Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the new active Flonicamid in the product Mainman 500 WG Insecticide

APVMA Product Number P66373

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PREFACE

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

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

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

The information and technical data required by the APVMA to assess the safety of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined in the APVMA's 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 **MAINMAN 500 WG 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 **7 October 2014** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

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

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

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

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

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

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

Further information

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

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

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

1 INTRODUCTION

Ishihara Sangyo Kaisha Ltd applied to the APVMA for approval of the new active constituent flonicamid and the registration of the new product Mainman 500 WG Insecticide.

Flonicamid is new to the Australian market and belongs to the nicotinoid class of insecticides and exhibits systemic and translaminar activity and inhibits feeding. The CropLife Australia's Insecticide Resistance Management Review Group has designated flonicamid as a Group 9, sub-group C, insecticide. Group 9 insecticides are selective homopteran feeding blockers. The proposed use pattern is subject to a CropLife anti-resistance management strategy. Restraints included on the proposed label are consistent with the current CropLife Australia resistance management strategy for Group 9 insecticides.

It is proposed to register Mainman 500 WG Insecticide, containing 500 g/kg flonicamid as a water dispersible granule in apples, cotton, cucurbits and potatoes. It is intended for the control of woolly aphid, mealybug, cotton aphid, green mirids, green peach aphid, melon aphid, silverleaf whitefly and potato aphid.

Mainman 500 WG Insecticide will be imported fully formulated and be available in 500 g, 1 kg and 5 kg pack sizes.

Flonicamid is currently registered in the USA, Canada, Germany and the United Kingdom.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Mainman 500 WG Insecticide, and approval of the new active constituent, flonicamid.

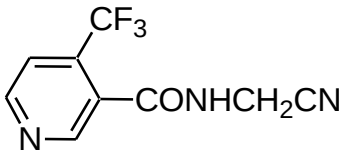
2 CHEMISTRY AND MANUFACTURE

2.1 Active Constituent

Manufacturing Site

The active constituent Flonicamid will be manufactured at 433 Mocnae-dong, Ansan-si, Gyeonggi-do, Republic of Korea.

Chemical Characteristics of the Active Constituent

COMMON NAME (ISO):	Flonicamid
IUPAC NAME:	*N*-cyanomethyl-4-(trifluoromethyl)nicotinamide
CAS NAME:	*N*-(cyanomethyl)-4-(trifluoromethyl)-3-pyridincarboxamide
PRODUCT NAME:	ISK Flonicamid 500 WG Insecticide
CAS REGISTRY NUMBER:	158062-67-0
MOLECULAR FORMULA:	$C_9H_6F_3N_3O$
MOLECULAR WEIGHT:	229.2
STRUCTURE:	
CHEMICAL FAMILY:	pyridinecarboxamide compounds

APVMA Active Constituent Standard for Flonicamid Active Constituent

Constituent	Specification	Level
Flonicamid	Flonicamid	Not less than 960 g/kg

Physical and Chemical Characteristics of the Active Constituent

MODE OF ACTION:	Starvation based on the inhibition of stylet penetration to plant tissues (selective feeding blocker).
APPEARANCE:	Physical state: Solid powder at 25^{o}C. Odour: Odourless. Not characteristic. Colour: Off-white (Munsell colour = N9.25/84.2%R)
APPEARNCE OF TEST ITEM IN PRESENCE OF METALS/METAL IONS. (OPPTS 830.6313)	Physical state: Solid fleecy product without visible extraneous matter. Odour: Not characteristic. Colour: Iron powder= Grey. Ferrous acetate= Beige. Aluminium powder= Grey and Aluminium acetate= Off-white.
MELTING POINT:	157.5 °C
RELATIVE DENSITY:	1.54 (20^{o}C/ 20^{o}C)
PH OF 1% AQUEOUS MIXTURE	4.5 at 25ºC
SOLUBILITY IN WATER:	5.2 g/L at 20±0.5 ºC
OCTANOL/WATER PARTITION COEFFICIENT (P_{OW}):	1.9 ($LogP_{ow}$ = 0.3) at 29.8°C. Purity of test substance 99.0%.
DISSOCAITION CONSTANT ($_{P}KA$)	11.60 at 20±1^{o}C in 5% ethanol/water between pH 10-12.
UV/VIS ABSORPTION (MAX.)	Neutral pH = λ_{max}265nm, pH <2 = λ_{max}266nm pH >2 = λ_{max}270nm, pH>12 = λ_{max}204nm
FLAMMABILITY (EEC A.10 METHOD):	Not flammable.
AUTO-FLAMMABILITY (EEC A.16 METHOD):	25^{o}C± 1^{o}C = 47.3 mN/m 40^{o}C± 1^{o}C = 47.0 mN/m (test item is surface active)
OXIDISING PROPERTIES:	None oxidizing. Based on the second criteria of the Orange book UN recommendations on the Transport of Dangerous Goods.

2.2 Product

Mainman 500 WG Insecticide

DISTINGUISHING NAME:	Mainman 500 WG Insecticide
FORMULATION TYPE:	Water Dispersible Granule (WG)
ACTIVE CONSITUENT CONCENTRATION:	Flonicamid (500g/kg)

PHYSICAL AND CHEMICAL PROPERTIED OF THE PRODUCT

APPEARANCE:	Brown granules with slight odour of ammonia
PH VALUE:	Brown granules with slight odour of ammonia
EXPLOSIVE PROPERTIES:	Not explosive
OXIDISING PROPERTIES:	No oxidising properties
FLAMMABILITY:	Not flammable
CORROSIVE HAZARD:	Not corrosive to HDPE containers
FLASH POINT:	Not applicable
ACTIVE SUSPENSIBILITY:	100% (60-105%) 99.8%
WE SEIVE TEST:	0.02% (Max 2% retained on a 75µm sieve)
PERSISTENT FOAM:	60mL 3 minutes 59mL (Max 60 mL foam after 1 minute)
DUST CONTENT:	9.2 mg (Max 1% <50 µm)
FLOWABILITY:	0% w/w retained. (Flow through sieve after maximum 5 lifting)
BULK DENSITY:	0.5 - 0.8
ATTRITION RESISTENCE:	97.1% (>90%)
PARTICLE SIZE DISTRIBUTION:	X_1= 250µm where R_x ± 90%, X2 = 850µm ≤ 10%
DISPERSIBILITY:	84.6% (60-105%)
STORAGE STABILITY	Stability data provided by the applicant indicates that the product is expected to remain within specification for at least 2 years when stored under normal conditions in High density Polyethylene (HDPE) packs.

3 TOXICOLOGICAL ASSESSMENT

The submitted toxicology data on flonicamid was extensive and comprehensive. The data included studies on toxicokinetics/metabolism, acute, short-term, sub-chronic, chronic and carcinogenicity (two species), reproduction and developmental studies, neurotoxicity and genotoxicity studies. Acute oral toxicity, sub-chronic and genotoxicity studies were conducted on a number of metabolites on flonicamid.

In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are generally used to develop acceptable limits for dietary or other intakes (ADI- Acceptable daily Intake and ARfD- Acute Reference Dose) at which no adverse health effects in humans would be expected.

The Office of Chemical Safety (OCS) within the Department of Health and Ageing, Australia conducted the toxicological assessment of flonicamid and the product Mainman 500 WG Insecticide.

3.1 Toxicokinetics and Metabolism

Radiolabelled flonicamid was rapidly absorbed in rats and maximum plasma concentrations ranged from 0.25 to 1 hour. In rats dosed with flonicamid, distribution within the tissues in both sexes were similar with highest concentrations found in the liver, kidney, adrenals and thyroid 30 minutes post dose. Levels of radioactivity decreased up to a 100-fold 168 hours post dose with less than 2% remaining in the carcass. The metabolites identified in rat urine and faeces were TFNG-AM, TFNG, TFNA-AM, OH-TFNA-AM, TFNA and TFNA-OH. The parent compound accounted for the majority of excreted residues in the urine with 52–60% in the low dose groups and 63–73% in the high dose group. The major metabolites in urine included TFNA-AM which accounted for 21–25% of the administered dose in the low dose group and 18–23% in high dose animals. TFNA-AM N-oxide, OH-TFNA-AM, TFNG-AM, IKI-220 N-oxide and TFNA accounted for less than 3.2% of the administered dose in urine. The parent compound accounted for the majority of excreted residue in the faeces (0.79–1.22% in high dose animals and 0.52–0.56% in low dose animals). TFNA-AM was the major metabolite in the faeces, accounting for 0.51–1.02% in the high dose animals. TFNA was present at 0.05–0.07% the faeces in low dose animals only. Elimination times for both sexes were similar at low doses, however at higher doses males exhibited a longer half-life of 11.6 hours compared to 6.8 hours in females. Elimination from the plasma occurred in a first order elimination manner. The majority of the administered dose, approximately 75–90%, was excreted in the urine within 24 hours at high and low dose levels in either sex. Minor excretion also occurred through the faeces, accounting for approximately 5% with the majority excreted within the first 48 hours. No radio label was detected in respired air. Biliary excretion

was not considered as a significant route of elimination as it accounted for 4% of the administered dose in both sexes in low dose animals and 4–5% in high dose animals, with the majority being excreted within the first 24 hours.

At end-use concentrations, dermal absorption of Mainman 500 WG Insecticide was estimated to be limited, based on results from an *in vitro* dermal absorption study that used humansplit thickness skin samples.

Acute Studies

Flonicamid technical was of low acute oral, dermal and inhalational toxicity in rats. It was non-irritating to rabbit skin but slightly irritating to the eye of rabbits. It was non-sensitising to the skin of guinea pigs.

The formulated product Mainman 500 WG Insecticide is of low acute oral, acute dermal and acute inhalation toxicity in rats. The product is a non-irritant to the skin of rabbits and is severely irritating to the eye of rabbits. The product is not a skin sensitiser in guinea pigs.

Systemic Effects

Repeat dose toxicity testing was performed using rats, mice and dogs. The primary target organs of toxicity were the liver in the rat, mouse and dog, the haematopoietic system in the dog, rat and mouse, and the lungs in mice (see carcinogenicity below).

In a short term dietary study in rats, a NOEL was established at 1000 ppm in both sexes (equivalent to 73.8 mg/kg bw/day in males and 81.9 mg/kg bw/day in females) based on decreased bodyweight gain in males only and decreased liver weight, increased cholesterol levels and changes in other blood chemistry, and haematology, parameters in both sexes at 5000 ppm. Kidney toxicity (increased organ weight and macroscopic and microscopic changes) was observed in males at 1000 ppm and greater. However, a slight to moderate increase was seen in hyaline droplet deposition in the proximal tubular cells of the kidney in males at 100 ppm and greater. The role of α2µ-globulin which accumulates in hyaline droplets in male rats, and kidney toxicity has been extensively investigated, and the data indicates that, as seen in this study, α2µ-globulin is sex specific (males) and an absence of hyaline droplets and other histopathological changes to the kidney are observed in female rats. Further, there is convincing evidence that the protein α2µ-globulin does not occur in humans. Consequently, OCS considers that the observed hyaline droplet nephropathy in male rats only was due to α2µ-globulin formation and is not relevant to humans.

Similar findings were seen in a subchronic dietary study in rats, with the observed hyaline droplet associated nephropathy in male rats not considered relevant to humans. A NOEL (No Observable Effect Limit) was established at 1000 ppm in both sexes (equivalent to 60.0 mg/kg bw/day in males and 72.3 mg/kg bw/day in females) based on increased liver weight in females, and histopathological changes to the liver accompanied by changes in relevant blood biochemistry parameters, along with changes in haematology parameters in both sexes and an increase in kidney weight with associated histopathological changes in the kidney.

A NOEL of 8 mg/kg bw/day was identified in both sexes in 13- and 52-week oral studies in dogs. This was based on increased incidence of vomiting and reduced body weight gain in both studies, along with mortality, an increase in thymus weight, and minor histopathological changes in the pancreas, thymus and kidneys in the 13-week study. In the 52-week study, an increase in mean corpuscular volume in males and mean

corpuscular haemoglobin and reticulocyte levels was also seen in both sexes that were suggestive of a treatment related effect on circulating red blood cells.

Carcinogenicity

In an 18-month dietary study in mice with daily dosing with flonicamid at 0, 250, 750 and 2250 ppm in both sexes, treatment related non-neoplastic findings were also observed, specifically focal alveolar/bronchiolar hyperplasia in both sexes at 250 ppm and greater, hepatocellular hypertrophy in males at 250 ppm and greater and in females at 2250 ppm. At 2500 ppm an increase in liver weight increased extramedullary haematopoiesis and pigment deposition in the spleen in both sexes and hypocellularity in the bone marrow in both sexes was observed. Furthermore, a statistically significant increase in the incidence of alveolar/bronchiolar adenomas was seen in male and female CD-1 mice at 250 ppm up and greater, and a statistically significant increase in the incidence of alveolar/bronchiolar carcinoma was observed at 750 ppm and greater in males and in females at 2250 ppm. However, on the basis of submitted mechanistic data (see below), the OCS considers the observed pulmonary tumours in CD-1 mice to be species and strain specific and of low relevance to humans. A NOEL could not be determined as treatment related histopathological changes were seen in the terminal bronchioles of the lungs in both sexes and in the liver of females at all dose levels. Thus, a LOEL (Lowest Observable Effect evel) of 250 ppm (equivalent to 29 and 38 mg/kg bw/day in males and females respectively) was identified in this study.

