Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active Constituent **Cyantraniliprole**

in the Product **DuPont Exirel Insecticide**

APVMA Product Number 64103

OCTOBER 2013

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PREFACE

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

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

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

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

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

About this document

This is a Public Release Summary.

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

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

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

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of **DuPont Exirel 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 **5 November 2013** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

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

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

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

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

Phone: + 62 2 6210 4748

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

Fax: + 62 2 6210 4776
Email: pesticides@apvma.gov.au

Further information

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

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

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

1 INTRODUCTION

Applicant

DuPont (Australia) Limited

Details of Product

It is proposed to register DuPont Exirel Insecticide, a suspoemulsion (SE) formulation containing 100 g/L cyantraniliprole. DuPont Exirel Insecticide is intended for use in cotton to control certain sucking and chewing insects– silverleaf whitefly, cotton aphid, cotton bollworm and native budworm.

It is proposed that the product be applied at a rate of 600 mL/ha with a maximum of two applications to be applied to any one crop per season.

Cyantraniliprole is an anthranilic diamide insecticide compound structurally related to chlorantraniliprole, and similar in mode of action to flubendiamide. The insecticidal mode of action involves unregulated activation of ryanodine receptor channels, leading to internal calcium store depletion that impairs regulation of muscle contraction. This results in lethargy and muscle paralysis in insects, leading to eventual death.
The insecticide enters larvae primarily by ingestion, but also by contact. The product also shows ovicidal, ovi-larvicidal and adulticide efficacy, depending upon the pest species. Exposure of the pest species typically results in rapid feeding cessation within a few hours of exposure, however the time to death may take 3 to 6 days, depending upon the species.

Cyantraniliprole is currently being considered for registration in the USA, Canada, and European Union for the control of sucking and chewing pests on cotton, oilseeds, fruit crops, tree nuts, vegetable crops and turf.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of DuPont Exirel Insecticide, and approval of the new active constituent cyantraniliprole.

This submission has been assessed under a global joint review (GJR) arrangement where registrations for the same formulation and uses have been submitted concurrently in Australia, Canada, France, UK, and the USA.

2 CHEMISTRY AND MANUFACTURE

2.1 Active Constituent

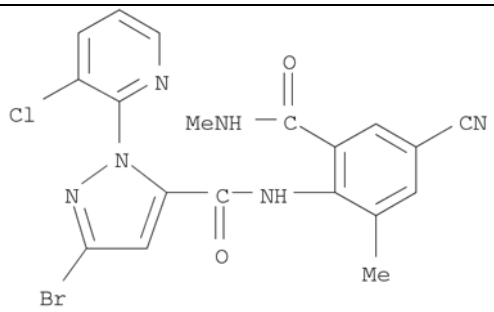
The active constituent cyantraniliprole is an insecticide which activates insect ryanodine receptors which results in depletion of intracellular calcium stores followed by muscle paralysis and death.

Manufacturing Site

The active constituent cyantraniliprole is manufactured by E I DuPont de Nemours & Co., Inc., DuPont Electronic Products, 1515 Nichols Road, Dayton, OH 45418-2712

Chemical Characteristics of the Active Constituent

Cyantraniliprole belongs to the anthranilic diamide family of compounds and has the following characteristics:

COMMON NAME:	Cyantraniliprole (ISO, AS approved)
IUPAC NAME:	3-bromo-1-(3-chloro-2-pyridyl)-4'-cyano-2'-methyl-6'-(methylcarbamoyl)pyrazole-5-carboxanilide
CAS NAME:	3-bromo-1-(3-chloro-2-pyridinyl)-N-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1H-pyrazole-5-carboxamide
CAS REGISTRY NUMBER:	736994-63-1
MANUFACTURER'S CODES:	DPX-HGW86
MINIMUM PURITY:	930 g/kg
MOLECULAR FORMULA:	$C_{19}H_{14}BrClN_6O_2$
MOLECULAR WEIGHT:	473.7
STRUCTURE:	
CHEMICAL FAMILY:	Anthranilic diamide
MODE OF ACTION:	Activates insect ryanodine receptors which results in depletion of intracellular calcium stores followed by muscle paralysis and death.

Physical and Chemical Properties of Active Constituent

PHYSICAL STATE	Solid	
ODOUR	No characteristic odour	
COLOUR	Off-white powder	
MELTING POINT	217-219 °C	
BOILING POINT	Not observed (melt at 224 °C and then decomposed at 350 °C) for purified active 98.4% w/w	
DENSITY (20^0C)	1.3835 g/cm^3	
pH at 21°C	5.61, 1% suspension in distilled water	
SOLUBILITY IN WATER (AT 20°C FOR 98.4% PURE ACTIVE)	14.24 mg/L (in pH4: 17.43, pH7: 12.33 and pH9: 5.94 mg/L) at pH 9, hydrolysis occurs.	
SOLUBILITY IN VARIOUS SOLVENTS (AT 20°C FOR THE TECHNICAL GRADE ACTIVE-97.0 % PURE AC)	**Solvent**	**g/L**
	Acetone:	6.54 g/L
	Ethyl acetate:	1.96 g/L
	Dichloromethane:	5.05 g/L
	Toluene:	0.576 g/L
	n-Octanol:	0.79 g/L
	Methanol:	4.73 g/L
	O-Xylene:	0.29 g/L
	Hexane	67 µg/L
VAPOUR PRESSURE (FOR 98.4% PURE ACTIVE)	5.133×10^{-15} Pa at 20°C 1.787×10^{-14} Pa at 25°C	
HENRY'S LAW CONSTANT (AT 20 °C FOR 98.4% PURE ACTIVE)	1.7×10^{-13} Pa/m^3/mol	
N-OCTANOL/WATER PARTITION COEFFICIENT	log K_{ow}, 1.94 (not pH dependent)	
DISSOCIATION CONSTANT (PKA)	8.80	
FLAMMABILITY	Not flammable	
AUTO- FLAMMABILITY	No self-ignition	
EXPLOSIVE PROPERTIES	Not explosive	
OXIDISING PROPERTIES	Not an oxidizing agent	

APVMA Active Constituent Standard for Cyantraniliprole Active Constituent

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

CONSTITUENT	SPECIFICATION	LEVEL
Cyantraniliprole	Cyantraniliprole	Not less than 930 g/kg

Based on a review of the data provided by the applicant, the APVMA is satisfied that the chemistry and manufacturing details of cyantraniliprole are acceptable.

2.2 Product

Physical and Chemical Properties of the Product

DISTINGUISHING NAME	DuPont Exirel Insecticide
FORMULATION TYPE:	Suspoemulsion (SE)
APPEARANCE	Liquid with off white colour
ACTIVE CONSTITUENT CONCENTRATION:	100 g/L Cyantraniliprole
BULK DENSITY at 22^{0}C:	0.982 g/cm^3
SURFACE TENSION at 22^{0}C:	25.9 mN/m
pH	5.6 at 1% aqueous dilution
PERSISTENT FOAM	0 mL after 12 min at max use rate of 0.4 % w/v
EXPLOSIVE PROPERTIES	Not explosive
OXIDISING PROPERTIES	No oxidising properties
FLAMMABILITY	Not flammable
CORROSIVE HAZARD	Not corrosive
PACK SIZES	1-10 L
PACKAGING MATERIAL	High density polyethylene (HDPE), Polyethylene/ethylene-vinyl alcohol (PE/EVOH), Polyethylene terephthalate (PET)
PRODUCT STABILITY	The formulated product is expected to be stable for at least two years when stored under normal conditions in the proposed commercial packaging.

Based on a review of the data provided by the applicant, the APVMA is satisfied that the chemistry and manufacturing details of Dupont Exirel Insecticide are acceptable.

3 TOXICOLOGICAL ASSESSMENT

The toxicological database for cyantraniliprole, which consists primarily of toxicity studies conducted in rats, mice and dogs, is extensive and considered sufficient to determine the toxicological profile of cyantraniliprole and characterise the risk to humans. In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Adverse-Effect-Level (NOAEL) 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.

The toxicology assessment of cyantraniliprole was conducted as part of a Global Joint Review (GJR) by scientists from the United States Environmental Protection Agency (US EPA), Health Canada Pest Management Regulatory Agency (PMRA), the United Kingdom Chemicals Regulation Directorate (CRD), the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) and the Office of Chemical Safety (OCS) within the Department of Health and Ageing. The US EPA was the primary reviewer for the toxicology studies, with all other GJR partners as secondary reviewers. Since the assessment report relies significantly on international assessment collaboration between the agency partners, the OCS has adopted the no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) approach with scientific justification for the adoption of these NOAEL/LOAEL positions.

Chemical Class

Cyantraniliprole is an anthranilic diamide insecticide compound structurally related to chlorantraniliprole, and similar in mode of action to flubendiamide. The insecticidal mode of action involves unregulated activation of ryanodine receptor channels, leading to internal calcium store depletion that impairs regulation of muscle contraction. This results in lethargy and muscle paralysis in insects, leading to eventual death.

3.1 Toxicokinetics and Metabolism

The absorption of cyantraniliprole after single low-dose oral administration was moderately high, with 62.6–80.4 % of material absorbed after low dose (10 mg/kg bw) administration. High dose (150 mg/kg bw) oral administration resulted in a lower overall absorption (31.4–40 %). Absorbed cyantraniliprole was distributed widely through the body and eliminated rapidly, with very low levels (< 1 %) of administered dose left in individual tissues at 7 days after dosing. Elimination of cyantraniliprole was approximately equivalent by the urinary and biliary routes. A slight sex difference in the absorption/elimination profile was noted, with female animals retaining slightly higher levels of radiolabel (reflected in longer $T_{1/2,}$ C_{max} and AUC values) compared with male animals.

Metabolism of cyantraniliprole was extensive, consisting of hydroxylation, N-dealkylation, oxidation and conjugation processes. No sex- or dose-related difference in metabolism was observed, and the metabolic profile from the ^{14}C-cyano- or ^{14}C-pyrazol-carbonyl-labelled experiments were similar. No evidence of bioaccumulation or persistence was observed, with tissue half-lives and tissue:plasma ratios in the repeat low-dose study (10 mg/kg bw, 14 days) indicating little tissue accumulation.

The dermal absorption of cyantraniliprole formulation was low, with an estimated human *in vivo* absorption of 0.2–0.8 % for concentrations between 1–100 g/L cyantraniliprole.

Acute Studies

Cyantraniliprole is of low acute toxicity by the oral route in rats (LD_{50} > 5000 mg/kg bw) and mice (LD_{50} > 5000 mg/kg bw), and by the dermal (LD_{50} > 5000 mg/kg bw) and inhalation (4-hr LC_{50} > 5200 mg/m^3) routes of exposure in rats. Cyantraniliprole is not a skin irritant in rabbits but is a slight eye irritant in the same species. Cyantraniliprole is not a dermal sensitiser in a LLNA study in mice. Additionally, while conflicting results were seen in two skin sensitisation studies (the maximisation test) in guinea pigs, these were seen using a test sample produced by an abandoned synthesis process (i.e. not the synthesis process to be used to produce the registered technical grade active constituent).

DuPont Exirel Insecticide (a suspo-emulsion formulation containing 100 g/L cyantraniliprole) is a low acute oral toxicant (LD_{50} > 5000 mg/kg bw) in the rat and mouse, a low acute dermal toxicant in the rat (LD_{50} > 5000 mg/kg bw) and a low acute inhalational toxicant in the rat (4-hour LC_{50} > 2400 mg/m^3). It is a moderate skin irritant in the rabbit, a slight eye irritant in the same species and a dermal sensitiser in the guinea pig Buehler assay.

Systemic Effects

Cyantraniliprole is generally of a low order of toxicity in all tested species in short term studies. Dogs were slightly more sensitive than rats to cyantraniliprole-mediated toxicity (particularly liver-related effects), with clear treatment-related and toxicologically significant effects occurring at lower dose levels (e.g. ~32 mg/kg bw/day in dogs vs 85 mg/kg bw/day in rats in 90-day studies). Mice were less sensitive than other tested species. The major systemic effects observed in repeat-dose toxicity studies consisted of alterations in the liver (increased weights, metabolic enzyme induction, hypertrophy), thyroid (follicular hypertrophy/hyperplasia, thyroid weights, effects on hormone homeostatis) and adrenal glands (vesiculation, rodents only).

Supplementary investigations on hepatic enzyme induction conducted in parallel with short-term and sub-chronic toxicity studies indicated that liver effects (hypertrophy, increased liver weights) observed in rodents were associated with increases in hepatic cytochrome P450 content and liver enzyme activity, and considered adaptive effects. Evidence of toxicologically significant histopathological findings in the liver (focal necrosis, vacuolation and other cellular alterations) were observed at higher dose levels only in rodents. However, in dogs, toxicologically significant findings, including clinical chemistry alterations and histopathological effects (e.g. hepatocellular degeneration) occurred with increasing length of study, with lower NOAEL/LOAELs reported in the 1-year dog study compared with the 90-day dog study.

In mechanistic studies, thyroid effects (hypertrophy/hyperplasia) were considered to be linked to increases in hepatic cytochrome P450 and UDPGT activity, leading to decreased plasma T4 hormone levels, and altering thyroid hormone homeostasis, including increases in thyroid stimulating hormone (TSH) levels. The increased TSH levels were considered to stimulate the thyroid, resulting in the observed hypertrophy/hyperplasia. Though OCS notes that no evidence of thyroid hypertrophy, hyperplasia or tumour formation was observed in long-term studies in rodents at dose levels close to the limit dose (700–1160 mg/kg bw/day), suggesting that the thyroid effects observed in short-term and sub-chronic duration studies are likely adaptive in this case and unlikely to be toxicologically significant.

Limited findings in the adrenal cortex (minor microvesiculation) were observed in rodent studies, but not in dogs. However, in the 90-day adrenal mechanistic study conducted in CD-1 mice, this finding could not be replicated, and detailed examination of adrenal tissues did not reveal treatment-related effects at the limit dose of 1120 mg/kg bw/day and basal urinary corticosterone levels were comparable between the control and treated groups. In the parallel mechanistic study in SD rats, limited incidence (4/10) of microvesicualtion was observed in males administered the limit dose of 1230 mg/kg bw/day, but no evidence of cytotoxicity or degeneration in adrenal tissue was observed, and furthermore no change was observed in corticosterone levels (basal or ACTH-stimulated). Overall, it is unlikely that the adrenal findings observed with cyantraniliprole administration at such high dose levels were toxicologically significant.

