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Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the new active Dinotefuran in the Product Starkle 200 SG Insecticide

APVMA Product Number P69398

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

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PREFACE

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

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health, Office of Chemical Safety (OCS), Department of the Environment (DotE), 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 Starkle 200 SG 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 Tuesday 22 September 2015 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

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

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

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

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

Phone: +61 6210 4701

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

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

Further information

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

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

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

1 INTRODUCTION

Applicant

AgNova Technologies Pty Ltd,

Suite 3, 935 Station Street

Box Hill North

Vic 3129

Details of the Product

It is proposed to register Starkle® 200 SG Insecticide, containing 200 g/kg dinotefuran, as a water soluble granule (SG) for use as an insecticide for the control of silverleaf whitefly, (*Bemisia tabaci* Biotype B) and green mirid, (*Creontiades dilutus*) in cotton.

Both Dinotefuran and Starkle 200 SG insecticide will be manufactured and formulated overseas.

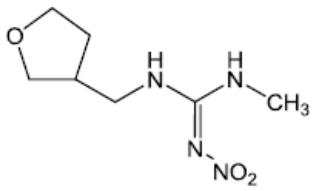
Dinotefuran has been registered for use in a range of products for various uses in crops, including cotton, in a number of overseas countries. Registration has been granted in Japan, the United States of America, South Korea, Taiwan, Thailand and Vietnam.

This publication provides a summary of the data reviewed and an outline of regulatory considerations for the proposed registration of Starkle 200 SG insecticide.

2 CHEMISTRY AND MANUFACTURE

2.1 Active Constituent

The chemical active constituent Dinotefuran has the following properties:

COMMON NAME (ISO):	Dinotefuran
CHEMICAL NAME:	*N''*-methyl-*N*-nitro-*N'*-[(tetrahydro-3-furanyl)methyl]guanidine
PRODUCT NAME:	Starkle 200 SG Insecticide
CAS REGISTRY NUMBER:	165252-70-0
EMPIRICAL FORMULA:	$C_7H_{14}N_4O_3$
MOLECULAR WEIGHT:	202.21
PHYSICAL FORM:	Solid (crystalline)
COLOUR:	White
ODOUR:	Odourless
MELTING POINT:	107.5^{0}C
DENSITY:	1.40 g/cm^3 at 20^{o}C
OCTANOL/WATER PARTITION COEFFICIENT (KOW):	-0.549 at 25^{0}C
STRUCTURAL FORMULA:	

The Chemistry Section of the APVMA has evaluated the chemistry aspects of dinotefuran active constituent (manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable.

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

CONSTITUENT	SPECIFICATION	LEVEL
dinotefuran	dinotefuran	990 g/kg minimum

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

2.2 Formulated Product

The Chemistry Section has evaluated the chemistry aspects of the product, Starkle 200 SG Insecticide (physico-chemical properties, formulation process, quality control procedures, batch analysis results, stability, analytical methods and packaging).

Starkle 200 SG Insecticide has the following properties:

Formulation type:	Water-soluble granule
Appearance:	White granule
Active constituent concentration:	Dinotefuran 200 g/kg
Bulk density	0.62 g/mL
pH (1% w/v aqueous solution)	6.2
Safety properties	Non-corrosive, not flammable or explosive

The product will be formulated in a number of locations using dinotefuran manufactured in Japan. The manufacturing and quality control procedures, including compliance with the release specifications, are acceptable.

The applicant provided the results of stability testing conducted using samples stored in polyethylene (the proposed commercial container type HDPE which is less permeable than polyethylene). Testing of all of the important parameters for this SG formulation was conducted. The results indicate that the formulated product is expected to be stable for at least two years when stored under normal conditions in the proposed commercial packaging.

2.3 Recommendation

Based on a review of the data provided by the applicant, the APVMA is satisfied that the chemistry and manufacturing details of Starkle 200 SG Insecticide are acceptable.

3 TOXICOLOGICAL ASSESSMENT

3.1 SUMMARY

Public Health Aspects and Toxicology

Mitsui Chemicals Agro, Inc. have submitted a data package seeking approval of the new active constituent dinotefuran (also referred to by its development identifier MTI-446). AgNova Technologies Pty Ltd have submitted a data package seeking registration of the new insecticide product, Starkle 200 SG Insecticide, containing dinotefuran at 200 g/kg.

Dinotefuran is a member of the neonicotinoid class of chemicals which act through binding to nicotinic acetylcholine receptors.

The data packages provided in the present submissions are extensive and appropriate for evaluation. The key studies in the main submission have been conducted in accordance with contemporary test guidelines under GLP and QA conditions.