In a follow up study to determine a NOEL, male and female mice received flonicamid daily in the diet at 0, 10, 25, 80 or 250 ppm. No treatment related toxicologically significant findings were seen at 10, 25 and 80 ppm. The NOEL for chronic oral toxicity was 80 ppm in both sexes (equivalent to 10.0 mg/kg bw/day in males and 11.8 mg/kg bw/day in females) based on an increased incidence of hyperplasia/hypertrophy of the epithelial cells lining the terminal bronchioles in both sexes, and an increased incidence of centrilobular hepatocellular steatosis in females at 250 ppm. Although incidence of alveolar/bronchiolar adenomas was seen in male mice at 250 ppm, on the basis of submitted mechanistic data (see below) the OCS considers the observed pulmonary tumours in CD-1 mice to be species and strain specific and of low relevance to humans.

In a combined chronic toxicity and carcinogenicity study, rats received flonicamid daily in the diet at concentrations of 0, 50, 100, 200 and 1000 ppm for males and 0, 200, 100 and 5000 ppm for females, for a period of up to 24 months. Based on the findings of this 104-week study the NOEL is 200 ppm in males (equivalent to 7.32 mg/kg bw/day) based on decreased bodyweight and bodyweight gain and fore-stomach erosion/ulceration at 1000 ppm, while the NOEL for female rats was established at 1000 ppm (equivalent to 44.1 mg/kg bw/day) based on reduced bodyweight and bodyweight gain, haematological changes indicative of mild anaemia, changes in blood biochemical parameters, increased relative liver and kidney weight with accompanying histopathological changes, and atrophy of the striated muscle fibre of the triceps surae at 5000 ppm. The test material was not carcinogenic to male or female rats.

Mechanism Studies: Lung Tumours in CD-1 Mice

In the 18-month dietary carcinogenicity studies in CD-1 mice, an increased incidence in bronchioloalveolar tumours was seen in the lung at 250 ppm and greater, with data from the two studies demonstrating males to be the more sensitive sex. It was seen from mechanistic studies that, compared to controls, a dose dependent increase in BrdU labelling in the terminal bronchioles of the lung was seen at 250 ppm and

greater in male CD-1 mice following dietary administration of flonicamid for 3 consecutive days in the diet. Thus, the observed increase in cell division in the lungs correlated with the concentration at which an increased incidence in pulmonary tumours was observed in CD-1 mice in the carcinogenicity studies. Additionally, a further mechanistic study indicated that, compared to controls, dietary administration of flonicamid to male CD-1 mice for 28 consecutive days at 2250 ppm (the only dose level tested, and the maximum dose level tested in the mouse carcinogenicity studies) resulted in increased cell division in the terminal bronchioles which was associated with a proliferation of Clara cells within the terminal bronchioles. Additionally in this study, compared to controls, in flonicamid treated CD-1 male mice longitudinal elongation and hyperplasia/hypertrophy of the Clara cells was seen, with the Clara cells being more compacted, with protruded cytoplasm and the secretory granules in the cytoplasm being slightly enlarged. While the observed increased proliferation of Clara cells and the observed morphological changes in these cells were rapidly reversible, being absent 7 days after the cessation of dosing in recovery animals.

Noting that following administration of flonicamid no evidence of necrosis, inflammation, or other lesions was seen in the terminal bronchioles of the study which used electron microscopy (or the other mechanistic studies employing light microscopy), and an absence of a mutagenic and/or genotoxicity potential for flonicamid *in vitro* and *in vivo*, OCS considers that the studies provide evidence suggesting that the lung tumours observed in CD-1 mice occur by a mitogenic mechanism that target Clara cells.

A further study in which male CD-1 mice were administered flonicamid or the metabolites TFNG, TFNA or TFNA-AM (the latter being the main metabolite detected in the urine and bile in oral toxicokinetic studies in Sprague Dawley rats) demonstrated that flonicamid and not its metabolites is responsible for the observed evidence of a mitogenic activity in CD-1 mice.

No increased incidence of lung tumours was seen in a 2-year dietary study in Wistar rats. In a further mechanistic study, in contrast to female CD-1 mice no increase in cell division (*i.e.* BrdU labelling) was seen in the terminal bronchioles of the lung in female Wistar rats administered 2250 ppm flonicamid in the diet for 3 consecutive days. Further, information in the scientific literature indicated that the incidence of Clara cells in the terminal bronchioles of rats (35%) was considerably less than in mice (80%). Thus, OCS considers that the data show that the observed pulmonary tumours likely occur in CD-1 mice and not Wistar rats due a mitogenic mechanism targeting Clara cells whose incidence is considerably greater in mice than rats.

Furthermore, an increased incidence of cell division in the terminal bronchioles was seen in male CD-1 mice but not male B6C3F1 and male C57/6J mice following dietary administration of 2250 ppm flonicamid for 3 consecutive days to all 3 mouse strains. Therefore, the study demonstrated that CD-1 mice are the more sensitive mouse strain to flonicamid treatment and their lung cells are more likely to be stimulated by a likely mitogenic mechanism. Thus, OCS considers that the study provides evidence that the observed flonicamid induced bronchioloalveolar tumours in CD-1 mice are not only species specific but likely strain specific.

OCS notes that there was no difference in the incidence of Clara cells in the terminal bronchioles between the 3 strains of mice (approximately 80% for each strain), though there is information in the scientific literature indicating a significant difference in the spontaneous incidence of bronchoalveolar tumours in CD-1 mice (33.4%/27.6% in males females) compared to B6C3F1 mice (19.1%/7.3%, and Wistar rats; 1.3%/2.6%). Further, in contrast to the findings seen between male CD-1, B6C3F1 and C57/6J mice, an increased incidence of cell division in the terminal bronchioles was seen in all 3 mouse strains following administration of isoniazid which is structurally similar to flonicamid. It was also reported from a secondary

source (not assessed by OCS) that isoniazid did not induce lung tumours in the AKR mouse strain which is similar to the C57 strain in the *'level of resistance'* to bronchioloalveolar lung tumours. Thus, taken together OCS considers that the data provides further evidence to support the observed tumours in CD-1 mice being strain specific and, additionally, possibly occurring due to an increased susceptibility of CD-1 Clara cells to a mitogenic action.

Finally, isoniazid which bears a structural similarity to flonicamid and exerted a greater mitogenic effect in male CD-1, B6C3F1 and C57/6J mice than flonicamid, has been widely used in the treatment of tuberculosis in humans and IARC concluded there was no epidemiological link between the use of isoniazid and human lung tumours. Furthermore OCS notes that the reported incidence of Clara cells in the terminal bronchioles of humans (22%) was less than that in rats (35%) and substantially less than that in mice (80%) as was the spontaneous incidence of bronchoalveolar tumours in humans (0.0025% and 0.0005% in males and females respectively).

Consequently, overall, OCS considers that based on the available data the observed bronchioloalveolar lung tumours in CD-1 mice (for which a NOEL of 80 ppm was established) are induced by flonicamid and not its metabolites. Further, these tumours likely occur by a mitogenic mechanism targeting Clara cells and, compared to rats, is not only species specific but strain specific to CD-1 mice, and possibly occur due to an increased susceptibility of CD-1 Clara cells to a mitogenic action. Isoniazid which bears a structural similarity to flonicamid, exerts a greater mitogenic effect in CD-1, B6C3F1 and C57/6J mice and has been used medically in humans with no evidence of inducing bronchoalveolar tumours. Considering significant morphological differences in the terminal bronchioles of humans (i.e. substantially less Clara cells) and a reduced susceptibility to spontaneous bronchoalveolar tumours, OCS indicated that the observed bronchioloalveolar lung tumours in CD-1 mice are of low relevance to humans.

Genotoxicity

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

Reproductive Toxicity

There was no evidence of reproductive toxicity in a two generation reproductive toxicity study in rats. Systemic toxicity observed in parental animals consisted of increased thyroid, liver, kidney and spleen weight together with microscopic changes in the kidneys. As for repeat dose studies in the rat, the observed nephrotoxicity in male rats was considered associated with α2µ-globulin formation and not relevant to humans.

A receptor binding assay was performed to determine the binding affinity of flonicamid for oestrogen receptors from F1 parental female blood from the above 2-generation rat study. It is considered that the data from this non-standard study does not provide any reliable evidence to support a hormone mediated effect in the 2-generation study.

Developmental Toxicity

In an oral developmental toxicity study in rats, a NOEL of 100 mg/kg bw/day was established for both maternal and developmental toxicity. The only observed treatment related maternal toxicity was increased liver weight and microscopic changes to the liver and kidney at 500 mg/kg bw/day. At this dose level an increased incidence of foetuses and litters with skeletal variations due specifically to an increased incidence of cervical rib was observed. No historical control data was provided to allow a more informed evaluation of the observed foetal findings, though it is considered that the observed skeletal variations are treatment related and unlikely to be a secondary non-specific consequence of the observed 'slight' maternal toxicity (*i.e.*, liver and kidney toxicity). It is considered that this singular finding alone in the presence of 'slight' maternal toxicity does not provide reliable evidence that flonicamid presents a hazard for developmental toxicity, rather it is only suggestive of a developmental toxicity potential.

In an oral developmental toxicity study in rabbits, a NOEL of 7.5 and 2.5 mg/kg bw/day was established for maternal and developmental toxicity respectively. A number of visceral malformation and variations were seen with accompanying marked maternal toxicity and are considered a secondary non-specific consequence of such. In the absence of maternal toxicity there was evidence of developmental toxicity, albeit in a small number of animals (abnormal lung lobation in 2/156 foetuses [1.28%] and absent kidney and ureter in 1/156 foetuses [0.64%]) though these finding were very rarely seen (0.09% for abnormal lung lobation) or absent from a historical database of 2177 foetuses (*i.e*., absent kidney and ureter).

OCS considers that based on the suggestion of a developmental toxicity potential in rats and limited evidence of developmental toxicity in rabbits, flonicamid be considered a possible developmental toxicant. In accordance with the NOHSC (National Occupational Health and Safety Commision) *Approved Criteria for Classifying Hazardous Substances* OCS has determined that Mainman 500 WG Insecticide is a hazardous substance and has assigned it the following risk phrases: *'R63- Possible risk of harm to unborn child'*.

Neurotoxicity

In the rat, no reliable evidence of a neurotoxicity potential was seen in an oral acute neurotoxicity study, an oral 28-day dose range finding neurotoxicity study and an oral sub-chronic neurotoxicity study, up to dose levels that produced systemic toxicity.

Other studies

Flonicamid metabolites TFNA, TFNA-AM, TFNG, TFNA-AM and TFNA-OH were all of low acute oral toxicity in the rat and not mutagenic in an Ames test with and without metabolic activation. Additionally, in two non-GLP subchronic oral studies of diminished regulatory value undertaken with the predominant metabolites TFNA and TFNG, no treatment related systemic toxicity was observed. The NOEL was established at the highest dose tested; 2000 ppm in males and 5000 ppm in females (equivalent to 136 and 409 mg/kg bw/day, respectively) for TFNA, and 2000 ppm in males and 5000 ppm in females (equivalent to 135 and 411 mg/kg bw/day, respectively) for TFNG.

3.2 Public Health Standards

Poisons Scheduling

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

Flonicamid was discussed at the February 2012 meeting of the ACCS. The delegate noted and agreed with the recommendation of the ACCS to include flonicamid in Schedule 6 of the SUSMP with no cut-off, along with an implementation date of 1st September 2012 (interim decision of the delegate). The delegate's final decision made on 30th May 2012 confirmed that flonicamid be listed in Schedule 6 of the SUSMP with no cut-off, along with an implementation date of 1st September 2012. Based on data subsequently submitted on Mainman 500 WG Insecticide containing 500 g/kg flonicamid, the current listing in Schedule 6 of the SUSMP with no cut-off remains appropriate.

NOEL/ADI/ ARfD

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

The ADI for flonicamid was established at 0.025 mg/kg bw, based on a NOEL of 2.5 mg/kg bw/day in a rabbit developmental study for developmental toxicity and using a default 100-fold safety factor to account for potential interspecies and intra-species variation.

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

The ARfD for flonicamid was established at 0.025 mg/kg bw, based on a NOEL of 2.5 mg/kg bw in a rabbit developmental study for developmental toxicity and using a default 100-fold safety factor to account for potential interspecies and intra-species variation.

4 RESIDUES ASSESSMENT

4.1 Introduction

Mainman 500 WG Insecticide contains the new active constituent flonicamid (Figure 1) and is proposed for use on apples, potato, cotton and cucurbits. As part of the residues assessment for flonicamid, plant and animal metabolism studies, supervised residue trials and trade aspects were considered.