No treatment-related effects were observed in rats upon short-term dermal administration of cyantraniliprole at up to the limit dose of 1000 mg/kg bw/d, and upon inhalational administration at up to 100 mg/m^3 in rats the top exposure concentration chosen due to poor solubility in water and concerns for *'particle overload'* in the lung at higher dose levels and achieving a MMAD ≤ 3m.

Carcinogenicity

Cyantraniliprole administration did not result in an increase in tumour formation in long-term repeat-dose oral toxicity studies in rats and mice.

Genotoxicity

Cyantraniliprole was not mutagenic or genotoxic in a conventional suite of *in vitro* studies with and without metabolic activation, or genotoxic in an *in vivo* bone marrow micronucleus assay in mice by the oral route.

Reproductive and Developmental Toxicity

There were no indications in rats of any effects on fertility after multi-generational exposure to cyantraniliprole. Parental effects reported revolved around dose-related thyroid changes (increased weights, follicular cell hypertrophy/hyperplasia). Offspring toxicity was only detected at dose levels considered maternotoxic in both the two-generation reproduction study and developmental toxicity studies. No evidence of teratogenicity was observed in developmental studies in the rat and the rabbit.

Neurotoxicity

Cyantraniliprole was not neurotoxic in acute and 13-week sub-chronic neurotoxicity studies in the rat.

Immunotoxicity

Cyantraniliprole was not immunotoxic in rodents at the limit doses tested.

Toxicological Studies on Metabolites

Acute toxicity, repeat-dose toxicity and/or genotoxicity studies on cyantraniliprole metabolites IN-JSE76, IN-PLT97, IN-F6L99 and IN-N5M09 indicated that the compounds were of low toxicity and not an *in vitro* mutagen and/or genotoxin and, thus, unlikely to be toxicologically significant when considered in the context of the cyantraniliprole hazard profile.

3.2 Public Health Standards

Poisons Scheduling

On the 6 February 2013, the delegate to the Secretary to the Department of Health and Ageing made a delegate only decision on cyantraniliprole that is 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 ADI for humans is the level of intake of an agricultural or veterinary chemical that 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 cyantraniliprole included several long-term oral toxicity studies and carcinogenicity studies in rodent and non-rodent species (dog), and was considered complete. The critical toxicological effect associated with cyantraniliprole administration in chronic toxicity studies is liver toxicity (clinical chemistry changes and increased organ weight) observed in a 1-year dog study at 6 mg/kg bw/day, with a NOAEL of 1 mg/kg bw/day. The default 100-fold safety factor, consisting of factors of 10 for potential intraspecies and interspecies variation, was considered appropriate in this instance.

Therefore, an ADI of 0.01 mg/kg bw/day was established, based on a NOAEL of 1 mg/kg bw/d in a 1-year oral study in beagle dogs, using a default 100-fold safety factor.

Acute Reference Dose

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 acute reference dose (ARfD) was not established for cyantraniliprole, as cyantraniliprole is of low acute toxicity, and did not demonstrate evidence of a genotoxic, neurotoxic, or reproductive/developmental toxicity potential after a single dose.

4 RESIDUES ASSESSMENT

DuPont Exirel Insecticide contains the new active constituent cyantraniliprole (figure 1) and is proposed for use to control various insect pests in cotton. As part of the residues assessment of cyantraniliprole, plant and animal metabolism studies, supervised residues trials and trade aspects were considered.

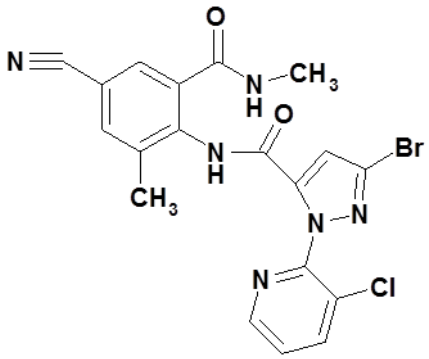


Figure 1: Cyantraniliprole (DPX-HGW86)

4.1 Metabolism

Plants

The metabolism of cyantraniliprole was investigated in rice, lettuce, cotton and tomato.

Rice

The uptake and metabolic fate of [^{14}C]-cyantraniliprole was investigated in rice after either foliar or soil applications. Two types of radiolabelled cyantraniliprole molecules were used during the study: [Cyano-^{14}C]-cyantraniliprole and [Pyrazole carbonyl-^{14}C]-cyantraniliprole. The formulated product used for foliar applications contained a mix of both these substances (with a ratio of 1:1 regarding specific activity) as active ingredients. Each formulated product used for soil applications contained either [Cyano-^{14}C]-cyantraniliprole or [Pyrazole carbonyl-^{14}C]-cyantraniliprole as active ingredient.

Three 150 g ai/ha applications were made to rice *via* foliar spray. They were made to plants at the 3–4 leaf stage and at 7 and 14 days after the initial application (BBCH 13–14 at each application). Alternatively, one 300 g ai/ha application of each radiolabel was made to rice *via* soil application at the 3–4 leaf stage (BBCH 13). Two days after the first application the crates from each treatment regime were flooded to a depth of ca. 3 cm and flooded conditions maintained until 2–3 days before final harvest.

The metabolism of cyantraniliprole in rice was similar after foliar and soil applications with highest TRRs observed following foliar treatment. The TRR in straw after foliar treatment was 0.45 mg equiv./kg compared to 0.28-0.30 mg equiv./kg following soil application. Cyantraniliprole was the major component of the residue in straw and grain, accounting for ≤44.9% (≤0.12 mg/kg) and ≤62.7% (≤0.014 mg/kg) respectively. In grain,

no metabolite was quantified above 0.01 mg equiv./kg and individual unextracted or unidentified residues were ≤0.01 mg equiv./kg.

Lettuce

The uptake and metabolic fate of [^{14}C]-cyantraniliprole was investigated in lettuce after either foliar or soil applications. The product used for foliar application contained a mix of [Cyano-^{14}C]-cyantraniliprole and [Pyrazole carbonyl-^{14}C]-cyantraniliprole (with a ratio of 1.35:1.00 regarding activity). The products used for soil application contained either [Cyano-^{14}C]-cyantraniliprole or [Pyrazole carbonyl-^{14}C]-cyantraniliprole.

Three 150 g ai/ha applications were made to lettuce *via* foliar or soil drench application. Foliar applications were made to plants 3 weeks post-emergence and at 7 and 14 days after the initial application. Soil drench applications were made 7 weeks post-emergence and at 7 and 14 days after the first application.

Uptake of soil-applied cyantraniliprole radioactive residues into lettuce was low. At maturity TRRs were 0.01 and 0.06 mg equiv./kg in [CN-^{14}C]-cyantraniliprole and [PC-^{14}C]-cyantraniliprole treated samples, respectively. Cyantraniliprole residues declined rapidly following foliar application. Higher residues detected immediately after each foliar application (7.79–10.84 mg equiv./kg) declined to 0.03 mg equiv./kg at maturity.

The metabolism of cyantraniliprole in lettuce was similar following foliar and soil drench applications. The principal component in mature lettuce was cyantraniliprole (37.1–69.0% TRR).

Cotton

The uptake and metabolic fate of [^{14}C]-cyantraniliprole was investigated in cotton after either foliar or soil applications. The product used for foliar application contained a mix of [Cyano-^{14}C]-cyantraniliprole and [Pyrazole carbonyl-^{14}C]-cyantraniliprole (with a ratio of 1:1 regarding activity). The products used for soil application contained either [Cyano-^{14}C]-cyantraniliprole or [Pyrazole carbonyl-^{14}C]-cyantraniliprole.

Three 150 g ai/ha applications were made to cotton *via* foliar or soil drench application. Foliar applications were made to plants 3 weeks post-emergence and at 7 and 14 days after the initial application (BBCH 16, 18 and 19). Soil drench applications were made 7 weeks post-emergence and at 7 and 14 days after the first application (BBCH 19 to 51).

Total residues in undelinted seed and lint were low (<0.01 mg equiv./kg) as were TRRs in immature leaves following soil drench treatment. TRRs in cotton gin by-products were 0.02-0.13 mg equiv./kg with highest residues observed following foliar treatment.

Cyantraniliprole was the principal residue in immature leaves following foliar treatment (19.7-70.7% TRR, 0.12–1.89 mg equiv./kg) and in cotton gin by-products following both treatment regimes (25.6-46.8% TRR, 0.01–0.04 mg/kg).

Tomato

The uptake and metabolic fate of [^{14}C]-cyantraniliprole was investigated in tomato after either foliar or soil applications. The product used for foliar application contained a mix of [Cyano-^{14}C]-cyantraniliprole and

[Pyrazole carbonyl-^{14}C]-cyantraniliprole (with a ratio of 1:1 regarding activity). The products used for soil application contained either [Cyano-^{14}C]-cyantraniliprole or [Pyrazole carbonyl-^{14}C]-cyantraniliprole.

Three 150 g ai/ha applications were made to tomatoes *via* foliar or soil drench application. Foliar applications were made to plants 3 weeks post-emergence (BBCH 14–15) and at 7 (BBCH 16) and 14 days (BBCH 53, 61) after the initial application. Soil drench applications were made 7 weeks post-emergence application (BBCH 19, 51) and 7 (BBCH 51) and 14 days (BBCH 55, 61) after the first application.

Total residues in fruit were low (<0.01 mg equiv./kg). The TRRs in leaves following soil drench treatment were also low with cyantraniliprole detected at <0.01 mg equiv./kg. Cyantraniliprole was the principal residue in immature leaves following foliar treatment (0.56–4.15 mg/kg).

Confined Rotational Crops

Two separate studies were provided. In the main study conducted under GLP, the rotational crops included lettuce, red beet, and wheat. A pilot study not conducted under GLP also included soybeans in addition to red beets and wheat as rotational crops.

Pilot study

Spring wheat (*Triticum aestivum*, cv. Katepawa), soybeans (*Glycine Max*, cv. Williams 82), and red beets (*Beta vulgaris*; cv. Detroit) were grown under confined conditions in the greenhouse. Seeds of each crop were sown into pots of Mattapeake soil/sand, mixed in a 1:1 ratio to simulate a sandy loam, 25 and 120 days after a single 300 g ai/ha treatment to soil with [PC-^{14}C]-cyantraniliprole.

Wheat straw

94.6 and 92.4% of TRR was extracted from straw of wheat plants sown 25 and 120 DAT, respectively. Parent was the major residue in straw from both aging periods (45.3–47.9% TRR, 0.359–0.521 mg/kg).

Wheat chaff

87.7 and 106% of TRR was extracted from chaff of wheat plants sown 25 and 120 DAT, respectively. Parent was the major residue in chaff from both aging periods (47.4–61.6% TRR).

Wheat grain

90.5 and 97.6% of TRR was extracted from chaff of wheat plants sown 25 and 120 DAT, respectively. Parent accounted for 9.7–14.6% of the TRR.

Soybean pods

86.4 and 88.6% of TRR was extracted from pods of soya plants sown 25 and 120 DAT, respectively. The major residues in pods sampled from plants grown in soil aged 25 days were IN-JCZ38 (24.1% TRR, 0.023 mg equiv./kg) and cyantraniliprole (14.0% TRR, 0.0132 mg/kg).

Soybean seeds

98.1 and 101% of TRR was extracted from seed of soya plants sown 25 and 120 DAT, respectively. The concentrations of all residues found in soybean seed were less than 0.01 mg equiv./kg for both soil-aging periods.

Soybean foliage

94.1 and 72.5% of TRR was extracted from seed of soya plants sown 25 and 120 DAT, respectively. Cyantraniliprole and IN-MLA84 were the main compounds identified, accounting for more than 10% TRR.

Red beet roots

In red beet roots from 25-day aged soil, four residues exceeded 10% of TRR. Those were cyantraniliprole with 26.8% of TRR (0.006 mg/kg), IN-N7B69 containing 24.8% of TRR (0.005 mg equiv./kg) and its glucoside conjugate 16.3% of TRR (0.003 mg equiv./kg), and IN-J9Z38
(representing 11.5% of TRR (0.002 mg equiv./kg).

For red beets grown in the 120 days aged soil the TRR was less than 0.01 mg equiv./kg.

Red beet foliage

The glucoside of IN-N7B69 was the major residue in foliage from the 25-day aged soil
(49.5% of TRR, 0.053 mg equiv./kg) and from the 120 day aged soil (40.0% of TRR, 0.015 mg equiv./kg).

GLP Study

Spring wheat (*Triticum aestivum* cv Paragon), lettuce (*Lactuca. sativa* cv Green Salad Bowl, a non-hearting cultivar) and red beets (Beta vulgaris cv Detroit Crimson Globe 2109) were grown under confined conditions, in a temperature-controlled glasshouse. One 450 g ai/ha application of compound labelled with 14C at either the carbon of the cyano group or at the pyrazole carbonyl was made to bare soil in separate plots. Seeds of each crop were sown 30 days and 120 days after treatment. After 365 days aging, a further sowing of spring wheat was made into the soil following harvest of the crop sown at 30 days. Lettuce and red beet were not planted at 365 days due to low residues levels being determined at earlier plant-back intervals. RAC samples of forage, hay, straw, and grain of spring wheat; foliage and roots of red beets; and whole lettuce were harvested.

TRRs for crops grown in soil treated with both labels ranged from <0.01 to 0.06 mg equiv./kg for wheat grain, 0.01 to 0.03 mg equiv./kg for red beet roots and 0.02 to 0.11 mg equiv./kg for lettuce. The TRRs in wheat commodities harvested from the 30, 120, and 365 day sowings into soil treated with both labels ranged between 0.09 to 0.31 mg equiv./kg for early forage, 0.31 to 1.62 mg/ equiv.kg for hay, and 0.27 to 0.97 mg equiv./kg for straw. TRRs in red beet foliage sampled from the 30 and 120 day sowings into treated soil ranged from 0.01 to 0.14 mg equiv./kg at all intervals.