In toxicokinetics studies in rats, dinotefuran was absorbed rapidly and overall oral absorption was high (> 90% absorption at 50 and 1000 mg/kg bw doses). After absorption, dinotefuran was widely distributed and detected in most examined tissues. Elimination of absorbed dinotefuran was rapid, with 85–99% of the administered radioactivity eliminated in urine within the first 24 hours, and > 90% excreted in the unchanged form. Bioaccumulation is not expected as only a small fraction of the administered dose was detectable in the residual carcasses at 168 h post dosing, noting a terminal half-life ($t_{1/2}$) of between 4 and 15 hours depending on dose. Following absorption, dinotefuran rapidly transferred across the placenta into foetal tissue and also into milk. Similar toxicokinetics profiles were seen in neonates.

Based on the findings of the acute toxicological studies evaluated, dinotefuran has low acute oral, dermal and inhalational toxicity in rats. Dinotefuran is not a skin irritant in rabbits but is a moderate eye irritant in the same species. Dinotefuran is not a skin sensitiser in the guinea pig. Based on the findings of the acute toxicological studies evaluated, Starkle 200 SG Insecticide has low acute oral, dermal and inhalational toxicity in rats. Starkle 200 SG Insecticide was a moderate eye and skin irritant in rabbits, and it was not a skin sensitiser in the guinea pig.

Dinotefuran was generally well tolerated across the species tested in repeat-dose toxicity studies, with decreases in body weight and decreased body weight gain identified as the main treatment-related effects. Carcinogenicity studies indicated that dinotefuran was not carcinogenic in mice or rats. Dinotefuran was negative in *in vitro* and *in vivo* mutagenicity and/or genotoxicity studies.

Dinotefuran was not a reproductive or developmental toxicant, as measured reproductive and developmental indices, including malformation/variation frequencies, were comparable with concurrent and/or historical controls. Across acute and subchronic studies, dinotefuran was not a neurotoxicant, and there were no observations that indicated dinotefuran was a developmental neurotoxicant or an immunotoxicant.

Occupational Health and Safety

Starkle 200 SG Insecticide is proposed for registration for the control of silverleaf whitefly and green mirid in cotton crops. Starkle 200 SG Insecticide will be applied by various ground boom or aerial applications up to a maximum of two times per cotton season.

The exposure and risk assessment information considered in this evaluation indicates that the use of Starkle 200 SG Insecticide in accordance with the proposed relevant label particulars is not expected to pose unacceptable risks to human health. Appropriate safety directions and personal protective equipment has been recommended to mitigate identified risks.

Conclusion

After consideration of the hazards associated with the active constituent and the proposed product, along with the exposure and risks expected with use of the proposed product, the OCS considers that the proposed use of dinotefuran and Starkle 200 SG Insecticide will not be an undue health hazard to humans and satisfies the safety criteria defined in Section 5A of the *Ag/Vet Code Act* (1994), when used in accordance with the relevant label particulars.

3.2 EVALUATION OF TOXICOLOGY

The submitted toxicology data on dinotefuran/ MTI-446 are extensive and comprehensive. The data include several studies on toxicokinetics/metabolism, acute, short-term, subchronic, chronic and carcinogenicity, reproduction and developmental studies, neurotoxicity, immunotoxicity and genotoxicity studies. Additionally, acute oral toxicity and genotoxicity studies conducted on metabolites of dinotefuran (DN phosphate, UF and MNG) have also been provided. The submitted data for this assessment of dinotefuran are of appropriate quality for regulatory consideration, and the database is considered adequate for the hazard characterisation of dinotefuran.

Chemical class

Dinotefuran is a member of the neonicotinoid class of chemicals. An area of concern for mammalian toxicity in this class is neurotoxicity, based on the mode of action in insects where neonicotinoids act through binding to nicotinic acetylcholine receptors. These receptors are also present in mammalian cells, including those present in the central and peripheral nervous system.

Toxicokinetics and metabolism

To determine the toxicokinetics and metabolic fate, dinotefuran was radiolabelled in two different locations: F-labelled (tetrahydrofuran) or G-labelled (guanidine moieties), and dosed orally or intravenously to rats. Rats were treated either by a single dose, or multiple daily doses for 7 or 15 days. The position of the radiolabel did not affect the absorption or excretion parameters. Absorption was rapid (T_{max} 15 min to 2 hours) after a single oral dose, with the absorption rate dependent on the dose administered. Elimination of radioactivity was rapid ($t_{1/2}$ = 3.64–7.86 hours at 50 mg/kg bw, 6.28–16.1 hours for 1000 mg/kg bw), with 84–99% of the administered radioactivity eliminated in urine within the first 24 hours following a single dose

administration. There was a very low probability of bioaccumulation as only a fraction of the administered dose was detectable in the residual carcasses 168 hours after dosing.