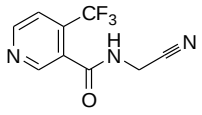


Figure 1: flonicamid

4.2 Metabolism

Plants

The metabolism of flonicamid was investigated in wheat, potatoes and peaches. The major metabolites were found to be *N*-(4-trifluoromethylnicotinoyl)glycine (TFNG) and 4-trifluoromethylnicotinic acid (TFNA).

Wheat

A single application of [^{14}C]-flonicamid, labelled with ^{14}C in the 3-position of the pyridyl ring, was made to wheat plants at a rate of 100 g ai/ha at a 21 day pre-harvest interval. An additional set of wheat plants were treated at an exaggerated rate of 500 g ai/ha, to generate additional residues for identification. Wheat plants were harvested at maturity and separated into straw, chaff and grain.

Approximately 76–89% of TRR was extractable from the straw, chaff and grain samples using this method. The amount of parent compound present in grain, straw and chaff was 0.083 ppm (29.9% of TRR), 1.021 (50.2% of TRR) and 1.467 ppm (40.7% of TRR), respectively. The major metabolite was identified as TFNG, accounting for 39.4% of TRR in grain, 19.6% of TRR in straw and 16.6% of TRR in chaff. TFNA accounted for 8.1% of TRR in grain, 2.0% of TRR in straw and 5.7% of TRR in chaff.

Based on these results a metabolic pathway was proposed for flonicamid in wheat (Figure 2). The main pathway of metabolism involved hydrolysis of –CN and –CONH functional groups in the molecule.

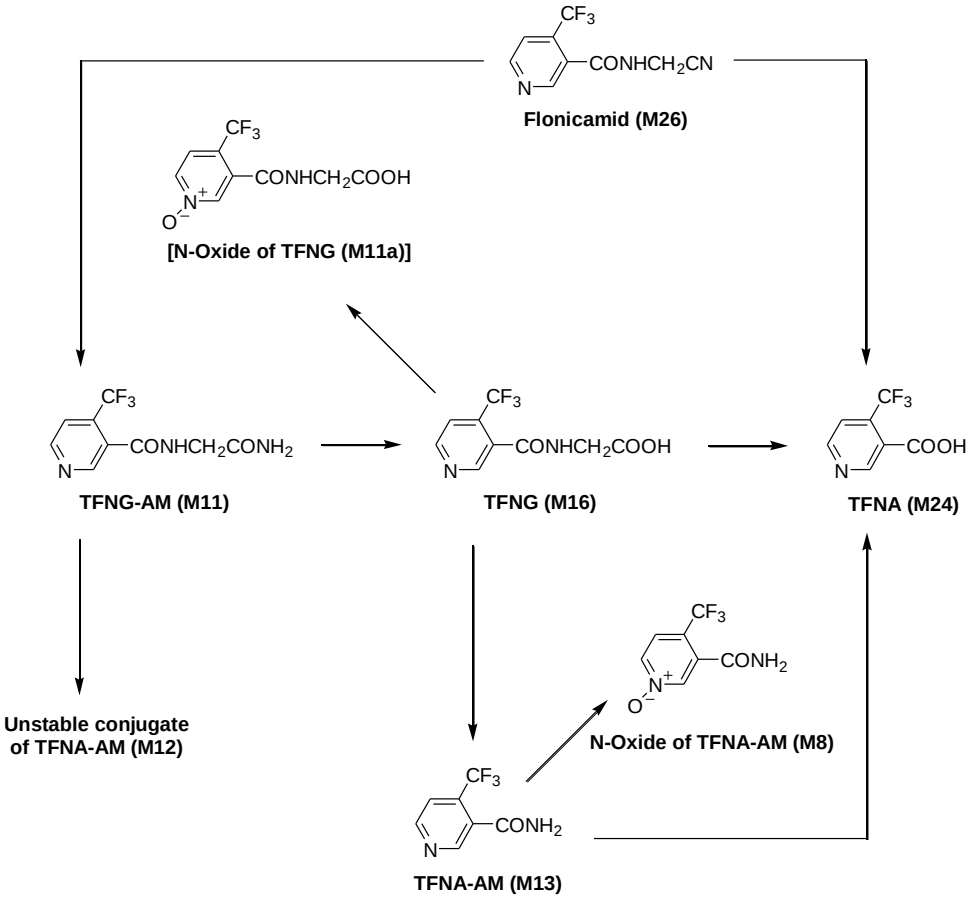


Figure 2: Proposed metabolic pathway of flonicamid in wheat

Peaches

Two applications of [^{14}C]-flonicamid, labelled with ^{14}C in the 3-position of the pyridyl ring, were made at two-week intervals at rates of 100 g ai/ha (1×) and 500 g ai/ha (5×). Mature peach fruits and foliage were harvested 21 days after the second application.

Approximately 89–98% of TRR was extractable from peach fruit and foliage using this method. The total radioactive residues in peach fruit were low. Parent compound in peach fruit accounted for 30.1% of TRR (0.03 ppm). TFNA was the major metabolite (49.3% of TRR, 0.05 ppm). The metabolite profile in the foliage was similar to the mature fruit.

Based on these results a metabolic pathway was proposed for flonicamid in peaches (Figure 3). The main pathway of metabolism involved hydrolysis of –CN and –CONH functional groups in the molecule.

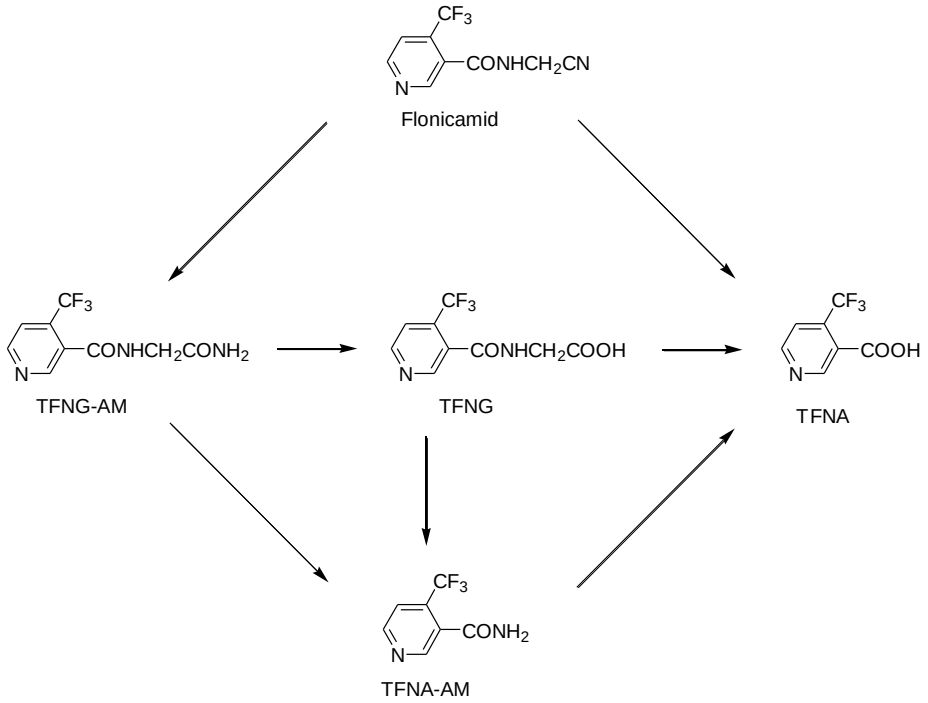


Figure 3: Proposed metabolic pathway of flonicamid in peaches

Potatoes

Two applications of [^{14}C]-flonicamid, labelled with ^{14}C in the 3-position of the pyridyl ring, were made at two-week intervals at rates of 100 g ai/ha and 500 g ai/ha. Potato tubers and foliage were harvested two weeks after the second application.

Approximately 90% of TRR was extractable from potato tubers and foliage using this method. The amount of parent compound present in tuber samples was 0.006 ppm (5.6% of TRR). Major metabolites in the tuber were TFNG (0.04 ppm, 39.3% of TRR) and TFNA (0.04 ppm, 34.4% of TRR). The metabolite profile in the foliage was similar to tubers.

Based on these results a metabolic pathway was proposed for flonicamid in potatoes (Figure 4). The main pathway of metabolism involved hydrolysis of –CN and –CONH functional groups in the molecule.

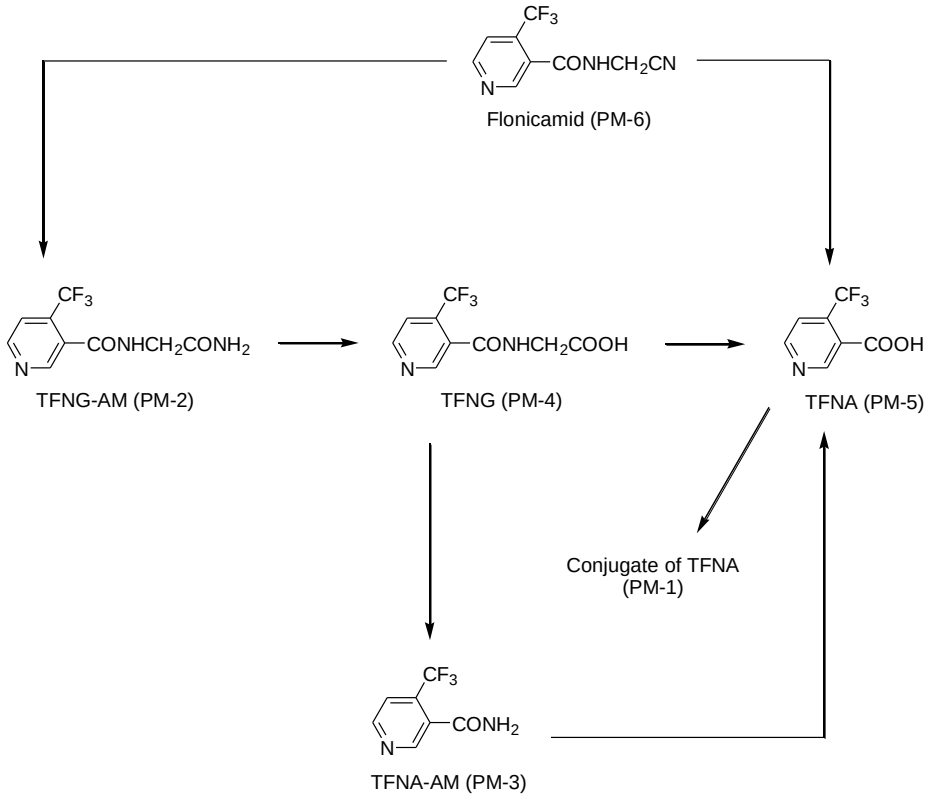


Figure 4: Proposed metabolic pathway of flonicamid in potato.

Livestock

The metabolism of flonicamid was investigated in laying hens and lactating goats. The major metabolite was found to be 4-trifluoromethylnicotinamide (TFNA-AM).

Lactating Goats

Two goats were orally dosed via gelatin capsule with [^{14}C]-flonicamid, labelled with ^{14}C in the 3-position of the pyridyl ring, once daily for 5 consecutive days. The dose was equivalent to approximately 10 ppm in the feed. Milk, urine, faeces and stanchion washes were collected during the dosing period. Animals were sacrificed within 5–8 hours of the last dose. Liver, kidney, omental fat, perirenal fat, loin muscle, rear leg muscle, heart and blood samples were collected.

Flonicamid was identified in milk (1.2% TRR, 0.001 ppm), muscle (2.0% TRR, 0.007 ppm), fat (5.5% TRR, 0.006 ppm), kidney (1.6% TRR, 0.01 ppm) and liver (0.6% TRR, 0.008 ppm). The main metabolite was identified as TFNA-AM and was identified in milk (97.4% TRR, 0.084 ppm), muscle (50.2% TRR, 0.17 ppm), fat (74.1% TRR, 0.1054 ppm), kidney (41.1% TRR, 0.27 ppm) and liver (29.4% TRR, 0.35 ppm).

Based on these results a metabolic pathway was proposed for flonicamid in lactating goats (Figure 5). The main pathway of metabolism involved hydrolysis of –CN and –CONH functional groups in the molecule.

