A risk to non-target arthropods was identified in the field of application, particularly for the parasitic wasp immediately following application. The risk decreases with time following the application. Off field, at 3 m, the only risk still identified is to the parasitic wasp immediately following application. This is addressed through an integrated pest management (IPM) system warning statement on the label.

7.5 Conclusions

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 under Section 14(1)(C) of the Agricultural and Veterinary Chemicals Code Act 1994 and the label also contains adequate instructions with respect to the environment.

8 EFFICACY AND SAFETY ASSESSMENT

The results of four field trials are presented testing the efficacy and crop safety of ISK Cyclaniliprole 50 SL for the control of codling moth in two varieties of apples at three different locations in Australia. The trials tested efficacy compared to untreated controls and compared to a range of currently registered commercial standard treatments.

The trials were appropriately designed as efficacy/crop safety trials, were statistically sound and subject to proper statistical analysis (analysis of variance). The trials were all conducted in actual orchard situations subjected to a range of codling moth pressures. The locations of the trial represented three distinct apple production areas in Australia (Tasmania, South Australia, and Queensland), and were typical of the environment in which the product would be used. Formulations, rates, and application timings were representative of label directions, and the trials included comparative treatments with registered commercial standard treatments.

8.1 Proposed product use pattern

The proposed use of ISK Cyclaniliprole 50 SL is for the control of codling moth on apples. More details on the proposed use are provided in Section 1.

8.2 Summary of evaluation of efficacy and crop (OR target animal) safety

Efficacy

All data were statistically analysed (analysis of variance) with LSD values generated at a significance level of 5%. Each of the four field trials demonstrated levels of efficacy in controlling levels of codling moth damage ranging from 60% to 100% across three different apple production locations in Australia and across two varieties. In all cases efficacy was equivalent to currently registered standard chemical treatments.

Crop (or Target animal) safety

The trials showed there was no crop phytotoxicity detected.

8.3 Conclusions

The data indicates efficacy and crop safety of ISK Cyclaniliprole 50 SL for the control of codling moth damage in apple trees.

9 LABELLING REQUIREMENTS

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

ISK CYCLANILIPROLE™ 50 SL INSECTICIDE

ACTIVE CONSTITUENT: 50 g/L CYCLANILIPROLE

GROUP	28	INSECTICIDE

For the control of insect pests in apples, as per the Directions for Use

CONTENTS: (1 L – 20 L)

ISK Biosciences Oceania Pty Ltd
Level 61, Governor Phillip Tower
1 Farrer Place, Sydney NSW 2000
Phone: *to be included*

RESTRAINTS

DO NOT apply by aircraft.
DO NOT apply if heavy rains or storms that are likely to cause runoff are forecast within 3 days.
DO NOT irrigate to the point of runoff for at least 3 days after application.
DO NOT apply more than 1.6 L product per hectare at a time.

SPRAY DRIFT RESTRAINTS

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

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

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

DO NOT apply with spray droplets smaller than a MEDIUM spray droplet size category according to nozzle manufactures specifications that refer to the ASAE S572 Standard or the BCPC Guideline.

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

DO NOT apply if there are aquatic and wetland areas including aquacultural ponds, surface streams and rivers within 30 metres downwind from the application area.

DO NOT apply when there are livestock, pasture or any land that is producing feed for livestock downwind from the application area and within the mandatory no-spray zone shown in the table below.

FOR GROUND APPLICATION	
Wind Speed Range at Time of Application	**Downwind No-Spray Zone**
3 to 20 kilometres per hour	20 metres

DIRECTIONS FOR USE

Crop	Pest	Rate	WHP	Critical Comments
Apples	Codling moth *(Cydia pomonella)*	**Dillute Spray: 60–80 ml/100 L water** **Concentrate spray:** Refer to Application, Apples section	28 days	Thorough coverage is essential to achieve best results. Select a spray volume appropriate for the size of trees and density of foliage. For best results apply 1500–2000 litres of water per hectare. **Codling Moth** Use the high rate of 80 ml/100 L for heavy infestations, and the low rate of 60 ml/100 L for mild infestations. Make first application just prior to or at the beginning of egg hatch. Applications typically provide 10–14 days of protection. Use pheromone trap catches and local degree day based spray timing advisories to determine the development of each codling moth generation. For effective resistance management make applications of ISK CYCLANILIPROLE 50 SL in one codling moth generation before rotating to an insecticide with a different mode of action (Non- Group 28) in the next generation. Make no more than 2 applications/crop with a 10 day minimum interval between treatments.