Wheat grain

The majority of the extracted radioactivity from grain planted 30 and 365 DAT was identified as cyantraniliprole (≤0.02 mg/kg, 13.6 to 36.3% TRR). The grain extracts from the 120 DAT [^{14}C]-cyantraniliprole treatment contained negligible amounts of radioactivity (0.004 mg equiv./kg and 0.008 mg equiv./kg) and were not investigated further.

Beet roots

The major component detected in extracts of roots from beets sown 30 DAT was cyantraniliprole, comprising 21.0 and 23.8% TRR in [CN-^{14}C]-cyantraniliprole and [PC-^{14}C] cyantraniliprole samples, respectively. The roots extracts from the 120 DAT sowing contained negligible amounts of radioactivity (0.007 mg equiv./kg and 0.009 mg equiv./kg) and were not analysed further.

Lettuce

The majority of the extracted radioactivity from lettuce planted 30 and 120 days after soil treatment was identified as cyantraniliprole (0.01 to 0.08 mg/kg, 39.6 to 69.1% TRR).

Wheat forage

The majority of the extracted radioactivity from wheat forage produced from plants sown 30, 120 days and 365 DAT (CN label only) was identified as cyantraniliprole (0.032 to 0.226 mg/kg, 25.2 to 72.7% TRR). In samples from plants sown 365 DAT (PC-label), one unidentified compound was quantified at 15.8 %TRR and 0.013 mg equiv./kg but was not considered to be of overall significance.

Wheat hay

The majority of the extracted radioactivity from wheat hay produced from plants sown 30, 120 days and 365 DAT was identified as cyantraniliprole (0.155 to 0.848 mg/kg, 29.5 to 53.4 %TRR).

Wheat straw

The majority of the extracted radioactivity from wheat hay produced from plants sown 30, 120 days and 365 DAT was identified as cyantraniliprole (0.062 to 0.437 mg/kg, 22.9 to 44.8 %TRR).

Red beet foliage

Only low levels of the extracted radioactivity could be identified. No individual identified component was above 0.05 mg equiv./kg.

Livestock

The metabolism of cyantraniliprole was investigated in laying hens and lactating goats.

Laying hen

The metabolism of cyantraniliprole in the laying hen was investigated using compound labelled with ^{14}C at either the carbon of the cyano group or at the pyrazole carbonyl. A group of 5 hens per radiolabel were dosed once daily for 14 days with ^{14}C-cyantraniliprole by gelatin capsule at a level of 10 ppm in the feed (dry weight). Two hens served as controls. Eggs were collected twice daily. Excreta were collected once daily. The hens were sacrificed approximately 23 hours after the last dose and samples of abdominal fat, muscle, skin with fat and liver were harvested.

Egg whites

Day 1–14 composite egg whites contained TRRs of 0.26 mg equiv./kg and 0.20 mg equiv./kg for the [CN-^{14}C]-cyantraniliprole and [PC-^{14}C]-cyantraniliprole label hen groups, respectively. Aqueous acetonitrile extracted 99–100% TRR. Parent was the major ^{14}C-residue representing 32–42% TRR (0.08 mg/kg). IN-MLA84 and IN-J9Z38 were principal egg white metabolites representing about 17–29% TRR (0.03-0.08 mg/kg parent equivalents) each for both labels.

Egg yolks

Day 1–14 composite egg yolks contained TRRs of 0.09 mg/kg parent equivalents. Aqueous acetonitrile extracted 79–83% TRR. Parent represented 9–10% TRR (0.01 mg/kg) in each composite. For the [CN-^{14}C]-cyantraniliprole labeled yolks, IN-MLA84 and IN-HGW87 each accounted for 12% TRR (0.01 mg/kg), IN-J9Z38 for 7.4% TRR and IN-MYX98 and IN-NBC94 constituted 5% and 0.9% TRR, respectively. IN-MLA84 and IN-J9Z38 were the principal ^{14}C-residues in the [PC-^{14}C]-composite yolks representing 17% TRR and 13% TRR, respectively.

Liver

TRR of liver from the [CN-^{14}C]-cyantraniliprole label hen group was 0.14 mg/kg parent equivalents while the TRR from the [PC-^{14}C]-cyantraniliprole label hen group was 0.17 mg/kg parent equivalents. Aqueous acetonitrile extracted 17% TRR from the [CN-^{14}C]-cyantraniliprole labeled liver while protease digestion liberated an additional 38% TRR. Aqueous acetonitrile extracted 23% TRR from the [PC-^{14}C]-cyantraniliprole labeled sample while protease digestion liberated an additional 38% TRR. Parent was not found in the aqueous acetonitrile extract nor in the protease digest in either label. IN-JCZ38, IN-K5A78, IN-K5A79, IN-K7H19, IN-MLA84, IN-MYX98 and IN-N7B69 were found as minor metabolites in either the aqueous acetonitrile extract or in the protease digest each representing <4% TRR (<0.01 mg/kg parent equivalents).

Muscle, fat and skin with fat

Extracts of the composite muscle samples, abdominal fat and skin with fat from either label each contained <0.01 mg equiv./kg TRR and were not analyzed further.

Lactating goat

The metabolism of cyantraniliprole in the lactating goat was investigated using compound labelled with ^{14}C at either the carbon of the cyano group or at the pyrazole carbonyl. There was one goat per radiolabel and one concurrent control. The treated goats were dosed once daily for 7 days with ^{14}C-cyantraniliprole by gelatin capsule at a level of 10 ppm in the feed. The range of feed intakes was 1.63–1.69 kg/day for both goats

dosed. Milk was collected twice daily, excreta was collected once daily. The goats were sacrificed approximately 23 hours after the last dose and samples of omental, renal and subcutaneous fat, muscle (loin, hind and fore quarter), liver, bile and GI tract were harvested.

Milk

For the goat dosed with [CN-^{14}C]-cyantraniliprole, TRR on Day 1 was 0.07 mg equiv./kg. Milk TRRs ranged from 0.09 mg equiv./kg on Day 2 to 0.11 mg equiv./kg on Day 7. Acetonitrile extracted 99.3% TRR. The major residue was parent accounting for 40% TRR (0.03 mg/kg). IN-MYX98 was the principal metabolite representing 15.1% TRR (0.01 mg/kg). IN-N7B69 comprised 12% of TRR equivalent to 0.008 mg/kg parent equivalents.

For the goat dosed with [PC-^{14}C]-cyantraniliprole, results were very similar to the goat receiving [CN-^{14}C]-cyantraniliprole. TRR on Day 1 was 0.10 mg equiv./kg. Milk TRRs ranged from 0.10 to 0.18 mg equiv./kg. Acetonitrile extracted 99% of TRR. Parent was the major radiochemical residue representing 50% TRR (0.07 mg/kg). The major metabolite was IN-MYX98, a hydroxylated metabolite, comprising 18% of TRR (0.03 mg/kg).

Liver

For the goat dosed with [CN-^{14}C]-cyantraniliprole, liver contained 0.43 mg equiv./kg TRR. Solvent extraction liberated 54% TRR while protease digestion liberated an additional 27% TRR. Parent was the major residue in liver accounting for 17%TRR (0.07 mg/kg). IN-K5A77 was the principal metabolite at 0.02 mg/kg.

Liver from the goat dosed with [PC-^{14}C]-cyantraniliprole contained 0.50 mg equiv./kg TRR. Extraction with aqueous acetonitrile recovered 60% of TRR. Protease digestion of the extracted liver released an additional 21% TRR. Parent was the major liver component comprising 27%TRR (0.14 mg/kg).

Kidney

For the goat dosed with [CN-^{14}C]-cyantraniliprole, kidney contained 0.14 mg equiv./kg TRR. Solvent extracted 63%TRR. HPLC analysis indicated that parent was the major ^{14}C-residue representing 13% TRR (0.02 mg/kg).

Kidney from the goat dosed with [PC-^{14}C]-cyantraniliprole had TRR of 0.21 mg equiv./kg. Solvent extracted 79% TRR. HPLC analysis showed that parent was the major ^{14}C-residue accounting for 19% TRR (0.04 mg/kg).

Muscle

Muscle from the [CN-^{14}C]-cyantraniliprole dosed goat had TRR of 0.03 mg equiv./kg. Solvent extracted 61% of the residue (0.02 mg/kg). HPLC analysis indicated the only significant residue was parent representing 30%TRR or 0.01 mg/kg.

Muscle from the goat dosed with [PC-^{14}C]-cyantraniliprole contained 0.04 mg equiv./kg TRR. Solvent extracted 81% TRR. The principal ^{14}C-residue was IN-MYX98 accounting for 32.8%TRR (0.01 mg/kg parent equivalents); parent represented 15.3%TRR or 0.01 mg/kg.

Fat

Omental, subcutaneous and renal fat were analyzed separately but reported as a mean in this summary.

For the goat dosed with [CN-^{14}C]-cyantraniliprole, the calculated mean TRR in fat was 0.05 mg equiv./kg. Solvent extraction removed 90%TRR. Parent represented 31%TRR (0.02) mg/kg and was the major ^{14}C-residue. IN-J9Z38 accounted for 26.9% TRR (0.01 mg/kg parent equivalents).

For the goat dosed with [PC-^{14}C]-cyantraniliprole, the calculated mean TRR in fat was 0.12 mg equiv./kg. Solvent extracted 98.3% TRR. Parent was the major radiochemical residue representing 45% TRR or 0.05 mg/kg. IN-J9Z38 represented 24% TRR (0.03 mg/kg parent equivalents).

A summary of the metabolites observed in the plant and animal metabolism studies for cyantraniliprole is given in Figure 2.

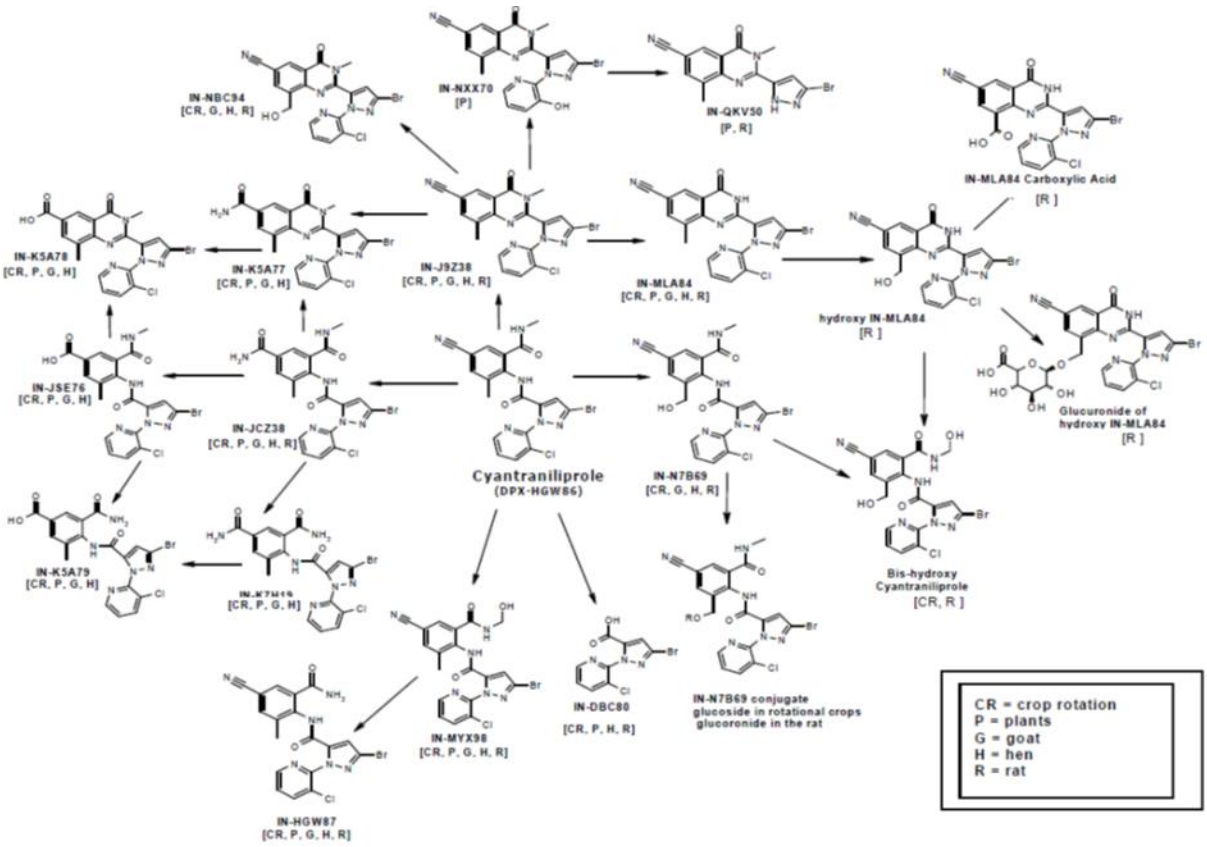


Figure 2: Metabolites observed in plant and animal metabolism studies.

4.2 Analytical methods

Cotton

In the Australian cotton trials provided with the application cotton seed, forage and trash samples were analysed for residues of cyantraniliprole (DPX-HGW86), IN-K7H19, IN-N7B69, IN-JCZ38, IN-MYX98, IN-J9Z38 and IN-MLA84 using analytical method DuPont 15736. The principle of the method involved extraction of specimens with acetonitrile/water. Extracts were centrifuged prior to dilution of the extract for LC/MS/MS analysis. The method LOQ was reported as 0.01 mg/kg for all measured analytes. The method was validated in cotton seed, forage and trash fortified separately with cyantraniliprole and metabolites at 0.01–2.00 mg/kg. The concurrent recoveries from the fortified samples were within acceptable limits as summarised below for parent.

Table 1: Summary of concurrent recoveries of cyantraniliprole from cotton matrices.

Analyte	Matrix	Fortification range	Average recovery	Coefficient of variation
Cyantraniliprole (DPX-HGW86)	Seed	0.01 – 2.0 mg/kg as DPX-HGW86	99.2% (n = 9)	3.5%
	Forage	0.01 – 2.0 mg/kg as DPX-HGW86	95.8% (n = 9)	2.8%
	Trash	0.01 – 2.0 mg/kg as DPX-HGW86	95.3% (n = 9)	3.8%

Animal commodities

In the dairy cattle and poultry transfer studies provided with the application, samples were analysed for cyantraniliprole and metabolites using analytical method 1552. Samples were extracted twice with acetonitrile. An aliquot of the extract is cleaned up by partitioning with hexane. Samples were further purified by a strong anion exchange solid phase extraction step. The final extracts were analysed by liquid chromatography with tandem mass spectrometry employing electrospray ionisation in positive mode.