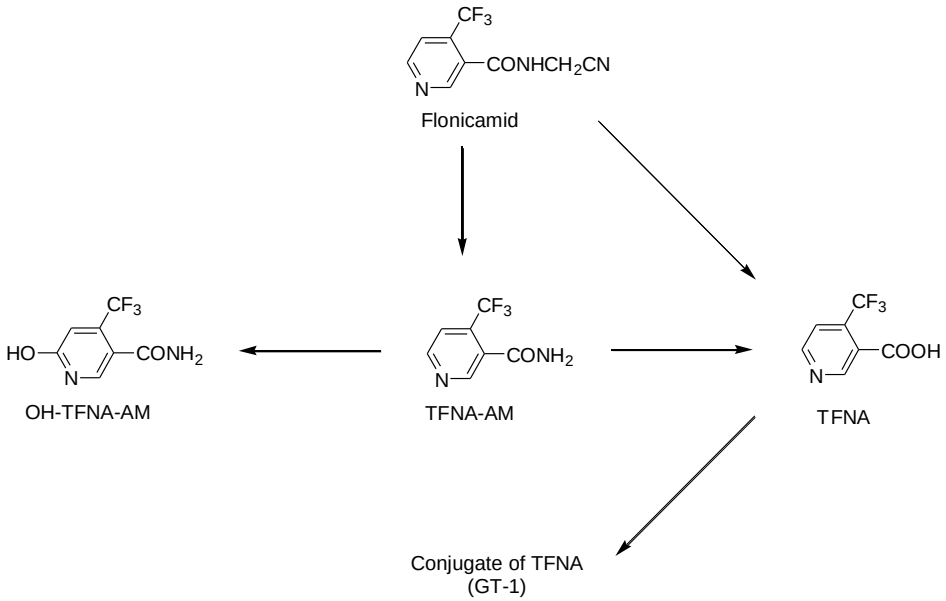


Figure 5: Proposed metabolic pathway of flonicamid in lactating goats

Laying Hens

Ten laying hens were orally dosed via gelatin capsule with [^{14}C]-flonicamid, labelled with ^{14}C in the 3-position of the pyridyl ring, for 5 consecutive days at approximately 10 ppm in the feed. Egg and excreta samples were collected during the dosing period. Animals were sacrificed within 6-6.25 hours of the final dose. Liver, kidney, breast muscle, thigh muscle, fat, skin and blood samples were collected.

Flonicamid was identified in egg white (2.5% TRR, 0.018 ppm), egg yolk (3.8% TRR, 0.019 ppm), muscle (0.6% TRR, 0.006 ppm), skin (0.4% TRR, 0.003 ppm), fat (0.7% TRR, 0.001 ppm), kidney (0.4% TRR, 0.005 ppm) and liver (0.3% TRR, 0.004 ppm). The main metabolite was identified as TFNA-AM and was identified in egg white (96.0% TRR, 0.71 ppm), egg yolk (94.7% TRR, 0.47 ppm), muscle (96.8% TRR, 0.96 ppm), skin (96.4% TRR, 0.68 ppm), fat (94.7% TRR, 0.14 ppm), kidney (76.4% TRR, 1.08 ppm) and liver (92.9% TRR, 1.10 ppm).

Based on these results a metabolic pathway was proposed for flonicamid in laying hens (Figure 6). The main pathway of metabolism involved hydrolysis of –CN and –CONH functional groups in the molecule.

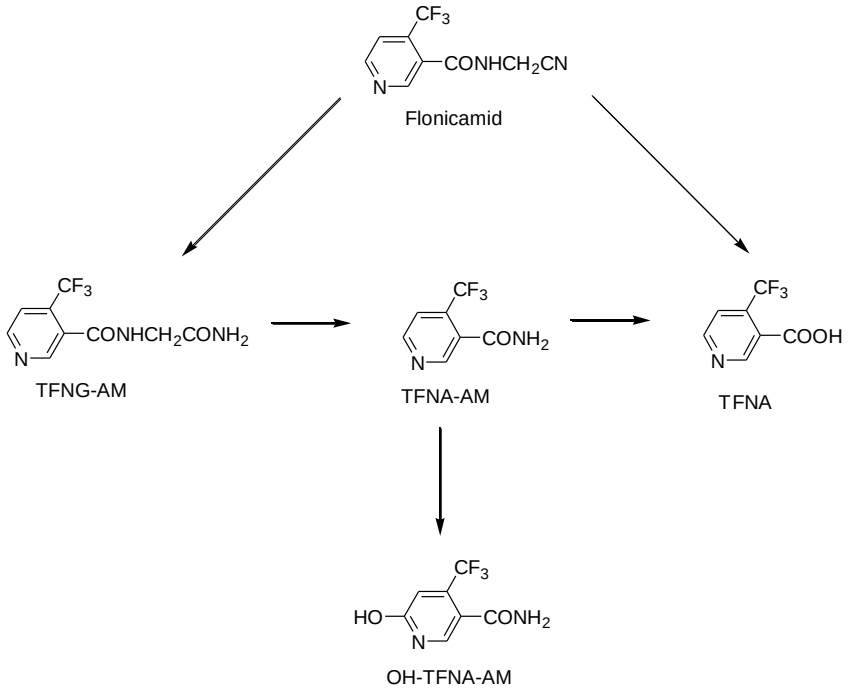


Figure 6: Proposed metabolic pathway of flonicamid in laying hens

4.3 Analytical methods

Pome fruit, potato, cucurbits

Residues of flonicamid and its metabolites were extracted from samples by shaking with acetonitrile:water. An aliquot was then acidified with HCl, $MgSO_4$ and NaCl, creating a partition between the acetonitrile (ACN) and water layers. An aliquot of the ACN layer was taken and analysed by ultra-performance liquid chromatography (UPLC) with positive-ion electrospray ionisation (ESI) tandem mass spectrometry (MS/MS). Quantitation of analyte was achieved by comparison with mixed external standards of flonicamid and its metabolites.

The LOQ (Limit of Quantification) was 0.01 mg/kg for flonicamid, TFNG, TFNA and TFNA-AM (each analyte component) in pome fruits, potatoes and cucurbits. Mean recoveries were between 70 and 110%. The relative standard deviations (RSD) for all commodities and all fortification levels were well below 20%.

Cotton

Residues of flonicamid and its metabolites TFNA, TFNA-AM and TFNG were extracted from cotton by shaking with acetonitrile:water. An aliquot of the ACN extracts was taken, and analysed for flonicamid and its metabolites by ultra-performance liquid chromatography (UPLC) with positive-ion electrospray ionization (ESI) tandem mass spectrometry (MS/MS). Quantitation of analyte was achieved by comparison with mixed external standards of flonicamid and its metabolites.

The LOQ was 0.01 mg/kg for flonicamid, TFNG, TFNA and TFNA-AM in cotton seed and lint for each analyte component. In hulls, meal and oil the LOQ was 0.02 mg/kg for each analyte and in the trash the LOQ was 0.05 mg/kg for each analyte. Mean recoveries were between 70 and 110%. The relative standard deviations (RSD) for all commodities and all fortification levels were well below 20%.

Animal tissue

Samples were shaken with acetonitrile:water, and they were reconstituted in a methanol/water/acetic acid solution and purified via Gel Permeation Chromatography (GPC). Analysis of flonicamid and its metabolites were determined by MS/MS detection using an HPLC (High Performance Liquid Chromatography) for separation.

The LOQ was 0.01 mg/kg for each analyte component, flonicamid, TFNG, TFNA, TFNA-AM and OH-TFNA-AM, in all animal commodities. Mean recoveries were between 70 and 110%. The relative standard deviations (RSD) for all commodities and all fortification levels were below 20%.

Milk

Ethanol was added to milk samples and the suspension was shaken. The ethanol/water phase was evaporated to aqueous remainder and the sample washed twice with hexane. The residue was dissolved in a water/acetonitrile/trifluoroacetic acid mixture. The concentrations of flonicamid and its metabolites were determined by MS/MS detection using a HPLC for separation.

The LOQ was 0.01 mg/kg for each analyte component, flonicamid, TFNG, TFNA, TFNA-AM and OH-TFNA-AM in all animal commodities. Mean recoveries were between 70 and 110%. The relative standard deviations (RSD) for all commodities and all fortification levels were below 20%.

Egg

Acetonitrile/water mixture was added to egg samples and the suspension was shaken well. An aliquot of the lower acetonitrile/water phase was taken and the residue dissolved in a methanol/water/acetic acid solution for GPC purification. The concentrations of flonicamid and its metabolites were determined by MS/MS detection in positive and negative mode using an HPLC for separation.

The LOQ was 0.01 mg/kg for flonicamid, TFNG, TFNA, TFNA-AM and OH-TFNA-AM in all animal commodities for each analyte. Mean recoveries were between 70 and 110%. The relative standard deviations (RSD) for all commodities and all fortification levels were below 20%.

Storage Stability

The storage stability of flonicamid and its metabolites TFNG, TFNA and TFNA-AM was shown to be satisfactory in plant commodities for up to 18 months and in animal commodities for up to 13 months. In the residue trials submitted, all samples were maintained under freezer conditions, (i.e.–18 °C) prior to analysis and tested within 13 months of collection.

Commodities of plant origin

Parent flonicamid and the metabolites TFNA and TFNG accounted for the majority of the identified residue. In some instances the metabolites TFNA and TFNG accounted for a significantly greater proportion of the total residue than parent flonicamid. A residue definition of the *sum of flonicamid, TFNG and TFNA, expressed as flonicamid* is recommended. This is consistent with the residue definitions established by the EU, Japan and the USA.

Commodities of animal origin

Based on the available animal metabolism data, analytical methods and toxicological advice, it is concluded that a suitable residue definition for animal commodities is the sum of flonicamid and TFNA-AM.

4.4 Residue Trials

Pome fruit

In support of the proposed use on pome fruit, the applicant has provided details of 13 Australian residue trials (8 on apples and 5 on pears) in addition to 15 residue trials from the USA (11 on apples and 4 on pears).

On the basis of the Australian and USA data (n=28, HR=0.38 mg/kg, STMR=0.085 mg/kg), an MRL (Maximum Residue Limit) of 0.7 mg/kg is recommended for flonicamid on pome fruit, in conjunction with a 21 day withholding period.

Potato

In support of the proposed use on potatoes the applicant has submitted 21 residue trials on potatoes (4 from Australia and 17 from the USA).

On the basis of the Australian and USA data (n=21, HR=0.12 mg/kg, STMR=0.04 mg/kg), an MRL of 0.2 mg/kg is recommended for flonicamid on potatoes, in conjunction with a 14 day withholding period.

Cotton

In support of the proposed use on cotton the applicant has submitted 21 residue trials on cotton (9 from Australia and 12 from the USA).

On the basis of the data provided (n=21, HR=0.64 mg/kg, STMR=0.25 mg/kg), an MRL of 1 mg/kg is recommended for flonicamid on cotton seed, in conjunction with a 7 day withholding period.

Cucurbits

In support of the proposed use the applicant has submitted 27 residue trials on cucurbits (10 from Australia and 17 from the USA).

On the basis of the available data (n=27, HR=0.36 mg/kg, STMR=0.17 mg/kg), an MRL of 0.7 mg/kg is recommended for flonicamid on cucurbits, in conjunction with a 1 day withholding period. No data were presented to allow consideration of effects in protected cropping systems on residue decline, therefore, use of flonicamid will be restricted to field grown systems.

4.5 Processing studies

The Australian and USA cotton trials include information on the concentration of residues during processing. The USA apple trials include information on the concentration of residues during processing.

Residues concentrated on processing to dry apple pomace by a factor of 5×. Applying this processing factor to the Australian and USA apple residue data (HR = 0.38 mg/kg, STMR = 0.09 mg/kg), the HR-P (Highest Residue-Processing) expected for dry apple pomace is 1.9 mg/kg, with an STMR-P (Supervised Trials Median Residues-Processing) of 0.45 mg/kg. An MRL of 3 mg/kg is therefore recommended for flonicamid in apple pomace, dry.

The Australian processing trials indicated that flonicamid residues do not concentrate in hulls, meal or refined oil. However, the US trials indicated that residues did concentrate on processing to cotton hulls and meal by a factor of 1.82× and 4.08×, respectively. Applying this processing factor to the Australian and USA fuzzy cotton seed residue data (HR = 0.64 mg/kg, STMR = 0.25 mg/kg), the HR-P expected for cotton hulls is 1.16 mg/kg, with an STMR-P of 0.46 mg/kg. The HR-P expected for cotton meal is 2.61 mg/kg, with an STMR-P of 1.02 mg/kg. An MRL of 3 mg/kg is therefore recommended for flonicamid in cotton seed meal and hulls.

4.6 Animal commodity MRLs

Potential animal feed commodities derived from crops treated with flonicamid include apple pomace and cotton seed, which may be fed to beef cattle at up to 20% and 30% of the diet, respectively. Cotton meal may be fed at up to 10% of the diet for poultry.

Based on the proposed use of *ISK Flonicamid 500 WG Insecticide*, the maximum animal dietary burden is from the consumption of cottonseed meal and hulls. The Applicant has presented the results of a feeding study on lactating dairy cattle and laying hens in which animals were dosed with a 1:1 mixture of flonicamid and TFNG twice daily for 28 days. TFNG is a plant metabolite that is found in most matrices.

On the basis of these feeding studies the potential flonicamid residues in animal commodities derived from livestock fed on these treated commodities (0.306 mg/kg flonicamid in the feed for cattle, 0.102 mg/kg flonicamid in the feed for poultry) are therefore expected to below the limits of quantification in all commodities. These results support the establishment of animal commodity MRLs for flonicamid at the limit of quantification, on the basis of the residue definition, as given below:

Table 1: MRL for animal commodities –

COMPOUND	FOOD	MRL (mg/kg)
MM 0095	Meat [mammalian]	*0.02 mg/kg
MO 0105	Edible offal (Mammalian)	*0.02 mg/kg
ML 0106	Milks	*0.02 mg/kg
PE 0112	Eggs	*0.02 mg/kg
PO 0111	Poultry, Edible offal of	*0.02 mg/kg
PM 0110	Poultry meat	*0.02 mg/kg

4.7 Estimated dietary intake

The chronic dietary exposure to flonicamid is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines[2] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for flonicamid is equivalent to <10% of the ADI.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. The acute dietary intake estimates for relevant commodities ranged from <1% of the ARfD up to <85% of the ARfD. Highest exposures were estimated for melons (2-6 yo and for adults) and for apples (2-6 year olds). The acute dietary exposure estimates for flonicamid are acceptable.