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

WITHHOLDING PERIODS:

HARVEST WITHHOLDING PERIOD:

Apples: DO NOT HARVEST FOR 28 DAYS AFTER APPLICATION

GRAZING WITHHOLDING PERIOD:

DO NOT allow livestock to graze treated orchards or cut for stock food.

GENERAL INSTRUCTIONS

Insecticide Resistance Warning

GROUP	28	INSECTICIDE

For insecticide resistance management, ISK Cyclaniliprole 50 SL Insecticide is a Group 28 insecticide. Some naturally occurring insect biotypes resistant to ISK Cyclaniliprole 50 SL Insecticide and other Group 28 insecticides may exist through normal genetic variability in any insect population. The resistant individuals can eventually dominate the insect population if ISK Cyclaniliprole 50 SL Insecticide and other Group 28 insecticides are used repeatedly. The effectiveness of ISK Cyclaniliprole 50 SL Insecticide on resistant individuals could be significantly reduced. Since occurrence of resistant individuals is difficult to detect prior to use, ISK Biosciences Oceania Pty Ltd accepts no liability for any losses that may result from the failure of ISK Cyclaniliprole 50 SL Insecticide to control resistant insects. ISK Cyclaniliprole 50 SL Insecticide may be subject to specific resistance management strategies. For further information contact your local supplier, ISK Biosciences Oceania Pty Ltd representative or local agricultural department agronomist.

Integrated Pest Management

Toxic to beneficial arthropods. In-crop residues are expected to be safe for beneficial arthropods 56 days after the last application. Minimise spray drift to reduce harmful effects on beneficial arthropods in non-crop areas.

Export of treated produce

Growers should note that suitable MRLs or import tolerances do not exist in all markets for produce treated with ISK Cyclaniliprole 50 SL Insecticide. 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 ISK Biosciences Oceania Pty Ltd or your industry body for the latest information on any potential trade issues and their management before using ISK Cyclaniliprole 50 SL Insecticide.

Mixing

Add the required amount of ISK Cyclaniliprole 50 SL Insecticide to clean water in half filled spray tank with the agitator or by-pass in operation. Maintain agitation while filling tank with remainder of water. Agitation must also be maintained throughout the spray operation.

Application:

To be effective ISK Cyclaniliprole 50 SL Insecticide requires thorough spray coverage. Ensure that equipment is properly calibrated to give an even distribution at the correct volume. Thorough coverage of the target area is essential. Apply in sufficient water, and using suitable application parameters (nozzles, pressure, boom height, speed, etc) to ensure thorough and even coverage. Use only MEDIUM spray droplets according to ASAE S572 definition for standard nozzles. Adjust water volumes according to the crop growth stage.

Apples: The same quantity of ISK Cyclaniliprole 50 SL Insecticide per hectare should be used when spraying by either the dilute or concentrate method.

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 run-off. 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 ISK Cyclaniliprole 50 SL Insecticide 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 set up and operation may also need to be changed, as the crop grows.

Concentrate spraying: Use a sprayer designed and set up for concentrate spraying (that is a sprayer which applies water volumes less than those required to reach the point of runoff) and matched to the crop being sprayed. Apply a minimum of 500 L water/ha. 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

1. Dilute spray volume as determined above: for example 1000 L/ha

2. Your chosen concentrate spray volume: for example 500 L/ha

3. The concentrate factor in this example is 2X (ie 1000 L ÷ 500 L = 2)

4. If the dilute label rate is 14 g/100 L, then the concentrate rate becomes 2 x 14, which is 28 g/100 L of concentrate spray.

The chosen spray volume, amount of product per 100 L of water, and the sprayer set up and operation may need to be changed as the crop grows. For further information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow industry Best Practices.

Compatibility

For information on the compatibility of ISK Cyclaniliprole 50 SL Insecticide with other products, contact your local ISK Biosciences Oceania Pty Ltd representative.

PROTECTION OF LIVESTOCK

DO NOT graze or feed treated crops to animals.

PROTECTION OF HANEY BEES AND OTHER INSECT POLLINATORS

Toxic to bees. DO NOT apply when the crop is in bloom. DO NOT spray while bees are actively foraging. DO NOT allow spray drift to flowering weeds or flowering crops in the vicinity of the treatment area. Before spraying, notify beekeepers to move hives to a safe location with an untreated source of nectar and pollen, if there is potential for managed hive to be exposed to the spray or spray drift.

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 spaying 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-rinse 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

May irritate the eyes. Avoid contact with eyes. Wash hands after use.

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.