The LOQ for the method is 0.01 mg/kg for cyantraniliprole and its metabolites (IN-HGW87, IN-J9Z38, IN-JCZ38, IN-K5A79, IN-K7H19, IN-N7B69, IN-MLA84, and IN-MYX98) in milk, eggs, liver, kidney, fat, meat and cream.

4.3 Residue definition

Commodities of plant origin

The parent compound, cyantraniliprole occurs as the major residue in all analysed commodities of plant origin (Primary and rotational crops). The following compounds have been identified in addition to parent:

IN-JCZ38, IN-J9Z38, IN-K7H19, IN-MLA84, IN-MYX98, IN-N7B69, IN-QKV54, IN-HGW87, IN-JSE76, IN-DBC80, IN-K5A77, IN-K5A78, IN-K5A79 and IN-NXX70.

The recommended definition for cyantraniliprole on commodities of plant origin is parent only both for risk assessment and compliance with MRLs.

Commodities of animal origin

The parent compound, cyantraniliprole occurred at significant levels in all matrices in the lactating goat and laying hen metabolism studies. A residue definition of parent is appropriate for commodities of animal origin for compliance with MRLs.

In the lactating goat and laying hen metabolism studies, the following compounds have been identified in addition to parent:

IN-JCZ38, IN-J9Z38, IN-K7H19, IN-MLA84, IN-MYX98, IN-N7B69, IN-HGW87, IN-JSE76, IN-DBC80, IN-NBC94, IN-K5A77, IN-K5A78 and IN-K5A79.

IN-J9Z38 was detected at up to 26.9% of the TRR (up to 0.029 mg/kg) in fat in the goat metabolism study. In the hen metabolism study IN-J9Z38 was detected in egg whites at up to 29.2% of the TRR (0.075 mg/kg). IN-MYX98 was detected at up to 18.3% of the TRR (0.026 mg/kg) in milk and 32.8% of the TRR (0.014 mg/kg) in muscle in the goat metabolism study. IN-MLA84 formed a significant proportion of the residue in liver and kidney in the dairy cattle transfer study, while IN-N7B69 formed a significant proportion of the residue in milk.

As toxicology data is not available to discount the importance of the major metabolites IN-J9Z38, IN-MLA84, IN-MYX98 and IN-N7B69 should be included in the risk assessment definition for cyantraniliprole for commodities of animal origin. The following entry is proposed to Table 3 of the MRL Standard:

Table 3

COMPOUND	RESIDUE
ADD:	
Cyantraniliprole	Commodities of plant origin: Cyantraniliprole Commodities of animal origin for enforcement: Cyantraniliprole Commodities of animal origin for dietary exposure assessment: Sum of cyantraniliprole and 2-[3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl]-3,8-dimethyl-4-oxo-3,4-dihydoquinazoline-6-carbonitrile (IN-J9Z38), 2-[3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl]-8-methyl-4-oxo-3,4-dihydroquinazoline-6-caronitrile (IN-MLA84), 3-bromo-1-(3-chloropyridin-2-yl)-*N*-{4-cyano-2-[(hydroxymethyl)carbamoyl]-6-methylphenyl}-1*H*-pyrazole-5-carboxamide (IN-MYX98) and 3-bromo-1-(3-chloropyridin-2-yl)-*N*-[4-cyano-2-(hydroxymethyl)-6-(methylcarbamoyl)phenyl]-1*H*-pyrazole-5-carboxamide (IN-N7B69), expressed as cyantraniliprole

4.4 Residue trials

Cotton

Australian and overseas trials on cotton have been supplied in support of the application. The proposed GAP is for a maximum of 2 applications at 60 g ai/ha with a 14 day WHP. In three Australian trials following 2 foliar applications of cyantraniliprole at 60 or 120 g ai/ha (1 - 2× proposed) residues of cyantraniliprole and its metabolites in cotton seed were all less than the LOD (0.003 mg/kg, n = 6) after a 14 day PHI. In addition one Australian trial was conducted as a reverse decline trial with no residues detected in the seed at 7 days after application at 1× and 2×. The US cotton trials do not match the proposed Australian GAP. An MRL of *0.01 mg/kg is recommended for cyantraniliprole on SO 0691 Cotton seed based on the Australian data.

Residues of cyantraniliprole in cotton forage at a 14 day PHI were 0.15, 0.23 and 0.28 mg/kg after 2 applications at 60 g ai/ha and 0.27, 0.38 and 0.43 mg/kg after 2 applications at 120 g ai/ha.

Residues of cyantraniliprole in cotton trash at a 14 day PHI were 0.34, 0.59 and 0.74 mg/kg after 2 applications at 60 g ai/ha and 0.76, 1.01 and 1.22 mg/kg after 2 applications at 120 g ai/ha.

Rotational crop field trials

Rotational crop field trials were conducted in North America and Europe.

North American studies

Five field rotational studies were conducted in the NAFTA region. Each involved 3 applications to bare soil at 150 g ai/ha with a 5 day retreatment interval. Targeted plant back intervals in 3 of the US trials were 14, 30, 120 and 365 days. Rotational crops investigated were lettuce/spinach, radish, oats and soybean. Two additional US studies targeted a 30 day plant back interval only and investigated root and tuber vegetables (turnip, sugar beet, garden beet, carrot, radish), legumes (peas, beans, soybeans), cereal grains (field corn, sweet corn, sorghum, rice, wheat), oilseeds (peanuts), berries and small fruit (strawberries) and nongrass animal feeds (Bermuda grass, alfalfa, bromegrass, clover, bluegrass). Highest residues in rotational crops from the NAFTA trials are summarised in Table 2. Residues are only reported only if they exceed 0.01 mg/kg in human edible commodities or 0.05 mg/kg in animal feedstuffs.

Table 2: Highest residues in crops sown as rotational crops in the NAFTA trials

RAC	PBI	Cyantraniliprole
Commodities for human consumption		
Leafy crops, Immature leaves	15	0.039
Leafy crops, Mature leaves	15	0.033
Leafy crops, Immature leaves	30	0.029
Leafy crops, Mature leaves	30	0.018
Cereals, Grain	30	0.01
Root crops, Root	30	0.015
Root crops, Root	120	0.009
Commodities used as feedstuff		
Cereals, Hay	15	0.13
Cereals, Straw	15	0.052
Root crops, Tops	15	0.046
Oilseeds, Forage	15	0.18
Oilseeds, Hay	15	0.1
Cereals, Forage	30	0.11
Oilseeds, Forage	30	0.14
Grasses, Forage	30	0.092
Cereals, Hay	30	0.21
Oilseed, Hay	30	0.63
Grasses, Hay	30	0.23
Pulses, Hay	30	0.14
Cereals, Straw	30	0.081
Cereals, Forage	120	0.048
Oilseeds, Forage	120	0.048

In the NAFTA trials residues of parent in commodities for human consumption were only above 0.01 mg/kg after a 15 or 30 day plant back interval. The highest parent residue of 0.039 mg/kg was detected in immature lettuce leaves from crops grown after a 15 day plant back interval.

In commodities used as feedstuffs, residues of parent above 0.05 mg/kg were also only observed after a 15 or 30 day plant back interval. The highest parent residue of 0.63 mg/kg was detected in soybean hay from crops grown after a 30 day plant back interval.

European studies

Two field rotational studies were conducted in the EU. The first study involved 3 applications to bare soil at a rate of 150 g ai/ha with a 5 day retreatment interval. The second study involved 2 applications to bare soil at 100 g ai/ha with a 7 day retreatment interval. The targeted plant back intervals in the first European study were 14, 30, 120 and 365 days. Crops investigated were lettuce, radish, spring oats and soybeans. The second study targeted plant back intervals of 14, 30, 120 and 270 days. The crops investigated were spinach, radish and spring barley.

No residue of cyantraniliprole or its metabolites was quantified above 0.01 mg/kg in commodities for human consumption and 0.05 mg/kg in feed items from the rotational crops in the European studies.

Conclusion on rotational crops

Although application rates in the rotational studies were higher than proposed for Australia (up to 3.75× total seasonal rate for cotton) they do suggest the possibility of low residues in rotational crops grown after short plant back intervals.

Based on a highest residue of 0.039 mg/kg in immature lettuce leaves it is recommended that an MRL of 0.05 mg/kg be established in Table 1 for cyantraniliprole on ‘All other foods’

Based on a highest residue of 0.63 mg/kg in soybean hay it is recommended that an MRL of 1 mg/kg be established in Table 4 for cyantraniliprole on Primary feed commodities.

4.5 Processing studies

In a cotton processing study there was no concentration of residues of cyantraniliprole in any of the fractions analysed. Given also that detectable residues are not expected to occur in cotton seed as a result of the proposed use, it is not necessary to establish separate MRLs for any commodities which are processed from cotton.

4.6 Animal Commodity MRLs

Animal transfer studies for cattle and poultry have been provided.

Cattle

Groups of 3 Holstein/Friesian cross dairy cattle per treatment group were dosed twice daily after milking with cyantraniliprole by gelatin capsule at 3, 10, 30 and 100 ppm in the feed for 28 days. An additional 3 cows were dosed at 100 ppm for 28 days to obtain depuration data. Two further cows served as controls. At dosing the cows weighed 437–680 kg. Milk was collected twice daily, and pooled on a daily basis. Cows were sacrificed within 24 hours of the last dose, except for the depuration group which were sacrificed at 4, 10 and 15 days post dosing. Samples of liver, kidney, muscle and fat were collected from all sacrificed animals.

Residues found in tissues and milk are summarised below:

Table 3: Average residues of cyantraniliprole and metabolites in milk products from lactating cows dosed with cyantraniliprole for 28 days

Matrix	**Analyte**	**Average residues of cyantraniliprole and metabolites mg/kg feed; values in milk represent the highest single day value**							
		3 ppm		**10 ppm**		**30 ppm**		**100 ppm**	
		Mean residue mg/kg							
Milk	Cyantraniliprole	0.030		0.11		0.25		0.71	
	IN-J9Z38	<0.01		<0.01		0.010		0.034	
	IN-MLA84	<0.01		<0.01		<0.01		<0.01	
	IN-MYX98	<0.01		<0.01		0.025		0.085	
	IN-N7B69	0.028		0.074		0.17		0.28	
Study day		**14**	**21**	**14**	**21**	**14**	**21**	**14**	**21**
Cream	Cyantraniliprole	0.072	0.059	0.2	0.15	0.63	0.46	1.9	1.7
	IN-J9Z38	0.014	0.011	0.032	0.027	0.085	0.066	0.37	0.31
	IN-MLA84	<0.01	<0.01	<0.01	<0.01	0.026	0.021	0.039	0.041
	IN-MYX98	<0.01	<0.01	<0.01	<0.01	0.020	0.023	0.066	0.079
	IN-N7B69	0.019	0.022	0.048	0.053	0.12	0.14	0.19	0.25
Skim milk	Cyantraniliprole	0.019	0.014	0.049	0.039	0.15	0.13	0.47	0.47
	IN-J9Z38	ND	ND	ND	ND	ND	<0.01	<0.01	<0.01
	IN-MLA84	ND	ND	ND	ND	<0.01	ND	<0.01	<0.01
	IN-MYX98	<0.01	<0.01	<0.01	<0.01	0.022	0.020	0.066	0.051
	IN-N7B69	0.019	0.020	0.047	0.057	0.12	0.13	0.22	0.18

ND = Not detected (<0.002 mg/kg)

Table 4: Residues of cyantraniliprole and metabolites in tissues from lactating cows dosed with cyantraniliprole for 28 days.

Matrix	Analyte	Mean (Max) residues of cyantraniliprole and metabolites in tissues			
		3 ppm	10 ppm	30 ppm	100 ppm
Muscle	Cyantraniliprole	<0.01 (0.011)	0.026 (0.037)	0.071 (0.092)	0.28 (0.33)
	IN-J9Z38	ND	<0.01	0.010 (0.018)	0.027 (0.043)
	IN-MLA84	ND	ND	<0.01	<0.01
	IN-MYX98	ND	<0.01	<0.01	0.01 (0.011)
	IN-N7B69	ND	<0.01	<0.01	<0.01
Liver	Cyantraniliprole	0.054 (0.066)	0.15 (0.16)	0.46 (0.60)	1.7 (2.1)
	IN-J9Z38	ND	<0.01	<0.01	0.015 (0.026)
	IN-MLA84	0.032 (0.043)	0.075 (0.099)	0.22 (0.29)	0.41 (0.57)
	IN-MYX98	ND	<0.01	<0.01 (0.026)	0.025 (0.025)
	IN-N7B69	<0.01 (0.01)	0.021 (0.024)	0.042 (0.046)	0.076 (0.079)
Kidney	Cyantraniliprole	0.023 (0.031)	0.084 (0.14)	0.20 (0.25)	0.73 (0.89)
	IN-J9Z38	ND	<0.01	<0.01 (0.013)	0.024 (0.031)
	IN-MLA84	<0.01 (0.011)	0.013 (0.017)	0.041 (0.044)	0.099 (0.13)
	IN-MYX98	<0.01	<0.01	0.034 (0.039)	0.14 (0.15)
	IN-N7B69	0.012 (0.015)	0.031 (0.031)	0.071 (0.081)	0.12 (0.15)
Fat	Cyantraniliprole	0.014 (0.015)	0.042 (0.066)	0.12 (0.15)	0.51 (0.58)
	IN-J9Z38	0.01 (0.012)	0.023 (0.031)	0.082 (0.12)	0.38 (0.45)
	IN-MLA84	ND	<0.01	<0.01	<0.01
	IN-MYX98	ND	<0.01	<0.01	<0.01
	IN-N7B69	<0.01	<0.01	0.010 (0.012)	0.020 (0.024)

ND = Not detected (<0.002 mg/kg)

Residues of parent and metabolites in tissues and milk after dosing at 100 ppm fell to <0.01 mg/kg after 10 days on clean feed.