Flonicamid has a K_{ow} log P = 0.30 indicating that it is not fat soluble. In the animal transfer study, detectable residues were higher in muscle than the fat. Potential for bioaccumulation is considered to be low.

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

4.8 Spray drift

From the animal transfer study provided a feeding level of 2.5 mg/kg resulted in residues of flonicamid and its metabolites below the LOQ (<0.01 mg/kg) in all commodities. Assuming pasture consists of 1500 kg dry matter/ha, this corresponds to a maximum deposition rate of 3.75 g/ha.

Spray drift modelling using APVMA spray drift standard application scenarios and calculations using the *AgDisp* program were used to determine the no spray zones required for ground and aerial application, respectively. On the basis of these calculations a no-spray zone for the protection of international trade is not considered necessary for Mainman 500 WG Insecticide.

4.9 Recommendations

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

Table 2:

COMPOUND		FOOD	MRL (MG/KG)
FLONICAMID			
ADD:			
SO	0691	Cotton seed	1
MO	0105	Edible offal (mammalian)	*0.02
PE	0112	Eggs	*0.02
VC	0045	Fruiting vegetables, Cucurbits	0.7
MM	0095	Meat [mammalian]	*0.02
ML	0106	Milks	*0.02
FP	0009	Pome fruits	0.7
VR	0589	Potato	0.2
PO	0111	Poultry, Edible offal of	*0.02
PM	0110	Poultry meat	*0.02

Table 3:

COMPOUND	RESIDUE
ADD:	
Flonicamid	Commodities of plant origin: sum of flonicamid, TFNG (*N*-(4-trifluoromethylnicotinoyl)glycine) and TFNA (4-trifluoromethylnicotinic acid), expressed as flonicamid Commodities of animal origin: sum of flonicamid and TFNA-AM (4-trifluoromethylnicotinamide), expressed as flonicamid

Table 4:

COMPOUND		ANIMAL FEED COMMODITY	MRL (MG/KG)
FLONICAMID			
ADD:			
AB	0226	Apple pomace, dry	3
		Cotton seed meal and hulls	3

The MRLs are recommended in conjunction with the following withholding periods:

Apples: DO NOT HARVEST FOR 21 DAYS AFTER APPLICATION.
Potatoes: DO NOT HARVEST FOR 14 DAYS AFTER APPLICATION.
Cotton: DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION.
Cucurbits: DO NOT HARVEST FOR 1 DAY AFTER APPLICATION.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

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

Pome fruit and cotton seed are considered to be major export commodities along with animal commodities derived from livestock that have been fed feeds (i.e. apple pomace, cotton seed meal and hulls) containing residues arising from the proposed use.

5.2 Destination and Value of Exports

Major export markets for Australian pome and cottonseed are presented below.

Major destinations for Australian pome and cottonseed exports[3]

Commodity	Major Destinations
Cottonseed	Japan, Republic of Korea, United States, Saudi Arabia, Taiwan
Apple	Indonesia, Papua New Guinea, Thailand, United Kingdom, Sri Lanka, Vietnam, East Timor
Pear	New Zealand, Canada, New Caledonia, Indonesia, Papua New Guinea, Vietnam, Hong Kong, India, Malaysia

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

5.3 Proposed Australian use-pattern

Mainman 500 WG Insecticide (500 g/kg flonicamid)

Crop	Pest	Rate	WHP	Critical Comments
Apples	Apply by dilute or concentrate spraying equipment. Apply the same total amount of product to the target crop whether applying this product by dilute or concentrate spraying methods. Refer to Application section of the label.			
	Woolly Apple Aphid *(Eriosoma lanigerum)*	**Dilute Spray:** 10 -14 g/100 L water (5-7 g ai/100L) **Concentrate spray:** Refer to Application, Apples section	21 days	Water quantities to be used depend on size of trees, development stage of trees and spraying equipment used. Use the higher rate under high pest pressure. A minimum re-treatment interval of 2 weeks must be observed.

[3] Australian Commodity statistics 2012 - http://www.daff.gov.au/abares/publications_remote_content/publication_series/australian_commodity_statistics

Crop	Pest	Rate	WHP	Critical Comments
	Tuber Mealybug *(Pseudococcus viburni)*	**Dilute Spray:** 14 -20 g/100 L water (7-10 g ai/100L) **Concentrate spray:** Refer to Application, Apples section		Do not apply more than 3 applications. Where applicable, use the higher rate under high pest pressure or to provide longer residual control.
Cotton	Cotton Aphid *(Aphis gossypii*) Green Mirid *(Creontiades dilutus)*	100-140 g/ha (50-70 gai/ha)	7 days	Apply to an aphid population in the early stages of development before honeydew is evident or aphid damage occurs. Thorough spray coverage is essential. This product should be used according to the Cotton Industry's Best Management Practices Manual and its associated Spray and Drift Management Plan. If repeat applications are required, alternate with products from a different insecticide group as per current Cotton Industry Insecticide Resistance Management Strategy. This use is also subject to a CropLife Insecticide resistance management strategy. DO NOT apply more than 2 sprays per crop per season.
Cucurbits Cucumber Pumpkin Rockmelon Squash Zucchini (excluding protected cropping situations)	Green Peach Aphid *(Myzus persicae)* Melon Aphid *(Aphis gossypii*)	100- 140 g/ha (50-70 gai/ha)	1 day	**DO NOT use in protected cropping situations.** Apply at first sign of aphid infestation. A minimum re-treatment interval of 2 weeks must be observed. Do not apply more than 3 applications. Where applicable, use the higher rate under high pest pressure.
	Silverleaf Whitefly *(Bemisia tabaci, B-type)*	200 g/ha (100 g/ai/ha) plus Hasten at 2 mL /100 L water		
Potatoes	Green Peach Aphid *(Myzus persicae)* Melon Aphid *(Aphis gossypii*) Potato Aphid *(Macrosiphum euphorbiae)*	140-200 g/ha (70-100 g ai/ha)	14 days	Apply at first sign of aphid infestation. A minimum re-treatment interval of 2 weeks must be observed. Do not apply more than 2 applications. Use the higher rate under high pest pressure.

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

WITHHOLDING PERIOD:

Apples: DO NOT HARVEST FOR 21 DAYS AFTER APPLICATION.
Potatoes: DO NOT HARVEST FOR 14 DAYS AFTER APPLICATION.
Cotton: DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION.
Cucurbits: DO NOT HARVEST FOR 1 DAY AFTER APPLICATION.

PROTECTION OF LIVESTOCK

DO NOT graze or feed treated crops to animals. DO NOT feed cotton fodder, stubble or trash to livestock.

5.4 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. Flonicamid has not been considered by Codex. The following relevant international MRLs have been established for flonicamid:

Commodity	Tolerance for residues arising from the use of flonicamid (mg/kg)			
	Australia	**EU**	**Japan**	**US**
Plant Commodities				
Residue Definition	Flonicamid Sum of flonicamd, TFNG and TFNA, expressed as flonicamid.	Flonicamid Sum of flonicamd, TFNG and TFNA, expressed as flonicamid.	Flonicamid Sum of flonicamd, TFNG and TFNA, expressed as flonicamid.	Flonicamid Sum of flonicamd, TFNG, TFNA and TFNA-AM, calculated as the stoichiometric equivalent of flonicamid.
Pome fruit	0.7[a]	0.2		0.2
Apple			1	
Japanese pear			0.5	
Pear			0.5	
Quince			0.2	
Loquat			0.2	
Cottonseed	1[a]	*0.05	0.5	
Cottonseed meal and hulls	3[a]			
Cotton, gin byproducts				6.0
Cotton, hulls				2.0
Cotton, meal				1.0
Cotton, undelinted seed				0.20
Potatoes	0.2[a]	0.1	0.3	
Vegetable, tuberous and corm, subgroup 1C				0.20
Other potatoes			0.2	
Potato, granules/flakes				0.40
Fruiting vegetables, Cucurbits	0.7[a]			
Vegetable, cucurbit, group 9, except cucumber				0.4
Cucumbers		0.5	2	1.5
Gherkins		0.5	2	
Courgettes (summer squash, marrow (patisson))		0.5		
Melons		0.3	2	
Pumpkins		0.3	0.4	
Watermelons		0.3	2	
Orinetal pickling melon (vegetable)			0.4	
Makuwauri melon			0.4	
Other cucurbitaoeous vegetables			0.4	

[a] proposed MRL

Commodity	Tolerance for residues arising from the use of flonicamid (mg/kg)			
	Australia	EU	Japan	US
Animal Commodities				
	Flonicamid	Flonicamid	Flonicamid	Flonicamid
Residue Definition	Sum of flonicamd and TFNA-AM, expressed as flonicamid.	Sum of flonicamd and TFNA-AM, expressed as flonicamid.	Sum of flonicamd, TFNA and TFNA-AM, expressed as flonicamid	Sum of flonicamd, TFNA and TFNA-AM, calculated as the stoichiometric equivalent of flonicamid.
Meat (mammalian)	*0.02[a]			
Cattle, meat		0.03	0.08	0.08
Sheep, meat		0.03		0.08
Goat, meat		0.03		0.08
Horse, meat		0.03		0.08
Swine, meat		0.03		
Other terrestrial mammals, meat			0.08	
Cattle, fat		*0.02	0.03	0.03
Sheep, fat		*0.02		0.03
Goat, fat		*0.02		0.03
Horse, fat		*0.02		0.03
Swine, fat		*0.02		
Edible offal (mammalian)	*0.02[a]			
Cattle, liver		0.03	0.08	
Sheep, liver		0.03		
Goat, liver		0.03		
Horse, liver		0.03		
Swine, liver		0.03		
Other terrestrial mammals, liver			0.08	
Cattle, kidney		0.03	0.08	
Sheep, kidney		0.03		
Goat, kidney		0.03		
Horse, kidney		0.03		
Swine, kidney		0.03		
Other terrestrial mammals, kidney			0.08	
Cattle, edible offal		0.03	0.08	0.08
Sheep, edible offal		0.03		0.08
Goat, edible offal		0.03		0.08
Horse, edible offal		0.03		0.08
Swine, edible offal		0.03		
Other terrestrial mammals, edible offal			0.08	
Poultry, meat	*0.02[a]	0.03	0.03	0.03
Poultry, fat		*0.02	0.03	0.03
Poultry, liver		0.03	0.03	
Poultry, kidney		0.03	0.03	
Poultry, edible offal	*0.02[a]	0.03	0.03	0.03
Milk	*0.02[a]	*0.02	0.03	0.03
Egg	*0.02[a]	0.05	0.04	0.04

[a] proposed MRL

5.5 Potential risk to trade

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

While several overseas countries have established flonicamid MRLs in pome fruit and cotton, some key Australian export markets for these commodities have not. As detectable residues are expected to occur when the product is used as directed this creates a potential risk to trade.

The proposed Australian residue definition for plant commodities is the same as that established in the EU and Japan (i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid). The USA has established a residue definition that also includes the metabolite TFNA-AM. However, from the trials provided residues of the metabolite TFNA-AM were not seen in pome fruit, potatoes or cucurbits and were only present at low levels in cotton.

The EU and USA have established MRLs for flonicamid in pome fruit of 0.2 mg/kg, below the proposed Australian MRL of 0.7 mg/kg. The residue considered as the highest residue in pome fruits was 0.38 mg/kg, and the supervised trial median was 0.085 mg/kg.

Flonicamid MRLs in cottonseed have been established in the EU, USA and Japan at *0.05, 0.2 and 0.5 mg/kg, respectively, below the proposed Australian MRL of 1 mg/kg. It is noted that the residue considered as the highest residue in cotton seed was 0.64 mg/kg, and the supervised trial median was 0.25 mg/kg.

The proposed Australian residue definition for animal commodities is the same as that established in the EU (i.e. the sum of flonicamid and TFNA-AM, expressed as flonicamid). The USA and Japan have established a residue definition that also includes the metabolite TFNA. However, Australian animal commodity MRLs have been established at the LOQ as detectable residues of flonicamid are not expected to occur in animals that have been fed treated feeds.

The applicant is proposing to mitigate the risk to trade through the inclusion of the following statement on the label:

Export of treated produce

Growers should note that suitable MRLs or import tolerances do not exist in all markets for produce treated with Mainman 500 WG Insecticide. In some situations export requirements may be met by limiting application number and/or imposing a longer withholding period than specified above. If you are growing produce for export, please check with Ishihara Sangyo Kaisha, Ltd or your industry body for the latest information on any potential trade issues and their management before using Mainman 500 WG Insecticide.