CONDITIONS OF SALE

ISK Biosciences Oceania Pty Ltd accepts responsibility for the consistent quality of the product; however since the use and application of the product is beyond control, the company accepts 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: 68689/62436

Bar code, label code
to be inserted

BN DOM

ABBREVIATIONS

ac	active constituent
ACCS	Advisory Committee on Chemicals Scheduling
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ANSES	French Agency for Food, Environment and Occupational Health and Safety
ARfD	Acute Reference Dose
AUC	Area Under Curve
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft – German Federal Biological Research Centre for Agriculture and Forestry
BBCH	Biologische **B**undesanstalt, **B**undessortenamt und **CH**emische Industrie – scale used for identifying phenological stages of plants
BCF	Bio-Concentration Factor
bw	bodyweight
^{o}C	Degrees Celsius
CEC	Cation Exchange Capacity
CHO	Chinese Hamster Ovary
CIPAC	Collaborative International Pesticides Analytical Council
Codex	Codex Alimentarius Commission
Codex CXLs	Codex Maximum Residue Limits
COEX	Co-extruded (packaging material)
COEX E-VAL	COEX material using EVOH Ethylene vinyl alcohol) resin under trade name EVAL
COEX PA	COEX material using polyamide
CRD	United Kingdom Chemicals Regulation D .irectorate
CT	product Concentration multiplied by Time
d	day
DAA	Days After Application

DAT	Days After Treatment
DNA	Deoxyribonucleic acid
DofE	Department of Environment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC	Emulsifiable Concentrate
EC	European Commission
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
Eq	equivalent
ESI	Export Slaughter Interval
EUP	End Use Product
Fo	original parent generation
F_1	first generation offspring
FRAC	Fungicide Resistance Action Committee
FSANZ	Food Standards Australia and New Zealand
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GJR	Global Joint Review
GLP	Good Laboratory Practice
GPMT	Guinea Pig Maximisation Test
GVP	Good Veterinary Practice

h	hour
ha	hectare
Hb	haemoglobin
Hct	Heamatocrit
HDPE	High Density Polyethylene
HEEG	Human Exposure Expert Group
Hg	Haemoglobin
Hg	Mercury
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HR	Highest Residue
HSIS	Hazardous Substances Information System
id	intradermal
Idf	food ingestion rate (dry weight) in grams per day
ID_{50}	dose that infects50% of the target population of organisms
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
IRM	Integrated Resistance Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
JMPR	Joint Meetings on Pesticide Residues
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
K_{ow}	Octanol-water partition coefficient
Kt	kilotonne
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
LOEL	Lowest Observable Effect Level
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
mN	milliNewton
MoA	Mode of Action
MoE	Margin of Exposure
mPa	milliPascal
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
ND	Not Detectable
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
Nm	nanonmetre
NOEC/NOEL	No Observable Effect Concentration Level
NOER	No Observable Effect Rate
OC	Organic Carbon
OD	Oil Dispersion (oil-based suspension concentrate)
OECD	Organisation of Economic Cooperation and Development
OGTR	Office of the Gene Technology Regulator

OM	Organic Matter
Pa	Pascals
PCV	Pack Cell Volume
PE	PolyEthylene
PEC	Predicted Environmental Concentration
PE/EVOH	Polyethylene with ethylene vinyl alcohol
PET	Polyethylene terephthalate
PHI	Post-Harvest Interval
pKa	Dissociation constant (acid)
PMRA	Pest Management regulatory Agency (Canada)
PNEC	Predicted No Effect Concentration
po	oral
PP	PolyPropylene
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
RCP	Restricted Chemical Product
RNA	Ribonucleic acid
s	second
sc	subcutaneous
SC	Suspension Concentrate
SCBA	Self-Contained Breathing Apparatus
SE	SuspoEmulsion
SG	Soluble granule
SFO	Single first order

STMR	Supervised Trials Median Residue
STMR-P	STMR corrected for processing
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SWA	Safe Work Australia
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T_{max}	Time to achieve maximum concentration
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
$T_{1/2}$	Elimination half-life
UDS	Unscheduled DNA Synthesis
µg	microgram
US EPA	United States Environmental Protection Agency
UV	Ultra Violet light
vmd	volume median diameter
WBC	White Blood Count
WG	Water Dispersible Granule
WHP	Withholding Period
w/v	Weight/volume

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	repels water
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Total Radioactive Residue (TRR)	The total amount of ^{14}C-labelled active constituent and its metabolites detected in residue studies
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

US EPA (1998). United States Environmental Protection Agency (US EPA). *The Pesticide Handlers Exposure Database (PHED), version 1.1-PHED Surrogate Exposure Guide, Estimates of Worker Exposure.* US EPA, Washington DC, United States, 1998.