The maximum livestock dietary exposure for cattle as a result of the proposed use will be as a result of the consumption of cotton seed (or cotton seed meal) as 30% of the diet as calculated below:

Cattle- 500 kg bw, 20 kg DM/day

Commodity	% in diet	Feed intake	Residue, mg/kg	% DM	Livestock dietary exposure		
					mg/animal	ppm	mg/kg bw
Cotton seed	30	6	0.01	88	0.068	0.0034	0.00014
Cotton seed meal	30	6	0.01	89	0.067	0.0034	0.00013

Given that detectable residues of cyantraniliprole are not expected to occur in cotton seed or meal as a result of the proposed uses it is appropriate to establish mammalian commodity MRLs at the respective LOQs. The following MRLs are appropriate:

MO 0105 Edible offal (mammalian) *0.01 mg/kg
MM 0095 Meat [mammalian][in the fat] *0.01 mg/kg
FM 0183 Milk fats *0.01 mg/kg
ML 0106 Milks *0.01 mg/kg

The residues values for risk assessment are *0.05 mg/kg for offal, meat [in the fat] and milk.

Poultry

Groups of 10 laying hens per treatment group were dosed daily with cyantraniliprole by gelatine capsule at 3, 10 or 30 ppm in the diet for 28 days. An additional 10 birds were dosed at 30 ppm for 28 days to obtain depuration data. A further group of 10 birds served as controls. Eggs from each group were collected twice daily and pooled on a daily basis. Birds were sacrificed within 6 hours of the last dose, except for the depuration group which were sacrificed at 5, 9 or 14 days after the last dose. Samples of liver, muscle (approximately equal quantities of leg and breast) and skin with fat were harvested.

Residues found in tissues and eggs are summarised below.

Table 5: Average residues of cyantraniliprole and metabolites in eggs.

Matrix	Analyte	Average residues of cyantraniliprole and metabolites (mg/kg feed); values in eggs represent the highest single day value					
		3 mg/kg		10 mg/kg		30 mg/kg	
		Mean residue (mg/kg)					
Eggs	Cyantraniliprole	0.082		0.17		0.80	
	IN-J9Z38	0.039		0.077		0.41	
	IN-MLA84	0.016		0.038		0.12	
	IN-MYX98	0.014		0.035		0.10	
	IN-N7B69	<0.002		<0.002		0.0029	
Study day		14	21	14	21	14	21
Egg whites	Cyantraniliprole	0.098	0.059	0.20	0.14	0.68	0.60
	IN-J9Z38	0.045	0.026	0.078	0.066	0.27	0.27
	IN-MLA84	0.015	0.015	0.034	0.033	0.092	0.093
	IN-MYX98	0.017	0.014	0.037	0.030	0.10	0.089
	IN-N7B69	<0.002	0.0023	<0.002	<0.002	0.0038	0.0036
Egg yolks	Cyantraniliprole	0.017	0.012	0.034	0.023	0.090	0.11
	IN-J9Z38	0.0081	0.0056	0.018	0.014	0.053	0.062
	IN-MLA84	0.0064	0.0077	0.017	0.016	0.039	0.046
	IN-MYX98	0.0086	0.0059	0.017	0.012	0.041	0.039
	IN-N7B69	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002

ND – Not Detected

Table 6: Residues of cyantraniliprole and metabolites in tissues.

Matrix	Analyte	Residues of cyantraniliprole and metabolites (mg/kg feed) in tissues		
		3 mg/kg	10 mg/kg	30 mg/kg
		Mean residue (mg/kg)		
Muscle	Cyantraniliprole	0.0034	0.0093	0.025
	IN-J9Z38	ND	ND	ND
	IN-MLA84	<0.002	<0.002	<0.002
	IN-MYX98	0.0041	0.012	0.025
	IN-N7B69	<0.002	<0.002	0.0026
Liver	Cyantraniliprole	0.017	0.041	0.13
	IN-J9Z38	<0.002	<0.002	<0.002
	IN-MLA84	0.015	0.043	0.096
	IN-MYX98	0.023	0.068	0.19
	IN-N7B69	0.0067	0.013	0.045
Skin with fat	Cyantraniliprole	0.0093	0.033	0.080
	IN-J9Z38	0.0029	0.0064	0.018
	IN-MLA84	<0.002	0.0034	0.0080
	IN-MYX98	0.0037	0.015	0.027
	IN-N7B69	<0.002	<0.002	0.0030

ND – Not Detected

Following cessation of dosing, residues rapidly declined. In eggs, muscle and skin with fat, all residues were <LOQ (0.01 mg/kg) by 5 days after the last dose. The corresponding sample of liver was not analysed. All residues in liver were <LOQ at 9 days after the last dose.

Oilseeds such as cottonseed can form up to 30% of the diet for poultry. Oilseed meals can form up to 20% of the diet. The estimated dietary exposure for poultry is calculated below.

Poultry- 2 kg bw, 0.15 kg DM/day

Commodity	% in diet	Feed intake	Residue, mg/kg	% DM	Livestock dietary exposure		
					mg/animal	ppm	mg/kg bw
Cotton seed	30	0.045	0.01	88	0.00051	0.0034	0.00025
Cotton seed meal	20	0.03	0.01	89	0.00033	0.0022	0.00016

The maximum estimated dietary exposure to cyantraniliprole for poultry is 0.0056 ppm. Given that detectable residues of cyantraniliprole are not expected to occur in canola or cotton seed or their meals as a result of the proposed uses it is appropriate to establish poultry commodity MRLs at the respective LOQs. The following MRLs are appropriate:

PE 0112 Eggs *0.01 mg/kg
PO 0111 Poultry, Edible offal of *0.01 mg/kg
PM 0110 Poultry meat [in the fat] *0.01 mg/kg

The residues values for risk assessment are *0.05 mg/kg for eggs, poultry offal and poultry meat [in the fat] respectively.

4.7 Estimated dietary intake

The chronic dietary exposure to cyantraniliprole is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines2 and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for cyantraniliprole is equivalent to 9% of the ADI.

It is concluded that the chronic dietary exposure to cyantraniliprole is acceptable.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food.

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

The Office of Chemical Safety recommended that an Acute Reference Dose is not necessary for cyantraniliprole. It is therefore not necessary to undertake NESTI calculations.

4.8 Bioaccumulation potential

The Log K_{ow} for cyantraniliprole is 2.02 (at pH 7). Fat solubility is low, although in the animal transfer study residues in fat were slightly higher than those in muscle. However, after dosing with cyantraniliprole at 100 ppm for 28 days, residues of parent in fat fell to below detectable limits after 10 days on clean feed. Potential for bioaccumulation is considered to be low.

4.9 Spray drift

The draft label indicates droplet VMD should be of medium spray quality according to ASAE S572 definition for standard nozzles. It is proposed to apply cyantraniliprole by both ground and aerial application. For ground application the draft label indicates the boom should be kept low to avoid spray drift.

In the dairy cattle animal transfer study provided in support of the application, dosing with cyantraniliprole at 3 ppm gave highest residues of 0.066 mg/kg in liver. For residues of parent to be at the LOQ (0.01 mg/kg) the maximum feeding level is 0.455 ppm. Assuming pasture consists of 1500 kg DM/ha this corresponds to a maximum permitted drift of 0.68 g ai/ha.

Calculations of the average deposition over a 300 metre field using the standard scenarios for ground and aerial application available on the APVMA web site and taking into consideration the half-life for cyantraniliprole in the target tissue indicate that no spray zones are not required for protection of international trade.

4.10 Recommendations

The following MRLs will be established:

Table 1

COMPOUND		FOOD	MRL (MG/KG)
ADD:			
Cyantraniliprole			
		All other foods	0.05
SO	0691	Cotton seed	*0.01
MO	0105	Edible offal (mammalian)	*0.01
PE	0112	Eggs	*0.01
MM	0095	Meat [mammalian][in the fat]	*0.01
FM	0183	Milk fats	*0.01
ML	0106	Milks	*0.01
PO	0111	Poultry, Edible offal of	*0.01
PM	0110	Poultry meat [in the fat]	*0.01

Table 3

COMPOUND	RESIDUE
ADD:	
Cyantraniliprole	Commodities of plant origin: Cyantraniliprole Commodities of animal origin for enforcement: Cyantraniliprole Commodities of animal origin for dietary exposure assessment: Sum of cyantraniliprole and 2-[3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl]-3,8-dimethyl-4-oxo-3,4-dihydoquinazoline-6-carbonitrile (IN-J9Z38), 2-[3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl]-8-methyl-4-oxo-3,4-dihydroquinazoline-6-caronitrile (IN-MLA84), 3-bromo-1-(3-chloropyridin-2-yl)-*N*-{4-cyano-2-[(hydroxymethyl)carbamoyl]-6-methylphenyl}-1*H*-pyrazole-5-carboxamide (IN-MYX98) and 3-bromo-1-(3-chloropyridin-2-yl)-*N*-[4-cyano-2-(hydroxymethyl)-6-(methylcarbamoyl)phenyl]-1*H*-pyrazole-5-carboxamide (IN-N7B69), expressed as cyantraniliprole

Table 4

COMPOUND	ANIMAL FEED COMMODITY	MRL (MG/KG)
ADD:		
Cyantraniliprole:		
	Primary feed commodities	1

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

Harvest:

Cotton: Do not harvest for 14 days after application.

Grazing:

Cotton: Do not allow livestock to graze crops, cotton stubble or gin trash treated with Exirel Insecticide.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Cotton seed (including derived oils and meals) is considered to be a major export commodity. Animal commodities from livestock that have been fed feeds containing residues arising from the proposed use are also exported.

5.2 Destination and value of exports

In 2010-11 Australia exported 18,200 tonnes of cotton seed oil. Information on the destination is not readily available. Major export destinations for cottonseed and oilseed meal (sum of cotton seed and sunflower seed meal) are Japan, South Korea and New Zealand (ABARES). The significant export markets for animal commodities are defined in Part 5B of Ag MORAG

5.3 Proposed Australian use-pattern

Du Pont Exirel Insecticide (100 g/L cyantraniliprole)

Crop	Pest	Rate/ha	Critical Comments
Cotton	Sucking insects; Silverleaf whitefly (*Bemisia tabaci* B biotype) Cotton aphid (*Aphis gossypii*) Suppression only Chewing insects; Cotton bollworm (*Helicoverpa armigera*) Native budworm (*H. punctigera*)	600 mL (60 g ai/ha) + Ethylated seed oil (refer Surfactant/Wetting agent section)	Heliothis – target eggs and hatchling (neonates or 1st instar) to small larvae (2nd instar) when they reach the economic spray threshold and before they become entrenched in hidden feeding sites, such as squares, flowers or bolls. Silverleaf whitefly – target early developing populations. Exirel is primarily active on the early nymph stage. A maximum of two (2) applications are to be applied to any one crop per season. Further treatments should be made with alternative mode of action insecticides.

Withholding periods:

Harvest:

Cotton: Do not harvest for 14 days after application.

Grazing:

Cotton: Do not allow livestock to graze crops, cotton stubble or gin trash treated with Exirel Insecticide.

5.4 Overseas registration and approved label instructions

No cyantraniliprole products are currently registered overseas, although registration in various crops is being considered in Canada, the EU and the USA as part of an OECD global joint review evaluation.

5.5 Comparison of Australian MRLS with Codex and overseas MRLS

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods. Cyantraniliprole has not been considered by Codex, but will be considered by the JMPR in 2013.

No overseas MRLs/tolerances have been established for cyantraniliprole in plant or animal commodities.

5.6 Potential Risk to Trade

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

Residues in cotton seed as a result of the proposed use are expected to be <0.01 mg/kg. The risk to Australia's trade in cotton seed is expected to be low. As quantifiable residues are also not expected to occur in cotton oils and meals the risk to the export trade in these commodities is also considered to be low.

The risk to trade in animal commodities derived from livestock consuming cotton seed and meal from treated crops is expected to be low as detectable residues are not expected to occur.

The risk to trade in animal commodities from livestock that have consumed feeds not directly treated with cyantraniliprole must also be considered. In the rotational studies provided with the application the highest residue in an animal feed was 0.63 mg/kg in soybean hay. OECD guidelines indicate soybean hay consists of 85% dry matter and may form up to 80% of the diet for beef cattle in Australia (40% for dairy). The estimated maximum livestock dietary exposure to residues in rotational crops is 0.59 ppm. A feeding level of 0.59 ppm would give a maximum predicted residue in liver of 0.013 mg/kg which is approximately at the LOQ. Given the conservatism in this assessment the risk to trade in animal commodities from livestock that have consumed feeds from rotational crops not directly treated with cyantraniliprole is considered to be low and acceptable.

The risk to trade in rotational crops which are major export commodities, such as cereals, pulses and oilseeds, is considered to be low and acceptable. The highest residue of cyantraniliprole in cereal grain in the rotational studies was 0.01 mg/kg. This was observed after treatment of bare soil at higher rates than proposed (3.75×) and a 30 day plant back interval. Given that in practice the application will be intercepted by the primary crop, it is considered unlikely that quantifiable residues will occur in the grains of cereals, pulses and oilseeds grown as rotational crops.

The APVMA is proposing to decide that the risk to trade is low and acceptable. Comment is being sought on this conclusion.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Cyantraniliprole (CAS: 736994-63-1) is currently not listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2012). With the available toxicology information, OCS classifies cyantraniliprole as a non-hazardous substance for human health according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). Thus, no human health risk phrases will be required for this new active constituent.

Based on the product acute toxicity studies and the concentration of cyantraniliprole in the product (10%), DuPont Exirel Insecticide is classified as a hazardous substance in accordance with NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following human health risk phrases assigned:

R38	Irritating to skin
R43	May cause sensitisation by skin contact

Formulation, packaging, transport, storage and retailing

The active constituent cyantraniliprole will be manufactured overseas. The product DuPont Exirel Insecticide will be formulated overseas and imported in 1–10 L high-density polyethylene (HDPE) containers with self-adhesive labels, with some packaging and labelling occurring in Australia.

Use pattern

DuPont Exirel Insecticide is a suspo-emulsion formulation containing 100 g/L cyantraniliprole. The product is intended for broadacre foliar application to cotton crops. Dupont Exirel Insecticide will be used at the label rate of 600 mL product/ha in cotton, twice per crop season. It is intended that the product will be applied in a minimum water volume of 100 L/ha by ground equipment and 30 L/ha by aerial equipment.