Comment is sought on the potential for flonicamid residues resulting from the proposed use of Mainman 500 WG Insecticide on pome fruit and cotton to prejudice Australian trade.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Flonicamid constituent (CAS: 158062-67-0) is listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2012) with the following risk phrases:

Xn; R22	Harmful if swallowed
Xn; R63	Possible risk of harm to unborn child

With the following cut-off concentrations:

Conc. ≥ 25%	Xn; R22, R63
25% < Conc. ≤ 5%	Xn; R63

6.1 Formulation, packaging, transport, storage and retailing

The active constituent flonicamid will be manufactured overseas. The product Mainman 500 WG Insecticide will be manufactured overseas and imported into Australia in sizes of 500 g, 1 kg and 5 kg HDPE bottles.

6.2 Use pattern

Mainman 500 WG Insecticide is formulated as a water dispersible granular (WG) formulation containing 500 g/kg flonicamid. Mainman 500 WG Insecticide is intended for the control of the following pests: cotton aphid and green mired in cotton; green peach, melon and potato aphids in potato; woolly apple aphid and tuber mealybug in apples;and, green peach and melon aphids and silverleaf whitefly in cucurbits. It is intended for professional use only.

The product is to be applied to all crops at a maximum individual application rate of 140-160 g formulation/ha (70-80 g active constituent/ha) using tractor mounted/trailed boom sprayer or tractor broadcast air assisted 500 L.

6.3 Exposure during use

This product is not intended for home/garden use. Farmers and their employees will be the main users of the product. Workers may be exposed to the product when opening containers, mixing/loading, application and cleaning up spills and equipment. The main route of exposure to the product and diluted spray will be dermal and inhalational, although ocular exposure is also possible during application of the dilute spray.

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used to estimate potential worker exposure. The toxic endpoint of concern and identified NOEL is derived from a repeat dose study in animals, and in this instance a margin of exposure (MOE) of 100 or above is considered acceptable. The MOE takes into account potential interspecies and intra-species variation, and the seriousness of the critical health effect of concern.

The MOE's associated with repeated use of the product when mixing and loading, application to pome and stone fruit by broadcast air assisted, application to potatoes and cotton by boom spray are acceptable (i.e. >100) without the use of personal protective equipment.

However, based on the product acute hazard of severe eye irritation and the potential systemic toxicity due to repeated exposure, it is recommended that when mixing, loading and applying the product, cotton overalls buttoned to the neck and wrist (or equivalent clothing) and goggles are worn.

6.4 Exposure during re-entry

Workers may be exposed to Mainman 500 WG Insecticide when re-entering treated areas. In the absence of worker exposure studies, the post-application exposure has been calculated using the Occupational Post-Application Risk Assessment Calculator Version 1 (8/9/00) EPA Policy 003.1.

The deciduous tree fruit, medium field/row crop, low/medium, root vegetables and cucurbit vegetable re-entry scenarios were used to estimate re-entry exposure, with high exposure potentials or very high exposure potentials selected to simulate a worst-case scenario for workers. The high and very high exposure potential lists activities such as thinning for deciduous tree fruit, hand harvesting for medium field/row crop, low/medium and root vegetables, and leaf thinning and turning for cucurbits.

The following re-entry statement is recommended.

Do not allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

6.5 Recommendations for safe use

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

6.6 Conclusion

The registration of Mainman 500 WG Insecticide containing 500 g/kg flonicamid for the control of cotton aphid and green mirid, in cotton; for the control of green peach, melon and potato aphids in potato; for the control of woolly apple aphid and tuber mealybug in apples; and for the control of green peach and melon aphids and silverleaf whitefly in cucurbits is supported.

Mainman 500 WG 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.

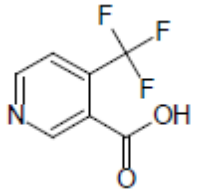
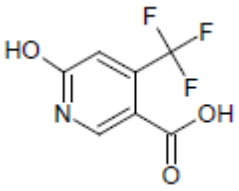
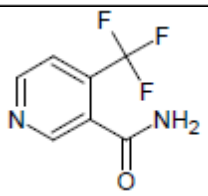
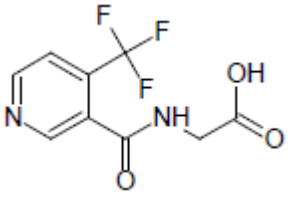
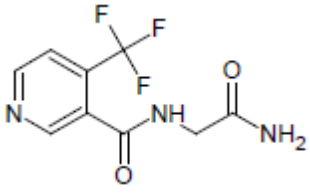
7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

Ishihara Sangyo Kaisha has applied for registration of the end use product Mainman 500 WG Insecticide containing the new active constituent flonicamid. This is the first time approval for flonicamid has been sought in Australia.

Flonicamid is a new insecticide intended for the control of aphids and mealybug in apples; for the control of aphids and mirids in cotton; for the control of aphids and silverleaf whitefly in cucurbits; and for the control of aphids in potatoes. The formulated material, Mainman 500 WG Insecticide (500 g flonicamid/kg), is to be applied by ground application only. The maximum application rate is 200 g formulation/ha with a maximum of up to three applications depending on the crop being treated. The minimum re-application interval is normally 14 days.

Degradates relevant to the environment

Code	Chemical name	Structural formula
TFNA	4-trifluoromethylnicotinic acid	
TFNA-OH	6-hydroxy-4-trifluoromethylnicotinic acid	
TFNA-AM	4-trifluoromethylnicotinamide	
TFNG	N-(4-trifluoromethylnicotinoyl)glycine	
TFNG-AM	N-(4-trifluoromethylnicotinoyl)glycinamide	

7.2 Environmental Fate

Comments on physicochemical properties

Flonicamid is readily soluble in water and, with its low vapour pressure and Henry's law values, only very slight volatile and not likely to volatilise from water. The octanol water value indicates flonicamid should not bio-concentrate.

Behaviour in soils

In laboratory aerobic soil degradation studies, flonicamid readily and rapidly underwent extensive microbially mediated degradation with the formation of either carbon dioxide or soil-bound residues. Laboratory DT50 (dissipation time 50%) values for flonicamid ranged from 0.7 to 1.8 days at 20ºC and 2.4 days at 10ºC in a North American and three European soils. DT90 (dissipation time 90%) values ranged from 2.3 to 6.0 days at 20ºC and 7.9 days at 10ºC.

Flonicamid degradation products also underwent ready degradation in the same four soils with mineralisation or formation of soil-bound residues. TFNA and TFNA-OH were the major degradates with maximum TFNA levels of 12.2 to 36.4% of the applied radioactivity at days one to three of the sampling period. Maximum levels of TFNA-OH ranged from 9.7 to 32.7% of the applied radioactivity from day 1 to day 7 of the sampling period. DT50 and DT90 values for TFNA ranged from, respectively, 0.3 to 1.0 and 1.0 to 3.3 days. For TFNA-OH, DT50s were 1.0 to 4.5 days and DT90s 3.4 to 15.0 days, with the higher values associated with incubation at 10 rather than 20ºC.

TFNG, TFNG-AM, and TFNA-AM were present in amounts ranging from, respectively, <8%, 7.8 to 10.2% and <8%. These minor degradates underwent ready mineralisation and/or formation of soil-bound residues. These minor degradation products had DT50s ranging from 0.1 to 4.5 days and DT90s of 0.4 to 14.8 days.

Field dissipation studies

Field dissipation studies of flonicamid and its degradation products were not provided and not considered required because of the fast degradation of the parent and its degradates seen in the laboratory soil degradation studies.

Dislodgeable foliar residues of flonicamid on leaf surfaces underwent a rapid decline with DT50s between 0.67 and 0.78 days.

Mobility

In the adsorption to soil experiments (four soils) the percentage of the flonicamid adsorbed to the soil using a 1:5 soil:test solution ratio ranged from 2.8 to 8.3% and, in a 1:2 soil:test solution ratio, the percentage adsorbed remained below 15%. Koc (soil organic carbon partition co-efficient) values ranged from 8 to 21 for the 1:2 soil:test solution ratio and 12 to 42 for the 1:5 ratio. Flonicamid is predicted to have very high mobility for the adsorption-phase these soils (Koc values of 0 to 50). Desorption behaviour of flonicamid from the soils was not investigated due to the minimal amounts of the test substance adsorbed.

Flonicamid soil degradation products had the following range of Koc values in the four soils (from the same locations as the soils used for the flonicamid adsorption studies): TFNA, 0.00 to 3.05; TFNG, 0.20 to 4.05; TFNA-OH, 1.60 to 4.39; TFNA-AM, 2.76 to 5.52 and TFNG-AM, 0.00 to 13.16. In a second series, using five soils, four of which came from locations different from those used in the first series, Koc values for TFNA-AM were 4.53 to 12.11 and, for TFNG-AM, 4.24 to 15.84. These Koc values indicate the flonicamid soil degradates would also have very high soil mobility.

Behaviour in water

Hydrolysis of flonicamid was not observed at pH 5 or 7 at 25°C and only slowly at 50° at pH 7 where the flonicamid half-life was 578 days. At pH 9 and 25°C, the half-life for flonicamid hydrolysis was 204 days. At 40 or 50°C, hydrolysis was much faster, with respective half-lives of 17.1 and 9.0 days. At environmental pH values, hydrolysis is not expected to be a significant route of flonicamid degradation.

When flonicamid in aqueous solution at pH 7 was continuously exposed to simulated sunlight for 15 days, limited degradation occurred with a calculated half-life for flonicamid under continuous radiation of 267 days. Photolytic degradation in aquatic systems is not indicated as being of significance in the environmental degradation of flonicamid.

Under aerobic aquatic conditions, flonicamid was extensively degraded in both the river and pond water/sediment systems with significant (59.1% of the applied radioactivity) mineralisation taking place in the river water phase after 145 days (15.6% mineralisation took place in the water phase of the pond water/sediment system over 136 days). Degradation followed hydrolysis of the cyano and amide bonds in the side chain of the flonicamid to give TFNG, TFNA-AM and TFNA. Hydroxylation of the TFNA then gave TFNA-OH. TFNA-AM and TFNG were considered to be degradative intermediates. Further degradation of the residues saw incorporation into the soil organic matter and mineralisation to carbon dioxide.

In the river water/sediment system, flonicamid degradation products never exceeded 4% of the applied radioactivity in the water phase or 2% in the sediment phase. In contrast, in the pond water/sediment system's water phase, TFNA-OH and TFNA were present from day 30 to 136 with maximum levels reached at days 42 (12.46% of the applied dose) and 30 (9.61% of the applied dose) respectively. In the sediment phase of the pond system, TFNA was the major degradation product (maximum of 9.18% of the applied radioactivity at day 42). Other flonicamid degradation products were present in levels not exceeding 3% of the applied radioactivity. These results were mirrored in the combined water and sediment phase results, with less than 4% of any one degradation product in the river system but with significant levels of TFNA-OH and TFNA in the pond system. TFNA-OH levels reached a maximum of 13.22% of the applied radioactivity at day 42 while the TFNA maximum of 17.88% of the applied radioactivity occurred on day 30. No other degradate in the total pond system exceeded 4% of the applied dose.

Half-lives of flonicamid in river and pond water were 37.3 and 30.3 days while in the whole river water/sediment and whole pond water/sediment systems, the DT50 values were, respectively, 43.6 and 35.7 days. Whole river and pond water/sediment systems DT90 values were, respectively, 144.8 and 118.7 days.

Under anaerobic aquatic/sediment conditions, flonicamid levels in the water phase steadily decreased over time. In the sediment, the levels of flonicamid were at maximum levels at day 3 of the study and thereafter declined. The major degradation product TFNA increased from 1.5% of the applied dose at day 1 to 75.7%

of the applied dose at day 365 with 56.2% of this in the water phase at that time. There were no other significant degradation products in the system. The flonicamid DT50 values were 88 days in the water phase and 121 days in the entire system. The flonicamid DT 90 values were 490 days in the water and 555 days in the entire system.

Behaviour in air

The calculated half-life of flonicamid in air as a result of reaction with hydroxyl radicals was 13.7 days, indicative of a slow photo-oxidation potential in air.

7.3 Environmental Effects

Birds

Flonicamid is practically non-toxic to birds via the oral route (LD50 > 2000 mg/kg body weight) and practically non-toxic to birds via the dietary exposure route (LC50 >5000 mg/kg feed). With respect to adverse effects on parent birds or reproductive performance, the no-observed-effect concentration for northern bobwhite exposed to flonicamid in the diet during the study was 1000 ppm (mg/kg feed) flonicamid. For mallard ducks, the no-observed effect concentration with respect to adverse effects on the parent birds or their reproductive performance was determined to be160 mg flonicamid/kg feed.

Aquatic organisms

Flonicamid, Mainman 500 WG Insecticide, and the flonicamid degradation products, TFNA, TFNA-OH, TFNA-AM and TFNG-AM, are practically non-toxic to fish and aquatic invertebrates on an acute basis (LC50 > 100 mg/L). Flonicamid is very slightly toxic to fish and aquatic invertebrates on a chronic basis (NOEC > 1 mg/L). Based on 72 h ErC50 results, flonicamid, Mainman 500 WG Insecticide and the flonicamid degradation products, TFNA, TFNA-OH, TFNA-AM and TFNG-AM, are practically non-toxic to the freshwater green alga *Pseudokirchneriella subcapitata* on an acute basis (ErC50 > 100 mg/L).

Terrestrial and soil organisms

Flonicamid is very slightly toxic to the honey bee (LC50 >100 µg/bee) via the contact route and slightly toxic to the honey bee (10 > LC50 ≤ 100 µg/bee) via the oral route. In the contact test, mortality amongst the exposed bees was low (8.0% at 48 hours) whereas in the oral toxicity test, there was 36.7% mortality from 48 to 96 hours. In the contact test, 82% of the surviving bees were exhibiting abnormal behaviour (primarily movement coordination difficulties and to a far lesser degree, apathy) after 96 hours. In the oral test and at the highest value tested, 60.5 µg flonicamid/bee, 50% of the bees were exhibiting adverse behaviour (movement coordination difficulties) at 24 hours, but this had decreased to 6.7% at 72 hours and 0% at 96 hours.

Mainman 500 WG Insecticide is very slightly toxic to honey bees via both the contact and oral exposure routes (LC50 > 100 µg/bee). In the contact test at 100 µg formulation/bee, there was 10% mortality after 48 hours while in the oral exposure, there was 53.3% deaths at the highest level tested (104.3 µg formulation/bee) after 96 hours. In the contact test, 34% of the surviving bees showed signs of

primarily movement coordination difficulties after 4 hours with 30% still showing adverse behaviour after 48 hours. In the oral exposure test, adverse behaviour was present at all dose levels after 4 hours exposure with 100% of the bees exposed to the highest test level (104.3 µg formulation/bee) showing movement coordination difficulties or, to a lesser degree apathy. By 96 hours, adverse effects were still being recorded but there was no apparent dose relationship.

Six tunnel tests and two field studies with honeybees exposed to flonicamid as 50% formulations at rates of up to 280 g/ha identified short term adverse effects on mortality and on foraging bees exposed to the formulated material. In cases where bees were not foraging when the application is made, minimal adverse effect occurred.

For other non-target terrestrial arthropods, laboratory tests on glass plates with a representative flonicamid formulation (50% WG) were conducted with *Aphidius rhopalosiphi (*LR50 >80 g ac/ha), *Typhlodromus pyri* (100% mortality at 80 g ac/ha), *Coccinella septempunctata* (LR50 >210 g ac/ha), *Poecilus cupreus* (LR50 and ER50 >45 g ac/ha), and *Orius laevigatus* (LR50 and ER50 >161 g ac/ha).

Higher tier (extended laboratory tests) with the same formulation were conducted at 85 g ac/ha with *Aphidius rhopalosiphi*, *Typhlodromus pyri*, *Coccinella septempunctata*, *Chrysoperla carnea* and *Episyrphus balteatus* with no adverse impacts on mortality, reproduction and/or food consumption at the limit dose (all LR50 and ER50 values >85 g ac/ha).

Flonicamid is not acutely toxic to the earthworm at up to and including soil concentrations of a nominal 1000 mg flonicamid/kg soil dry weight. The short half-life of flonicamid in soils seen in laboratory studies predicts that long-term exposure of earthworms will not occur.

Based on a study conducted to OECD guideline requirements, microbially mediated soil carbon and nitrogen transformation processes, flonicamid demonstrated no long-term influence on these soil processes after exposure to 0.104 and 0.274 mg of a 50% flonicamid formulation/kg soil dry weight (calculated as equivalent to ~80 and 200 g formulated product/ha).

Non-target terrestrial plants

A screening test for phytotoxicity identified that flonicamid, as Mainman 500 WG Insecticide, was not phytotoxic at rates of up to 100 g for vegetative vigour of growing plants or up to 300 g flonicamid/ha for seedling emergence and growth.

7.4 Risk Assessment

Based on short-term and chronic avian dietary intakes calculated from the worst case use patterns proposed by the draft Mainman 500 WG Insecticide label and their comparison with appropriate calculated short-term and chronic dietary intakes, the calculated risk quotients show the proposed uses of Mainman 500 WG Insecticide are not expected to result in unacceptable acute or chronic/reproduction risks to birds.

Using worst case calculations, the risks of flonicamid and its degradates to fish, aquatic invertebrates, algae and aquatic plants as a result of spray drift, runoff or movement to groundwater are acceptable based on risk quotients determined from comparison of worst case predicted water concentrations from single and multiple

applications of the ISK formulation with the most sensitive ecotoxicity endpoints for aquatic species. Consequently, refinement of the risk to aquatic species was not required nor was there demonstrated need to establish specific downwind no-spray zones or buffer distances to protect aquatic species.

Laboratory studies indicated use of Mainman 500 WG Insecticide as proposed is not expected to result in unacceptable risk of mortality to honey bees or the insects for which they are surrogates. However, transient adverse effects on behaviour to bees exposed to the formulated material were observed in standard laboratory oral and contact tests. Tunnel tests and field studies with honeybees exposed to flonicamid as 50% formulations at rates of up to 280 g/ha identified short term adverse effects on mortalities and on foraging bees exposed to the formulated material. In cases where bees were not foraging when the application was made, minimal adverse effects occurred. As a result, an advisory protection statement on the label is proposed that Mainman 500 WG Insecticide may have adverse effect on honey bees for a short period after application which may be minimised if spraying takes place when bees are not foraging.

In-field risks were assessed for other non-target arthropods for proposed uses in cucurbits (3× 100 g ac/ha, 14d interval), apples (3× 70 g ac/ha, 14d interval), potatoes (2× 80 g ac/ha, 14d interval), and cotton (2× 70 g ac/ha, 14d interval). Considering the extended laboratory toxicity data and crop-specific foliar interception factors, risks were determined to be acceptable for foliar and ground dwelling arthropod species. An off-field assessment for other non-target arthropods was not considered necessary as the in-field risks were determined to be acceptable.

The risk quotient from a comparison of a theoretical worst case soil concentration of flonicamid and the earthworm 14 day LC50 of > 1000 mg flonicamid/kg soil, dry weight was <0.001 which readily meets the requirement that the risk quotient be < 0.1 for acute risk to earthworms to be acceptable. Consequently, the proposed uses of Mainman 500 WG Insecticide are not expected to result in unacceptable acute risk to earthworms. Because flonicamid is not expected to persist in soils, based on laboratory DT50 values of not greater than 3 days, chronic exposure of earthworms to flonicamid is unlikely to occur and chronic/reproductive risks to this indicator species are expected to be acceptable. chronic/reproductive risks to this indicator species are expected to be acceptable.

Based on available information, it is expected that the proposed uses of Mainman 500 WG Insecticide will be unlikely to have effects on microbially mediated soil nitrogen and carbon transformation processes.

Consideration of the screening test indicating no phytoxicity indicates the proposed uses of Mainman 500 WG Insecticide should be acceptable without the need to establish downwind no-spray zones.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed Use Pattern

It is proposed that Mainman 500 WG Insecticide (500g/kg flonicamid as a water dispersible granule) be used for the control of various insect pests in apples, cotton, cucurbits and potatoes. It will be used at the rate of 14-20g/100L in apples, 140g/ha in cotton, 140g/ha and 200g/ha in cucurbits and 160g/ha in potatoes.

8.2 Summary of Evaluation Of Efficacy and Crop safety

Twenty-eight trials were submitted in support of this application. Seventeen of the trials were conducted in Australia and eleven overseas, two of which were crop-safety only trials. For the overseas trials supporting argument was provided to justify relevancy to the application.

In each trial treatments were replicated four times and included an appropriate industry standard and un-treated controls. In all trials the candidate was applied at label rate and 2x label rate. Treatment application methodology, methods of assessment and data presentation were acceptable. Data were analysed using analysis of variance (ANOVA) and least significant (LSD) means separation.

Apples:

Data from two trials against tuber mealybug (*Pseudococcus viburni)* and four against woolly apple aphid (*Eriosoma lanigerum)* were submitted in support of the proposed use in apples. The trials were conducted in QLD, TAS and VIC. The candidate was applied at rates ranging from 3.5 to 40 (2x label rate) g/100L (with and without surfactant) with either 2 or 3 applications applied at 8 to 17 day intervals. Assessments of leaf and/or fruit and shoot infestations per tree (incidence/severity) and crop safety were made at various intervals after each application.

The submitted data demonstrated efficacy against woolly apple aphid and tuber mealybug at the proposed label rate, equivalent to the industry standards and significantly better than the untreated controls. No phytotoxic effects to apple leaves or fruit were observed at any of the assessment dates in any of the treatments in any of the trials.

Cucurbits:

Data from four Australian (VIC and QLD) efficacy and safety trials and one overseas crop safety laboratory trial (Japan) on adjacent and succeeding crops were submitted in support of the proposed use in cucurbits. The Australian trials were conducted against melon aphid (*Aphis gossypii*) in zucchini and silverleaf whitefly (*Bemisia tabaci*) in cucumber and rockmelon. The candidate was applied at between 35 and 400 (2x maximum label rate) g/ha, with and without the addition of an adjuvant (silverleaf whitefly only). Between one and three applications were made at 2, 3, 7, 9 or 10 day intervals. In the overseas trial the product was applied at 200, 400 and 600 (3x maximum label rates) g/ha and crop safety was assessed at 7 and 14 days after treatment. Eleven crop species including melon and nineteen crop species including cucumber and melon were tested in the adjacent and succeeding crop trials, respectively.

Melon Aphids: At the proposed label rate of 140 g/L, significantly lower melon aphid numbers were present compared with the un-treated controls and the industry standards at 7DDA. At 15DAA, no significant differences were recorded between any of the treatments dues to an influx of winged aphids which produced large numbers of first instars. There was no evidence of phytotoxicity in any of the treatments at any of the assessment dates.

Silverleaf Whitefly: At the proposed label rate in rockmelons there were significantly lower numbers of adults than in the un-treated control at up to 21 days after application (DAA) 3 and against nymphs at 7DAA2.The addition of a wetter 0.2% v/v resulted in lower nymph number sat up to 14DAA3. There were no signs of phytotoxicity to leaves, flowers or fruit of the treated rockmelon plants.

At the proposed label rate in cucumber, significantly lower numbers of nymphs were recorded than in the un-treated control. Numbers were comparable to the industry standard throughout the trial and this was reflected in the subsequently lower adult and egg populations later in the trial. No signs of phytotoxicity were observed on the leaves, flowers or fruiting structures.

Green Peach Aphid: While no data were submitted to demonstrate efficacy against green peach aphid (Myzus peraicae), bridging argument was provided. The argument together with demonstrated efficacy against this pest in potato considered adequate to support the proposed use in cucurbits.

Adjacent and Succeeding Crop Safety Trial: Eleven crop species including melon and nineteen crop species including cucumber and melon were tested in the adjacent and succeeding crop trials, respectively. In the adjacent crops trial, no signs of damage in melons were observed at 200g product/ha (1x label rate for silverleaf whitefly control and approximately 1.5x label rate for green peach aphid and melon aphid). In the succeeding crops trial, no signs of damage in either cucumber or melon plants were observed at 600g product /ha. The candidate at the proposed label rates for use in Australia were safe to use on cucumber and melon.

Potatoes:

Potatoes: One Australian (SA) and ten overseas (UK, Belgium, France and Gernamy) trials, one of which was crop safety-specific, were conducted against green peach aphid (*Myzus persicae*) and potato aphid (*Macrosiphum euphorbiae*). Single applications were made at between 20 and 160 g/ha for the combined efficacy/crop safety trials and two applications at 169 and 320 g/ha at 21 day intervals in the crop safety specific trial. In the combined efficacy and safety trials, assessments of aphid numbers on 10 or 20 plants/plot and crop safety were made at various times between 0 and 21 after treatment. In the crop safety-specific trial, plant vigour, tuber yields and phytotoxic effects were assessed between 1 and 21 days after each application. Tuber germination following storage was also recorded.

At proposed label rate the candidate was significantly better than the un-treated control and comparable with the industry standard for both green peach aphid and potato aphid. While no data were presented to demonstrate efficacy against melon aphid (*Aphis gossypii*), bridging scientific argument was provided. The argument together with demonstrated efficacy against melon aphid in cotton and cucurbits was considered adequate to support the proposed use in potato. No phytotoxicity was observed for any of the treatments at any of the assessment dates in any of the trials.

In crop-specific trial, at greater than the proposed label rate the candidate demonstrated an absence of adverse effects on plant health and growth, yield and subsequent germination of tubers in potatoes.

Cotton:

Six Australian trials covering dryland and irrigated cotton were conducted in NSW and QLD against cotton aphid (*Aphis gossypii)* and green mirid, (*Creontiades dilutes*). Single applications were made at rates of between 35 and 400 (approximately 2.5x label rate) g/ha, with or without the inclusion of a suitable wetting agent (cotton aphids, only). Pest infestations were recorded at various times from pre-spray and between 3 and 25 days after treatment. Depending on the trial assessment of infestation numbers were assessed on between 20 and 100 leaves/plot or insects were collected using the beat sheet method from 4 metre rows/plot and then counted. Visual assessments of crop damage were made at each assessment date.

Cotton Aphid: At the proposed label rate the candidate demonstrated effective control that was comparable to the industry standards. Cotton plants treated with the candidate had significantly fewer plants infested with cotton aphid and significantly fewer numbers of aphids were on the plants compared to the un-treated controls. Inclusion of a wetter did not improve either the incidence or severity of aphid control.