The Australian cotton growing season lasts approximately six months. The maximum application frequency for the proposed crop types is two applications per crop season.

Exposure during use

Farmers and their employees will be the main users of DuPont Exirel Insecticide. Domestic use of the product is not expected. Product applications may lead to unintended bystander exposure *via* chemical spray drift. This may be in the form of a single random exposure of bystanders in the vicinity of the treated areas, or repeat exposures of residents who reside adjacent to areas being treated with the product. It is expected that good agricultural practices will be followed.

Workers may be exposed to the product when opening containers, mixing/loading, application, and cleaning up spills and equipment. It is expected that the main routes of exposure to the product will be dermal and inhalation, with limited ocular exposure possible during foliar application of the diluted product.

No occupational exposure studies have been conducted for DuPont Exirel Insecticide. 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 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 inter-species and intra-species variation and the seriousness of the critical health effect of concern.

The moderate skin irritation associated with use of the product will require the prescription of personal protective equipment (PPE). When opening the container, mixing, loading and applying the product acceptable MOEs (i.e. > 100) were achieved when cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves are worn.

Exposure during re-entry

Post application activities may include crop scouting and harvesting activities, along with general crop maintenance activities (e.g. weeding) expected for cotton crops. Workers may be exposed to DuPont Exirel Insecticide when re-entering treated areas.

Post-application exposure has been estimated using the US EPA Occupational Post-Application Risk Assessment Calculator Version 1 (8/9/00)—US EPA Policy 003.1. MOE estimates have been determined to be acceptable for all expected post-application activities, and on this basis, there are not expected to be re-entry risks associated with dermal contact with crops treated with DuPont Exirel Insecticide. Thus, no re-entry statement is required.

Recommendations for safe use

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

DuPont Exirel Insecticide 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

Du Pont (Australia) Ltd have applied for approval of the new active constituent (ac) cyantraniliprole and registration of the insecticide Du Pont™ Exirel™ insecticide, containing 100 g ac/L cyantraniliprole as the sole active constituent in an SE formulation. This product will be marketed for use to control insect pests in cotton (chewing insects- cotton bollworm & native budworm and the sucking insects - silverleaf whitefly & cotton aphid). Cyantraniliprole is a second generation ryanodine receptor insecticide.

7.2 Environmental Fate

Physicochemical properties

Cyantraniliprole is moderately soluble in water (~17 mg/L at pH 4 to ~6 mg/L at pH 9 [at 20°C]), very slightly volatile (5.1×10^{-15} Pa at 20°C) and very slightly volatile from water (non-dimensional Henry's Law Constant $H = 6.9 \times 10^{-17}$ at 20°C). The dissociation constant (pKa = 8.8 at 20°C) indicates that behaviour of the substance in the environment may be affected by pH. Based on the n-octanol/water partition coefficient (log K_{OW} = 1.94), cyantraniliprole is not expected to bioaccumulate.

Route and rate of degradation in soil

DT50 values for cyantraniliprole in aerobic soil degradation studies (incubated in the dark) with five soils ranged from 8.7 to 91.9 d (geomean = 30.7 d) according to best fit models. Therefore degradation of cyantraniliprole in aerobic soil can be classified as readily degradable (DT50 at 20° C and pF2 < 20 d) to slightly degradable (DT50 60-180 d). DT90 values ranged from 66.2-376 d (geomean = 197 d). Degradation of cyantraniliprole appeared to be faster under anaerobic conditions (DT50 = 4.4 d). Under aerobic conditions degradation proceeded along two pathways, the IN-J9Z38 pathway and the IN-JCZ38 pathway. Formation of small amounts of $^{14}CO_2$ from radiolabelled cyantraniliprole indicated that the parent compound can be mineralised, and characterization of non-extractable residue infers that small molecules formed may become a part of soil organic matter. Degradation in anaerobic soil followed the same degradation route (DT50 = 4.4 d), but the IN-JCZ38 pathway became less significant.

Laboratory soil aerobic metabolism studies with nine individual metabolites generated in soil metabolism or photolysis studies showed that all metabolites generated continue to degrade, though with widely differing degradation rates.

Degradation in soil under photolysis conditions (exposed to simulated sunlight in cycles of ~12 h light:~12 h dark) was clearly mediated by the moisture content of the soil. In soil, which was moist at the start but not maintained moist, very little degradation occurred during the study period and the only degradation product observed was IN-J9Z38, which formed due to hydrolytic degradation in soil. However, when soil was maintained in a moist condition, degradation occurred much more rapidly (DT50/DT90 for photodegradation = 12.2/40.5 d [corrected for degradation in the dark control]). The same products found in aqueous

photolysis studies (IN-NXX70 and IN-QKV54) were also formed in soil, and an additional metabolite formed from photolysis of IN-J9Z38 (IN-RNU71), was also identified.

Dissipation of cyantraniliprole and its metabolites were investigated in soil dissipation studies under field conditions carried out at ten different locations in Europe, Canada, and the United States. Based on the best fitting kinetic model in each case, the DT50 values at the ten field sites ranged from 9.7 to 44 days (geomean = 17.2 d), whereas the DT90 values ranged much more widely, from 55.5-333 d (geomean = 157 d). The longest field DT90s (246 to 333 d) belonged to cold weather locations in New York, Missouri, Manitoba and Germany, where soil was frozen for some portion of the study duration.

Based on the laboratory soil studies, it was concluded that there were seven major soil degradation products: IN-J9Z38, IN-JCZ38, IN-JSE76, IN-K5A77, IN-K5A78, IN-K5A79, and IN-PLT97. These metabolites were monitored in the field soil dissipation studies, and all were detected at some time in every study, with the exception of IN-K5A79 in one study. The three photodegradation products IN-RNU71, IN-QKV54 and IN-NXX70 were also monitored in some of the field studies. It was concluded that as much as 5% photolysis may be expected if suitable conditions of moist soil and abundant sunlight are available, but that in the field photodegradation is not likely to be a major dissipation mechanism for cyantraniliprole due to downward movement of cyantraniliprole below the soil surface and shading by crop plants. Based on these data, cyantraniliprole and its major metabolites are not expected to accumulate in soil under field conditions.

Mobility in soil

Batch adsorption studies were conducted with cyantraniliprole and nine metabolites on five soils. For cyantraniliprole, K_{FOC} values ranged from 128 to 266 mL/g (median = 225 mL/g). Based on these results, cyantraniliprole is classified as having medium to high mobility in soil. Mobility of the metabolites ranged from highly to very highly mobile for IN-JSE76 and IN-K5A79 (median K_{FOC} respectively = 25 and 36 mL/g) to slightly immobile to immobile for IN-J9Z38 and IN-QKV54 (median K_{FOC} respectively = 4774 and 4120 mL/g).

In regard to mobility of parent cyantraniliprole and its metabolites in the field, in most studies (7 out of 10) there was negligible movement of residues to deeper soil horizons and the lowest horizons sampled always had residues below the limit of detection. Cyantraniliprole never moved beyond the upper soil horizons. However at three sites (France, Washington and Texas) movement of small amounts of some metabolites (IN-JSE76, IN-K5A78, IN-K5A79 and IN-PLT97) to the lowest horizon sampled (~ 90 cm) was observed. Typically the level of these metabolites was at or below the limit of quantification (LOQ = 1 ppb).

Fate and behaviour in water

The rate of hydrolysis of cyantraniliprole in water is pH dependent, with DT50 values at 20°C calculated from aqueous photolysis studies being 260.5, 60.7 and 1.77 d, respectively, at pH 4, 7 and 9. Therefore cyantraniliprole can be classified as slightly hydrolysing (DT50 > 30 d) at pH 4 and 7, and readily hydrolysing (DT50 1-4 d) at pH 9. The major transformation product detected was IN-J9Z38.

Photochemical degradation of cyantraniliprole in water was very rapid, with a DT50 of <1 d. As with photolysis on moist soil, photolysis in water showed an entirely different pathway for degradation to that in soil or water in the absence of light, forming the major metabolites IN-NXX70 and IN-QKV54.

In laboratory studies conducted in the dark under aerobic conditions, degradation of cyantraniliprole in water sediment systems was generally more rapid than degradation in soil. The total system DT50 at 20°C was 25.1 d in aerobic sandy sediment and 3.87 d in aerobic silty sediment (DT90 respectively = 83.4 and 12.8 d). Therefore cyantraniliprole can be classified as fairly to readily degradable in water/sediment systems under aerobic conditions (DT50 total system respectively, 20-60 d or < 20 d). Similarly rapid initial degradation occurred in a Japanese flooded rice soil study, where the total system DT50 with incubation at 25°C was 20.6 d, but the rate of degradation slowed and the DT90 was much longer (939 d). Degradation in anaerobic water sediment systems was also rapid, with DT50's of 2.1 d and 11.9 d in the total systems (DT90 = 11.2 and 39.6 d, respectively). The degradation in aerobic systems proceeded along the same pathways that were identified for soil, but primarily through the IN-J9Z38 pathway.

In another study the effect of exposure to natural sunlight on degradation of cyantraniliprole in water/sediment systems was evaluated under aerobic conditions at 20-25°C and in sterile pH 7 buffer. Cyantraniliprole was readily degraded in both the water/sediment systems (DT50 = 3.6 d in a silty loam system and 4.5 d in a sand, ie comparable or faster than that with similar systems incubated in the dark). Degradation in the sunlight-exposed sterile pH 7 buffer was more rapid than hydrolysis at pH 7 in the dark (DT50 = 14.1 d compared to 60.7 d), but considerably slower than in the continuous irradiation laboratory aqueous photolysis study (DT50s < 1 d), probably due to lower intensity of the outdoor radiation. Evaluation of the metabolites formed indicated that photodegradation played an important role in degradation under the conditions of this outdoor study.

Fate and behaviour in air

Volatilisation is not expected to be a significant route of dissipation for cyantraniliprole or to result in long range atmospheric transport. The estimated DT50 for cyantraniliprole in air is 0.33 d, thus the substance is not expected to be persistent in air.

Bioconcentration

The whole-fish bioconcentration factors of cyantraniliprole in bluegill sunfish at mean measured concentrations of 9.41 and 93.8 µg ac/L were <1, indicating that cyantraniliprole does not bioconcentrate in fish.

7.3 Environmental Effects

In addition to cyantraniliprole, the toxicity of various formulations and of cyantraniliprole metabolites was evaluated. Studies were generally conducted to standard test guidelines (eg OECD and US EPA).

Birds

Cyantraniliprole is practically nontoxic to birds with acute oral or short term dietary exposure (acute oral LD50 > 2250 mg ac/kg bw for both bobwhite quail and zebra finch; 5 d dietary LC50 > 5620 ppm for both bobwhite quail and mallard duck). Reproduction studies indicated NOECs of 1000 ppm for both bobwhite quail and mallard duck.

Aquatic organisms

Fish

Based on the results of acute toxicity studies conducted with the active constituent, cyantraniliprole is categorised as at worst slightly toxic to fish (LC50 > 10 mg ac/L), with little or no toxicity up to the limit of solubility in the test media (96 h LC50 to rainbow trout, bluegill sunfish, channel catfish and sheepshead minnow, respectively, > 12.6, > 13.0, > 10.0 and > 12.0 mg ac/L).

Early life stage toxicity studies with cyantraniliprole indicated a 90 d NOEC of 10.7 mg ac/L to rainbow trout, and a 33 d NOEC of 2.9 mg ac/L (LOEC = 5.8 mg ac/L, effects on total length) to sheepshead minnow. Thus cyantraniliprole can be classified as very slightly toxic to fish with chronic exposure (NOEC > 1 mg ac/L).

Aquatic invertebrates

Based on the results of acute toxicity studies conducted with the active constituent, cyantraniliprole is classified as very highly toxic (LC50/EC50 ≤ 0.10 mg/L) to the waterfleas *Daphnia magna* (48 h EC50 = 0.0204 mg ac/L) and *Ceriodaphnia dubia* (48 h LC50 = 0.040 mg ac/L) and to mayfly nymphs (*Centroptilium triangulifer* – 48 h LC50 = 0.0715 mg ac/L) and caddisfly larvae (*Lepidostoma ontario* – 48 h LC50 = 0.0748 mg ac/L). It is highly toxic (LC50/EC50 in the range 0.10 to 1.0 mg/L) to the amphipod *Gammarus pseudolimnaeus* (48 h LC50 = 0.172 mg ac/L), chironomid *Chironomus riparius* (48 h LC50s = 0.719 mg ac/L) and eastern oyster (*Crassostrea virginica*) (96 h EC50 = 0.45 mg ac/L), moderately toxic (LC50/EC50 in the range 1.0 to 10.0 mg/L) to the amphipod *Hyalella azteca*, mysid shrimp (*Americamysis bahia*) and the freshwater crayfish *Procambarus clarkia*. It is slightly toxic (LC50/EC50 in the range 10.0 to 100 mg/L) to stonefly nymphs (*Soyedina carolinensis* - 48 h LC50 = 14 mg ac/L) and the oligochaete *Lumbriculus variegates*.

A 21 day chronic toxicity study of cyantraniliprole to *Daphnia magna* indicated NOEC and LOEC values of 0.00969 and 0.0147 mg ac/L, respectively, based upon treatment-related effects on total live young and total immobile young. A 7 day chronic toxicity study of cyantraniliprole to *Ceriodaphnia dubia* indicated a NOEC of 0.005 mg ac/L and LOEC of 0.020 mg ac/L (7 d survival and mean young reproduction). Thus cyantraniliprole can be classified as highly toxic to aquatic invertebrates with chronic exposure (NOEC < 0.01 mg ac/L).

An acute toxicity study conducted with the cyantraniliprole 100 g/L SE formulation (as used for Du Pont™ Exirel™ insecticide) indicated that the formulation is highly toxic and the active constituent very highly toxic to *Daphnia magna* (48 h EC50 = 0.232 mg formulation [nominal concentration], 0.0185 mg ac/L [mean measured concentration]). Thus the toxicity of the 100 g ac/L SE formulation is consistent with the active constituent content.