Green Mirids: At the proposed label rate, cotton plants treated with the candidate had significantly lower numbers of nymphs and total mirids present compared to the un-treated controls. The level of control achieved was equivalent to the industry standards tested.

The candidate was demonstrated to be safe to cotton at up to approximately 2.5 label rate. No phytotoxic effects were observed in any of the treatments at any of assessment times in any of the trials.

Crop Safety

The information presented indicated that Mainman 500 WG Insecticide is safe to use on the nominated crops when used as directed. No phytotoxic effects were observed in any of trials presented. Therefore, Mainman 500 WG Insecticide can be considered to be of low phytotoxicity and no label warnings are needed.

Resistance Management

Flonicamid belongs to the nicotinoid class of insecticides and exhibits systemic and translaminar activity and inhibits feeding. CropLife Australia's Insecticide Resistance Management Review Group has designated flonicamid as a member of the Group 9, sub-group C, class of insecticides. Group 9 insecticides are selective homopteran feeding blockers. The proposed use pattern is subject to a CropLife anti-resistance management strategy. Restraints included on the proposed label are consistent with the current CropLife Australia resistance management strategy for Group 9 insecticides.

8.3 Conclusion

The trial data presented substantiates the claims on the proposed label for Mainman 500 WG Insecticide. The directions for use, restraints, situations, pests and advice or critical comments on crop safety, application techniques, withholding periods, resistance warnings all appear to be appropriate.

Therefore, in terms of evidence for the efficacy of the product and its safety to target and non-target species, the application by Ishihara Sangyo Kaisha Ltd for the registration of for Mainman 500 WG Insecticide is supported when used in accordance with the proposed label instructions and Good Agricultural Practice (GAP).

9 LABELLING REQUIREMENTS

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

Mainman™ 500 WG INSECTICIDE

ACTIVE CONSTITUENT: 500 g/kg FLONICAMID

GROUP	9C	INSECTICIDE

For the control of aphids and mealybug in apples; for the control of aphids and mirids in cotton; for the control of aphids and silverleaf whitefly in cucurbits; and for the control of aphids in potatoes

NET CONTENTS: (500 g, 1 kg, 5 kg)

ISK Biosciences Oceania Pty Ltd
Level 61, Governor Phillip Tower,
1 Farrer Place, Sydney NSW 2000

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

DIRECTIONS FOR USE

RESTRAINT:
Do not apply by aircraft.

SPRAY DRIFT RESTRAINTS:
Except when applying with orchard airblast equipment, **DO NOT** apply with spray droplets smaller than a MEDIUM spray droplet size category according to nozzle manufactures specifications that refer to the ASAE S572 Standard or the BCPC Guideline.
DO NOT apply when wind speed is less than 3 or more than 20 kilometres per hour as measured at the application site.
DO NOT apply during surface temperature inversion conditions at the application site.
DO NOT direct the spray above trees during airblast application.
TURN OFF outward pointing nozzles at row ends and outer rows during airblast applications.

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

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

Crop	Pest	Rate	WHP	Critical Comments
Apples	Apply by dilute or concentrate spraying equipment. Apply the same total amount of product to the target crop whether applying this product by dilute or concentrate spraying methods. Refer to Application section of the label.			
	Woolly Apple Aphid *(Eriosoma lanigerum)*	**Dilute Spray:** 10 -14 g/100 L water **Concentrate spray:** Refer to Application, Apples section	21 days	Water quantities to be used depend on size of trees, development stage of trees and spraying equipment used. Use the higher rate under high pest pressure. A minimum re-treatment interval of 2 weeks must be observed. Do not apply more than 3 applications. Where applicable, use the higher rate under high pest pressure or to provide longer residual control.
	Tuber Mealybug *(Pseudococcus viburni)*	**Dilute Spray:** 14 -20 g/100 L water **Concentrate spray:** Refer to Application, Apples section		

Cotton	Cotton Aphid *(Aphis gossypii*) Green Mirid *(Creontiades dilutus)*	100-140 g/ha	7 days	Apply to an aphid population in the early stages of development before honeydew is evident or aphid damage occurs. Thorough spray coverage is essential. This product should be used according to the Cotton Industry's Best Management Practices Manual and its associated Spray and Drift Management Plan. If repeat applications are required, alternate with products from a different insecticide group as per current Cotton Industry Insecticide Resistance Management Strategy. This use is also subject to a CropLife Insecticide resistance management strategy. DO NOT apply more than 2 sprays per crop per season.
Cucurbits Cucumber Pumpkin Rockmelon Squash Zucchini (excluding protected cropping situations)	Green Peach Aphid *(Myzus persicae)* Melon Aphid *(Aphis gossypii*)	100- 140 g/ha	1 day	**DO NOT use in protected cropping situations.** Apply at first sign of aphid infestation. A minimum re-treatment interval of 2 weeks must be observed. Do not apply more than 3 applications. Where applicable, use the higher rate under high pest pressure.
	Silverleaf Whitefly *(Bemisia tabaci, B-type)*	200 g/ha plus Hasten at 2 mL /100 L water		
Potatoes	Green Peach Aphid *(Myzus persicae)* Melon Aphid *(Aphis gossypii*) Potato Aphid *(Macrosiphum euphorbiae)*	140-200 g/ha	14 days	Apply at first sign of aphid infestation. A minimum re-treatment interval of 2 weeks must be observed. Do not apply more than 2 applications. Use the higher rate under high pest pressure.

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

WITHHOLDING PERIODS:
Apples: DO NOT HARVEST FOR 21 DAYS AFTER APPLICATION
Potatoes: DO NOT HARVEST FOR 14 DAYS AFTER APPLICATION
Cotton: DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION
Cucurbits: DO NOT HARVEST FOR 1 DAY AFTER APPLICATION

GENERAL INSTRUCTIONS

Insecticide Resistance Warning

GROUP	9C	INSECTICIDE

For insecticide resistance management, Mainman 500 WG Insecticide is a Group 9C insecticide. Some naturally occurring insect biotypes resistant to Mainman 500 WG Insecticide and other Group 9C insecticides

may exist through normal genetic variability in any insect population. The resistant individuals can eventually dominate the insect population if Mainman 500 WG Insecticide and other Group 9C insecticides are used repeatedly. The effectiveness of Mainman 500 WG Insecticide on resistant individuals could be significantly reduced. Since occurrence of resistant individuals is difficult to detect prior to use, ISK Biosciences Oceania Pty Ltd accepts no liability for any losses that may result from the failure of Mainman 500 WG Insecticide to control resistant insects. Mainman 500 WG Insecticide may be subject to specific resistance management strategies. For further information contact your local supplier, ISK Biosciences Oceania Pty Ltd representative or local agricultural department agronomist.

Export of treated produce
Growers should note that suitable MRLs or import tolerances do not exist in all markets for produce treated with Mainman 500 WG Insecticide. In some situations export requirements may be met by limiting application number and/or imposing a longer withholding period than specified above. If you are growing produce for export, please check with ISK Biosciences Oceania Pty Ltd or your industry body for the latest information on any potential trade issues and their management before using Mainman 500 WG Insecticide.

Mixing
Add the required amount of Mainman 500 WG Insecticide to clean water in half filled spray tank with the agitator or by-pass in operation. Maintain agitation while filling tank with remainder of water. Agitation must also be maintained throughout the spray operation.

Application:
To be effective Mainman 500 WG Insecticide requires thorough spray coverage. Ensure that equipment is properly calibrated to give an even distribution at the correct volume. Thorough coverage of the target area is essential. Apply in sufficient water, and using suitable application parameters (nozzles, pressure, boom height, speed, etc) to ensure thorough and even coverage. Use only MEDIUM spray droplets according to ASAE S572 definition for standard nozzles. Adjust water volumes according to the crop growth stage.

Apples: The same quantity of Mainman 500 WG Insecticide per hectare should be used when spraying by either the dilute or concentrate method.
Dilute spraying: Use a sprayer designed to apply high volumes of water up to the point of run-off and matched to the crop being sprayed. Set up and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient water to cover the crop to the point of run-off. Avoid excessive run-off. The required water volume may be determined by applying different test volumes, using different settings on the sprayer, from industry guidelines or expert advice.
Add the amount of Mainman 500 WG Insecticide specified in the Directions for Use table for each 100 L of water. Spray to the point of run-off. If water volume exceeds 1000 L/ha, total rate of Mainman 500 WG Insecticide must not exceed 200 g/ha. The required dilute spray volume will change and the sprayer set up and operation may also need to be changed, as the crop grows.
Concentrate spraying: Use a sprayer designed and set up for concentrate spraying (that is a sprayer which applies water volumes less than those required to reach the point of runoff) and matched to the crop being sprayed. Apply a minimum of 500 L water/ha. Set up and operate the sprayer to achieve even coverage throughout the crop canopy using your chosen water volume. Determine an appropriate dilute spray volume (see *Dilute Spraying* above) for the crop canopy. This is needed to calculate the concentrate mixing rate. The mixing rate for concentrate spraying can then be calculated in the following way:

EXAMPLE ONLY
1. Dilute spray volume as determined above: for example 1000 L/ha
2. Your chosen concentrate spray volume: for example 500 L/ha
3. The concentrate factor in this example is 2X (i.e. 1000 L ÷ 500 L = 2)
4. If the dilute label rate is 14 g/100 L, then the concentrate rate becomes 2 x 14, which is 28 g/100 L of concentrate spray.
The chosen spray volume, amount of product per 100 L of water, and the sprayer set up and operation may need to be changed as the crop grows. For further information on concentrate spraying, users are advised to

consult relevant industry guidelines, undertake appropriate competency training and follow industry Best Practices.

Compatibility
For information on the compatibility of Mainman 500 WG Insecticide with other products, contact your local ISK Biosciences Oceania Pty Ltd or UPL Australia Limited representative.

PRECAUTION
Re-entry period
DO NOT enter treated areas until the spray has dried unless wearing cotton overalls buttoned to the neck and wrists (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

PROTECTION OF LIVESTOCK
DO NOT graze or feed treated crops to animals. DO NOT feed cotton fodder, stubble or trash to livestock.

PROTECTION OF HONEY BEES AND OTHER INSECT POLLINATORS
Mainman 500 WG Insecticide may have adverse effect on honey bees for a short period after application which may be minimised if spraying takes place when bees are not foraging.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
DO NOT contaminate streams, rivers or waterways with the chemical or used containers.

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

STORAGE AND DISPOSAL
Store in the closed, original container in a cool, well-ventilated area. Do NOT store for prolonged periods in direct sunlight. Triple rinse containers before disposal. Add rinsings to the spray tank. Do not dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush or puncture and deliver empty packaging to an approved waste management facility. If an approved waste management facility is not available bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots in compliance with relevant Local, State or Territory government regulations. Do not burn empty containers or product.

SAFETY DIRECTIONS
Will damage the eyes. Avoid contact with eyes. When opening the container, preparing the product for use and using the product, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and goggles. If product in eyes, wash it out immediately with water. Wash hands after use. After each day's use, wash gloves and contaminated clothing.

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

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

CONDITIONS OF SALE
ISK Biosciences Oceania Pty Ltd and UPL Australia Limited accepts responsibility for the consistent quality of the product; however since the use and application of the product is beyond control, the company accepts no responsibility whatsoever for any loss, damage or other result following the use of the product whether

used in accordance with directions or not; other than those mandatorily imposed by statutes, the liability is limited to the replacement of the goods and is conditional upon a claim made in writing and, where necessary, a sufficient part of the goods being returned for proper examination by the company within thirty days of sale.

APVMA Approval Number: 66373/53527

Bar code, label code
to be inserted

BN DOM

ABBREVIATIONS

ac	active constituent
ACN	Acetonitrile
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
BrdU	Bromodeoxyuridine
bw	bodyweight
^{14}C	Carbon 14
Cd-1	Cluster of differentiation 1
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
EL_{50}	Effective Loading rate lethal to 50% of the test population
EI	Export Interval
EGI	Export Grazing Interval
ER_{50}	Effect (sub-lethal) rate that cause 50% of maximal defined response in test population
ESI	Export Slaughter Interval
EUP	End Use Product
Fo	original parent generation

g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
HCl	Hydrogen chloride
Hct	Heamatocrit
Hg	Haemoglobin
HR	Highest residue
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
IARC	International Agency for Research on Cancer
id	intradermal
im	intramuscular
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

LR50	Lethal rate required to kill half (50%) of the test population
$MgSO_4$	Magnesium Sulphate
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NaCl	Sodium Chloride
NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
STMR	Supervised Trials Medium Residues
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration

TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Clara Cells	The Clara cells are a group of cells, sometimes called "non-ciliated bronchiolar secretory cells", found in the bronchiolar epithelium of mammals including man, and in the upper airways of some species such as mice. One of their main functions is to protect the bronchiolar epithelium.
Carcinogenicity	The ability to cause cancer
CD1 Mice	A laboratory strain of outbred mice used extensively in toxicological and chemical carcinogenicity bioassys
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	repels water
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

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

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