Acute toxicity studies with 12 metabolites of cyantraniliprole that occurred in soil and/or water fate studies were conducted with *Daphnia magna*. In all cases the metabolites were clearly less toxic than cyantraniliprole, though with a 48 h EC50 = 0.40 mg as/L the metabolite IN-PLT97 is classified as highly toxic. Limit tests (apparent limit of solubility in the dilution water) with some other metabolites indicate they were at most highly toxic (48 h EC50 > 0.184 mg as/L for IN-NXX70, > 0.22 mg as/L for IN-J9Z38, > 0.287 mg as/L for IN-QKV54 and > 0.85 mg as/L for IN-K5A77). The other metabolites are moderately toxic (EC50

= 1.85 mg as/L for IN-JCZ38, > 2.7 mg as/L for IN-RNU71) to slightly toxic (48 h EC50 = 22.5 mg as/L for IN-JSE76, > 31 mg as/L for IN-K5A78 and IN-K5A79). Chronic toxicity studies indicated 21d NOEC values of 0.24 mg as/L (limit of solubility in the dilution water) for IN-J9Z38 and 0.117 mg as/L (21 d LOEC = 0.2036 mg as/L) for IN-K5A77 (slightly toxic with chronic exposure).

Sediment dwelling organisms

28-day toxicity tests were conducted with ^{14}C-cyantraniliprole and *Chironomus riparius* in water in the presence of sediment. When the test was conducted with the test substance applied to sediment, the NOEC was 0.019 mg ac/kg sediment dry weight (nominal concentration, maximum concentration tested). When the test was conducted with the test substance applied to the overlying water, the NOEC was 0.01 mg ac/L (nominal concentration, maximum concentration tested – at most moderately toxic).

Algae and aquatic plants

Studies indicated that cyantraniliprole can be classified as moderately toxic to at most slightly toxic to green and blue-green algae and diatoms. The species tested were a freshwater green alga (*Pseudokirchneriella subcapitata* – 72 h E_bC50, E_rC50 > 13 mg ac/L), a blue-green alga (*Anabaena flos-aquae* – 72 h E_bC50, E_rC50 > 15 mg ac/L), a freshwater diatom (*Navicula pelliculosa* – 72 h E_bC50, E_rC50 > 14 mg ac/L), and a marine diatom (*Skeletonema costatum* - 72 h E_bC50 = 3.2 mg ac/L [approximate], E_rC50 > 10 mg ac/L). A study with the freshwater duckweed *Lemna gibba* indicated similarly low toxicity to aquatic plants (7 d EC50 > 10 mg ac/L).

A study with *Pseudokirchneriella subcapitata* and the 100 g ac/L SE formulation indicated a 72 h E_bC50 = 8.10 mg formulation/L (equivalent to 0.825 mg ac/L) and 0-72 h E_rC50 = 33.3 mg formulation/L (equivalent to 3.39 mg ac/L). Thus this formulation is more toxic than would be expected solely from the active constituent content.

Other terrestrial vertebrates

Cyantraniliprole and the metabolites IN-JSE76 and IN-PLT97 are practically non-toxic to mammals following a single exposure (rat acute oral LD50 > 5000 mg ac/kg bw). The NOAEC for reproductive and fertility effects with rats in a two-generation reproductive study was 20000 ppm feed (corresponding to 1344 mg ac/kg/day), whereas that for parent rats was 20 ppm (1.4 mg ac/kg/day, LOAEC = 200 ppm) and that for offspring was 200 ppm (13.3 mg ac/kg/day, LOAEC = 2000 ppm).

Bees

Acute exposure bee toxicity tests were conducted with cyantraniliprole active constituent and the 100 g/L SE, 100 g/L OD and 200 g/L SC formulations. With the active constituent, the 48 h LD50 was >0.1055 µg ac/bee with oral exposure, and with contact exposure the 72 h LD50 was > 0.0934 µg ac/bee. With the 100 g/L SE formulation, the 96 h LD50 was 0.92 µg ac/bee (8.76 µg formulation/bee) with oral exposure, and with contact exposure the 96 h LD50 was 2.78 µg ac/bee (26.5 µg formulation/bee). Studies were also provided with the 100 g/L OD and 200 g/L SC formulations, indicating oral LD50 values of ~0.4 µg ac/bee and contact LD50s of ~0.6 µg ac/bee. Therefore cyantraniliprole can be categorised as toxic to honeybees with acute oral or contact exposure (acute LD50 in the range 0.1 to 1 µg/bee).

An extended laboratory foliage residue toxicity test indicated no treatment related mortality or behavioural effects after exposure to dried residues on foliage.

Semi-field (tunnel) and field studies were conducted with different formulations of cyantraniliprole, involving a range of application rates, spray timings and crops. Overall, these show limited, short term effects on mortality, flight activity and behaviour of bees following application to flowering plants at rates of 10–150 g ac/ha. Effects were more commonly observed when application occurred during bee flight, but in some cases effects still occurred when application was made after bee flight (effects on mortality then only occurred at high rates). In general, effects were not observed when applied only prior to flowering (or from limited evidence, via drip irrigation rather than spray application). There were no significant effects on bee brood or colony strength, except in an unusual semi-field study where exposure occurred to cyantraniliprole on wheat plants treated with sugar solution to simulate insect honeydew and in one field study with oilseed rape where possible effects on overwintering capacity were noted with application made during flowering during bee flight.

Glasshouse studies with ^{14}C-labelled cyantraniliprole demonstrate that following foliar or soil application, cyantraniliprole and various metabolites are translocated into pollen and anthers of canola, sunflower, tomato, zucchini and *Phacelia tanacetifolia*. Residue evaluations were made in field trials with a range of crops and with *Phacelia*.

Insect/mite predators and parasites

Tier 1 and 2 laboratory studies conducted with the 100 g/L SE and OD formulations indicated cyantraniliprole ranges widely in toxicity to non-target terrestrial arthropods. With the SE formulation, for the cereal aphid parasitoid wasp *Aphidius rhopalosiphi* the 48 h LR50 = 2.06 g ac/ha (Tier 2 study) whereas for the predatory mite *Typhlodromus pyri* the 7 d LR50 and ER50 was > 300 g ac/ha. With spiders (*Pardosa* spp) (SC formulation only) the 14 d NOEC (mortality and feeding) = 400 g ac/ha. Toxicity to other species fell between these values: LR50 = 43.3 g ac/ha for the ladybird beetle *Coccinella septempunctata* and LR50 212.6 g ac/ha for the lacewing *Chrysoperla carnea* [Tier 2 studies with the SE formulation]; ER50 (reproduction) = 56.4 g ac/ha for the rove beetle (*Aleochara bilineata*) [Tier 2 study with the SC formulation]. Additional laboratory studies indicated effects on mortality declined with aging of the residues to which the insects were exposed, to ~10% or less by 14 days after the final application. Another study indicated there was < 50% effect on the hatching rate of aphid mummies or reproduction of parasitic wasps after direct application to mummies of the OD formulation at up to 150 g ac/ha. Field studies confirmed low toxicity to predatory mites in vineyards.

Earthworms and other soil non-target macro-organisms

Cyantraniliprole is very slightly toxic to earthworms (*Eisenia foetida*) with acute exposure (14 d LC50 > 1,000 mg ac/kg soil dw) and also showed low toxicity in an earthworm reproduction study (56 d NOEC = 1000 mg ac/kg soil dw). Similarly low toxicity was observed in studies undertaken with nine metabolites of cyantraniliprole.

In laboratory studies, cyantraniliprole was highly toxic to collembola (28 d NOEC to *Folsomia candida* = 0.08 mg ac/kg soil dw), but only very slightly toxic to soil mites (14 d NOEC to *Hypoaspis aculeifer* = 1000 mg

ac/kg soil dw). Major metabolites ranged from very slightly toxic to moderately toxic to collembola and slightly toxic to very slightly toxic to soil mites.

Litter bag studies conducted with cyantraniliprole at a rate simulating ongoing annual use at 300 g ac/ha and with 6 metabolites indicated no significant effects on straw decomposition compared to controls after exposure to treated soil for 6 months. Evaluations of soil microarthropod fauna in conjunction with the cyantraniliprole litter bag study indicated no significant effects on the abundance of different taxa of collembola or soil mites. In a separate study with very high application rates (totalling up to ~2460 g ac/ha), for some treatments there were transient effects on individual species of collembola, but not on the class Collembola as a whole.

Microbial activity

There were no harmful long term impacts on soil microbial nitrogen or carbon transformation with cyantraniliprole or its metabolites at soil concentrations of ~0.14 mg and ~1.41 mg ac/kg soil dw (corresponding to concentrations arising in the surface 5 cm of soil with application rates of 10.5 and 105 g ac/ha).

An activated sludge, respiration inhibition test indicated < 25% inhibition from cyantraniliprole concentrations up to and including 100 mg ac/L, indicating low toxicity to sewage microorganisms.

Terrestrial plants

Tier 1 screening tests at an application rate of 150 g ac/ha were conducted with the 100 g/L OD formulation and a range of crop/pasture species. Tier 2 rate response tests with individual species then followed where there was a significant difference in a parameter from the control. The most sensitive species were tomato with pre-emergence application to soil (21 d ER50 > 150 g ac/ha, 21 d ER25 = 123 g ac/ha, 21 d NOER = 37.5 g ac/ha), and onion with post emergence application to seedlings (21 d ER50 > 150 g ac/ha, 21 d NOER = 75 g ac/ha).

7.4 Risk Assessment

Du Pont™ Exirel™ insecticide will be applied by both ground application (boomspray) and aerial application (fixed wing aircraft or helicopter). For cotton, a maximum of two applications per crop season at a rate per application of 600 mL product/ha (60 g ac/ha) will be used, with a minimum spray interval of 7 days. For worst case risk assessment the higher use regime on cotton was generally considered.

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

For aquatic exposure, predicted concentrations in water in a 15 cm deep, 3 m wide pond downwind of the treated area were compared to the most sensitive endpoint for acute exposure (48 h EC50 = 20.4 µg ac/L for *Daphnia magna*). Assessment based on the acute aquatic endpoint for cyantraniliprole will also be protective of chronic aquatic and sediment exposure (21 d NOEC = 9.69 µg/L for *Daphnia magna*, 28 d NOEC for *Chironomus riparius* = 10 µg ac/L) and for exposure to cyantraniliprole metabolites. For consideration of repeated application, based on overall consideration of aquatic studies a DT50 for cyantraniliprole in water of

9.3 days was used (degradation may be much faster in the presence of sunlight, but may be limited by turbidity). Evaluation of spray drift indicated that downwind no-spray zone buffers are required to protect organisms living in water or sediment from spray drift with both ground and aerial application.

Modelling also indicated that the risk to aquatic ecosystems from the run-off of cyantraniliprole is acceptable. Based on a worst case screening model, predicted concentrations of cyantraniliprole were < 0.1 µg ac/L and well below the acute toxicity endpoint for *Daphnia magna*. Worst case modelling for cyantraniliprole metabolites indicated that one (IN-JSE76) may reach groundwater at concentrations in the range 0.1-1 µg ac/L, but in all cases predicted concentrations were well below the corresponding acute toxicity endpoints for *Daphnia magna*.

Bees may be exposed to residues of cyantraniliprole translocated into pollen and nectar, as well as to direct contact with spray or fresh residues on treated plants. Consideration of the acute oral and contact toxicity of cyantraniliprole to bees indicated an acceptable risk, but at all rates tested with the SE formulation there were temporary impacts on behaviour. Field and semi-field studies indicated that effects on bees from sprays made before flowers open are unlikely (rates up to 90 or 150 g ac/ha), though residues may be present in pollen and nectar. The studies found short term effects on mortality, behaviour and flight activity/foraging ability when spray was applied during flowering during bee flight (including at rates down to 12 g ac/ha). Such short term effects were also found when spray was applied during flowering after bee flight, but these were less severe than when made during bee flight and did not occur with applications at low rates. Overall, there was no impact on bee brood or colony development.

No unacceptable effects on populations of non-target mites or spiders exposed in-field or off-field are expected from the proposed uses in canola and cotton, and the risk to lacewings is also acceptable. However, there is a risk of harmful effects to parasitoid wasps in and downwind of the treated field. At the rate used on cotton, there is a risk of harmful effects to ladybird beetles and rove beetles within the treated field, but the risk to downwind areas is acceptable at the edge of the field. With application at the lower rate in canola, the risk to ladybird beetles and rove beetles is acceptable even with direct overspray. Studies indicate that the risk to parasitoid wasps, ladybird beetles and rove beetles reduces to acceptable levels for insects exposed 14 d after the final application.

Comparison of worst case predicted soil concentrations of cyantraniliprole and its metabolites with acute and chronic exposure endpoints for earthworms indicates an acceptable risk to earthworms, even after repeated long-term application. Comparison of predicted worst case concentrations in soil with the endpoints from laboratory studies indicates an acceptable risk to soil mites, but an unacceptable risk to collembola. A litter bag study and associated soil fauna study indicate that the risk to non-target soil macro-organisms (including collembola) and the breakdown of organic matter is acceptable under the proposed use patterns. The risk to soil microorganisms from residues of cyantraniliprole and its metabolites was also found acceptable.

For terrestrial plants, NOERs of 37.5 g ac/ha for pre-emergent application and 75 g ac/ha for post-emergent application were considered. It is concluded that no harmful effects on off field non-target terrestrial plant species are expected at the maximum single application rate of 60 g ac/ha. Based on the available data, most species would not be harmed by direct overspray to soil or foliage.

In considering the submitted data, DSEWPaC has given particular attention to the potential risks to organisms in the aquatic environment from spray drift and run-off, to bees and other terrestrial arthropods in

the treated field and off field, and to environmental exposure arising from persistence of metabolites of cyantraniliprole in soil and sediment. Based on the submitted data, the risks to birds, mammals, plants, earthworms and soil-dwelling arthropods, terrestrial invertebrates such as mites and spiders, and soil nitrogen and carbon metabolism processes were found acceptable. A risk that can be managed with specification of appropriate downwind no-spray zones to aquatic areas was identified to aquatic invertebrates with the proposed uses. Risks that can be managed through appropriate label statements were identified to bees and certain susceptible insect species that may be used in Integrated Pest Management.

8 EFFICACY AND SAFETY ASSESSMENT

The applicant seeks registration of the proposed new product, DuPont Exirel Insecticide, a suspoemulsion (SE) formulation containing 100 g/L cyantraniliprole for use in cotton to control certain Lepidopteron sucking and chewing insects.

Data from fifteen field trials were presented to demonstrate that DuPont Exirel Insecticide can be used in cotton to control certain chewing and sucking insect pests – silverleaf whitefly, cotton aphid, cotton bollworm and native budworm.

Trials conducted in Qld, NSW and WA demonstrated efficacy of DuPont Exirel Insecticide in cotton for Silverleaf whitefly (Bemisia tabaci B biotype), cotton bollworm (Helicoverpa armigera), native budworm (H. punctigera) and suppression only of cotton aphid (Aphis gossypii). The supportive trials were conducted in key cotton growing regions and environments over four seasons.

The trials were conducted using suitable methodology following randomised complete block design (RCBD) with 4 or more replicates and included industry standard comparison treatments & untreated controls. Pest pressure was recorded to be moderate to high in most trials. Treatment application and methods of assessment used in the trials were considered acceptable. Visual assessment was made of phytotoxicity.

Data obtained from the trials were analysed by appropriate statistical analytical method (ANOVA) and the mean separation were done through LSD test.

The data from seven trials (Qld 3 trials, NSW 2 trials, WA 2 trials) demonstrated efficacy and crop safety at the proposed label rate against the target stages of Helicoverpa spp.). Data generated from two trials (Qld 1 trial, NSW 1 trial) also demonstrated efficacy & crop safety at the proposed label rate against silverleaf whitefly. For the cotton aphid, data from 5 efficacy trials (Qld 4 trials, NSW 1 trial) demonstrated suppression of the pest.

Among the fifteen trials, seven trials (Qld 3 trials, NSW 2 trials, WA 2 trials) demonstrated crop safety and crop protection when used in cotton. No phytotoxicity was evident on cotton crop at treatments used at up to 2.5x the proposed label rate. This adequately supports the proposed claim for use of DuPont Exirel Insecticide at the rate of 600 mL/ha.

The label claims and instructions proposed in the Claims for Use statement, the Directions for Use table and the recommendations and statements on the labels for DuPont Exirel Insecticide is consistent with the results of the trials and other information presented.

The proposed restraints, critical comments, general instructions, methods of application & relevant statements, IPM statements, resistance warning & mode of action statements and protection statements all appear appropriate.

Therefore, in terms of the evidence of the efficacy and crop safety of the product, the application by DuPont Australia Limited to register DuPont Exirel Insecticide for the control of certain sucking and chewing insects as per the label claims is supported when used in accordance with the proposed label instructions.

9 LABELLING REQUIREMENTS

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

DuPont™

Exirel®

insecticide

DUPONT®

ACTIVE CONSTITUENT: 100 g/L CYANTRANILIPROLE

GROUP	28	INSECTICIDE

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

Contents: 10 L

DIRECTIONS FOR USE
RESTRAINTS:
DO NOT apply if heavy dew is present on crops, or if rainfall is expected within 2 hours of application.

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 BCPC Guideline.
DO NOT apply during surface temperature inversion conditions at the application site.
DO NOT apply when wind speed is less than 3 or more than 20 km per hour are measured at application site.
Users of this product MUST make an accurate written record of the details of each spray application within 24 hours following application and KEEP this record for a minimum of 2 years.
The spray application details that must be recorded are:

1. date with start and finish times of application;
2. location address and paddock/s sprayed;
3. full name of this product;
4. amount of product used per hectare and number of hectares applied to;
5. crop/situation and weed/pest;
6. wind speed and direction during application;
7. air temperature and relative humidity during application;
8. nozzle brand, type, spray angle, nozzle capacity and spray system pressure measured during application;
9. name and address of person applying this product.

(Additional record details may be required by the state or territory where this product is used.)

MANDATORY NO-SPRAY ZONES
DO NOT apply if there are aquatic or wetland areas including aquacultural ponds downwind from the application area and within the mandatory no-spray zones shown in the table below:

No-Spray zones for Protection of the Aquatic Environment		
FOR AERIAL APPLICATION		
Wind Speed Range at Time of Application	**Downwind No-Spray Zone**	
	Fixed-Wing	**Helicopter**
From 3 to 8 kilometres per hour	140 metres	100 metres
From 8 to 14 kilometres per hour	160 metres	
From 14 to 20 kilometres per hour		
FOR GROUND APPLICATION		
From 3 to 20 kilometres per hour	5 metres	

For use in all States where appropriate for the crop and/or insect pest.

CROP	PEST	RATE/HA	CRITICAL COMMENTS
Cotton	Sucking insects; Silverleaf whitefly (*Bemisia tabaci* B biotype) Cotton aphid (*Aphis gossypii*) Suppression only Chewing insects; Cotton bollworm (*Helicoverpa armigera*) Native budworm (*H. punctigera*)	600 mL + ethylated seed oil (refer Surfactant/Wetting agent section)	Heliothis - target eggs and hatchling (neonates or 1st instar) to small larvae (2nd instar) when they reach the economic spray threshold and before they become entrenched in hidden feeding sites, such as squares, flowers or bolls. Silverleaf whitefly – target early developing populations. Exirel® is primarily active on the early nymph stage. A maximum of two (2) applications are to be applied to any one crop per season. Further treatments should be made with alternative mode of action insecticides.

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

WITHHOLDING PERIODS

HARVEST

COTTON: DO NOT HARVEST FOR 14 DAYS AFTER APPLICATION.

GRAZING

COTTON: DO NOT ALLOW LIVESTOCK TO GRAZE CROPS, COTTON STUBBLE OR GIN TRASH TREATED WITH EXIREL® INSECTICIDE.

EXPORT OF TREATED PRODUCE: Suitable Maximum Residue Limits (MRLs) or import tolerances for produce treated with Exirel® insecticide may not be established in some countries. Consult with your exporter or DuPont before applying Exirel® insecticide to crops from which produce is to be exported.

GENERAL INSTRUCTIONS

DuPont™ Exirel® insecticide is an anthranilic diamide insecticide in the form of a suspo emulsion, and is to be mixed with water and applied as a foliar spray. DuPont™ Exirel® is particularly active on some sucking and chewing (Lepidopteran) insect pests.

DuPont™ Exirel® should be applied after careful field monitoring of pest populations to determine the need for application, the correct timing of the initial application and of any subsequent applications. Subsequent applications are dependent on economic thresholds, as well as the growth rate of new unprotected cotton terminals.

For *Helicoverpa* species, spray applications should be timed to coincide with egg hatching and before larvae are entrenched in protected feeding sites.

DuPont® Exirel® enters larvae primarily by ingestion, but also by contact. The product also shows ovicidal, ovi-larvicidal and adulticide efficacy, depending upon the pest species. Exposure of the pest species typically results in rapid feeding cessation within a few hours of exposure, however the time to death may take 3 to 6 days, depending upon the species.

INTEGRATED PEST MANAGEMENT

Application of DuPont™ Exirel® according to this label is expected to be safe to predatory mites, spiders and lacewings, but may have adverse effects on parasitoid wasps, ladybird beetles and rove beetles in the treated field and parasitoid wasps in downwind areas reached by spray drift.

INSECTICIDE RESISTANCE WARNING **GROUP 28 INSECTICIDE**

For insecticide resistance management DuPont™ Exirel® insecticide is a Group 28 insecticide.

Some naturally occurring insect biotypes resistant to Exirel® 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 Exirel® and other Group 28 insecticides are used repeatedly. The effectiveness of Exirel® on resistant individuals could be significantly reduced. Since the occurrence of resistant individuals is difficult to detect prior to use DuPont accepts no liability for any losses that may result from the failure of Exirel® to control resistant insects.

Strategies to minimise the risk of insecticide resistance are available. To help prevent the development of resistance to Exirel® observe the following instructions:

- Use Exirel® in accordance with the current Insecticide Resistance Management (IRM) strategy for your region.
- Apply Exirel® or other Group 28 insecticides using a "window" approach to avoid exposure of consecutive insect pest generations to the same mode of action. Multiple successive applications of Exirel® or other Group 28 insecticides are acceptable if they are used to treat a single insect generation.
- Following a "window" of Exirel® or other Group 28 insecticides, rotate to a "window" of applications of effective insecticides with a different mode of action.
- The total exposure period of all "Group 28-active windows" applied throughout the crop cycle (from seedling to harvest) should not exceed 50% of the crop cycle.
- Incorporate IPM techniques into the overall pest management program.
- Monitor insect populations for loss of field efficacy.
- Cultivate all cotton fields as soon as possible after picking to destroy over-wintering pupae of *Helicoverpa armigera*.

For further information contact your farm chemical supplier, consultant, local Department of Agriculture or Primary Industries, or local DuPont Representative.

For additional information on insect resistance, modes of action and monitoring visit the Insecticide Resistance Action Committee (IRAC) on the web at http://www.irac-online.org

MIXING

Fill spray tank to ¼ to ½ full of water. Measure the amount of Exirel® required for the area to be sprayed. Add Exirel® directly to the spray tank with the agitation engaged. Mix thoroughly to disperse the insecticide. Once dispersed, the material must be kept in suspension at all times by continuous agitation. Use mechanical or hydraulic means, **DO NOT** use air agitation, premix or slurry.

If spray solution is left standing, ensure thorough re-agitation of the spray mix until fully resuspended. **DO NOT** allow spray mix to sit overnight, as resuspension may be difficult.

SURFACTANT/WETTING AGENT

Use an ethylated seed oil at 0.5% v/v, (e.g. Hasten* @ 500 mL/100 L).

DO NOT add a surfactant/wetting agent if:

- mixing with another product which already contains a surfactant and/or the product label advises not to add a surfactant.
- mixing with a liquid fertiliser

ACIDIFICATION OF THE SPRAY TANK

If the pH of the spray tank after all products have been added and mixed is above pH 8, adjust to pH 8 or less using a registered acidifying agent. If the spray tank pH is 8 or less no adjustment of the spray tank pH is necessary. Spray tanks of pH 8 or less can be held for up to 8 hours before spraying. **DO NOT** store the spray mixture overnight in the spray tank.

APPLICATION

Droplet VMD should be of medium spray quality according to ASAE S572 definition for standard nozzles.

Ground application

Apply as a *blanket* spray or as a *banded* spray. Ensure thorough spray coverage on the foliage, using appropriate fan nozzles. Apply in a minimum spray volume of 100 L/ha and keep the boom low to avoid spray drift. A minimum spray pressure of 275 kPa (40 psi) should be used with fan nozzles applying insecticides. **Higher pressure reduces droplet size, DOES NOT improve canopy penetration and may increase drift potential.** WHEN HIGHER FLOW RATES ARE NEEDED, USE A HIGHER-CAPACITY NOZZLE INSTEAD OF INCREASING PRESSURE. For band spraying, increase the number of fan nozzles per crop row as the plant size increases.

Aerial application

DuPont™ Exirel® must only be applied with aircraft fitted with accurately calibrated equipment. Apply a minimum total spray volume of 30 L/ha with nozzles (e.g. Micronaire rotary atomisers, CP nozzles or conventional hydraulic nozzles) set to medium spray quality according to ASAE S572 definition for standard nozzles. A spray drift minimisation strategy should be employed at all times when applying this product. **DO NOT apply Exirel® using Ultra Low Volume (ULV) methods.**

Compatibility

Since formulations may be changed and new ones introduced, it is recommended that users premix a small quantity of the desired tank mix and observe possible adverse changes (settling out, flocculation etc).

Avoid complex tank mixtures of several products or very concentrated spray mixtures.

Spray Equipment Cleanout

Prior to application, start with clean, well-maintained application equipment. Immediately following application, thoroughly clean all spray equipment to reduce the risk of forming hardened deposits which might become difficult to remove. Drain spray equipment. Thoroughly rinse sprayer and flush hoses, boom, and nozzles with clean water.

Clean all other associated application equipment. Take all necessary safety precautions when cleaning equipment. **DO NOT** clean near wells, water sources or desirable vegetation. Dispose of waste rinse water in accordance with local regulations.

PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS

DO NOT apply under weather conditions, or from spraying equipment, that may cause spray to drift onto near-by non-target plants/crops, cropping lands or pastures.

PROTECTION OF LIVESTOCK

Toxic to bees. Will kill foraging bees directly exposed through contact during spraying and while spray droplets are still wet. May harm bees in hives which are over-sprayed or reached by spray drift. Beekeepers who are known to have hives in, or nearby, the area to be sprayed should be notified no less than 48 hours prior to the time of the planned application so that bees can be removed or otherwise protected prior to spraying.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

Very toxic to aquatic life. Drift and run off from treated areas may be hazardous to aquatic organisms in neighbouring areas. **DO NOT** contaminate wetlands or watercourses with the product or used containers.

STORAGE AND DISPOSAL

Store in the closed, original container in a dry, well-ventilated area, as cool as possible out of direct sunlight.

Triple or preferably pressure rinse containers before disposal. Add rinsings to spray tank. **DO NOT** dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and deliver empty packaging for appropriate disposal at 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.

PRECAUTION

DO NOT use human flaggers/markers unless they are protected by engineering controls such as vehicles with enclosed cabs.

SAFETY DIRECTIONS

May irritate the eyes. Will irritate the skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. When opening the container and preparing spray and using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and 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 13 11 26.

IN A MEDICAL EMERGENCY CALL
1800 674 415 All hours

MATERIAL SAFETY DATA SHEET
Additional information is listed in the Material Safety Data Sheet (available from http://www.dupont.com.au).

NOTICE TO BUYER
To the extent permitted by law all conditions and warranties and statutory or other rights of action which buyer or any other user may have against DuPont or Seller are hereby excluded. DuPont hereby gives notice to buyer and other users that it will not accept responsibility for any indirect or consequential loss arising from reliance on product information or advice provided by DuPont or on its behalf unless it is established that such information or advice was provided negligently and that the product has been used strictly as directed. DuPont's liability shall in all circumstances be limited to replacement of the product or a refund of the purchase price paid therefore.

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ABBREVIATIONS

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

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

NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OD	Oil Dispersion
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
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.
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 P_{ow}	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

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