The vast majority (> 90%) of the absorbed dose (both the oral and intravenous routes) was eliminated via the urine, with faecal excretion accounting for only 1–3% of the absorbed dose. Regardless of radiolabel position, the majority of the administered dose was excreted unchanged, with less than 10% metabolised through enzymatic hydroxylation, oxidation, reduction, and acetylation. Single oral doses of dinotefuran administered to pregnant and lactating rats indicated a rapid absorption of the dose and transfer across the placenta to foetal tissue and into milk, at concentrations 50 – 100% higher than that in plasma. Non-contiguous repeat dosing with dinotefuran showed a similar pattern to that of a single dose, with rapid uptake and transfer to milk. A trend towards increasing concentration of dinotefuran in the milk was noted with multiple doses.

In general terms, the position of the radiolabel, dose level, sex or duration of dosing did not appear to affect the distribution of dinotefuran in tissues. The highest levels in tissues were found in the kidney, stomach, and urinary bladder within 30 mins of a single dose (indicative of fast absorption and excretion). After 7 days, the majority of tissues had residual levels of dinotefuran that were below the level of detection, with the exception of very low levels in the skin and kidneys of males and the mammary glands of females.

After oral administration of dinotefuran to neonatal rats, similar patterns of absorption, distribution, metabolism, and elimination were seen in pups compared to adults, except for apparent slower rates of absorption and elimination in pups. The rate differences may have been caused by the incompletely developed gastrointestinal system and kidneys in pups. Percutaneous absorption was examined *via* several aqueous dilutions of dinotefuran administered to rats. Dinotefuran in aqueous solution was moderately absorbed through the skin with a potentially absorbable fraction of 36.21, 26.50 and 10.28% of the administered dose for the 0.003, 0.03 or 0.3 mg/cm^2 doses respectively after 24 hour-exposure. With the available data, completion of absorption after dermal administration could not be confirmed, and further refinement of the dermal absorption factor was not possible in this case due to the methodology used in the study (including the use of cyanoacrylate tape strips and pooling of tape strips).

Acute toxicity

Dinotefuran has low acute toxicity by the oral route in rats and mice, and low acute toxicity by the dermal and inhalational routes in rats. Dinotefuran was not a skin irritant in rabbits. Two separate eye irritation studies were submitted. In one study, dinotefuran was identified as a moderate eye irritant in rabbits; however, in another study in the same species, dinotefuran was non-irritating to the eye. No information was provided to indicate why the two submitted eye irritation studies on dinotefuran technical had these divergent results, and on available information, the OCS has conservatively considered dinotefuran to be a moderate eye irritant. Dinotefuran was not a skin sensitiser by the Maximisation method in the guinea pig.

Repeat-dose toxicity studies

Short term studies were carried out in four different species, mouse, rat, rabbit and dog. While noting that some studies were range-finding in nature (and hence of limited regulatory value), dinotefuran was generally well tolerated across the species tested, with minimal signs of toxicity after oral or dietary administration. In mice and rats treated for 4 weeks in the diet, effects were limited to lower body weights and body weight

gains at the highest doses tested (50000 ppm). Preliminary studies in rabbits *via* oral gavage indicated toxicity (hypoactivity and tremors) at doses of 300 and 1000 mg/kg bw/d. A one week preliminary study in dogs reported inappetency at high doses of 30000 and 40000 ppm.

Range-finding short term dermal studies in rats indicated possible localised effects, including atonia. However, this was not seen in the definitive 4 week study, where no systemic toxicity was seen at up to 1000 mg/kg bw/d. A repeat dose 4 week inhalational study in rats indicated minor haematology ratio effects at the highest dose tested, 2080 mg/m^3 along with slightly reduced body weight gains in all male treatment groups (220, 660 and 2080 mg/m^3); however, the reduced body weight gains were not considered to be severe enough to preclude the establishment of a NOEL for this study.

In subchronic dietary studies in three species (mouse, rat and dog), treatment with dinotefuran over 13 weeks was generally well tolerated. The major effect in all species was reduced body weight and body weight gains at high dose levels. Additionally, in rodents minor changes in clinical chemistry were noted at high dose levels. In the subchronic dog study, the initial high doses (30000 and 40000 ppm) were lowered to 8000 and 16000 ppm after serious effects were seen, including body weight loss and faecal effects (altered output). Minor changes were seen in clinical chemistry, but were not considered to be toxicologically significant. Toxicologically significant decreases in overall body weight gain was seen in all treated female groups, 1600, 8000 and 24000 ppm, which precluded the establishment of a NOEL in females for this study.

Chronic toxicity was examined in three species (mouse, rat and dog). In a one year dog study, body weights and body weight gain were statistically reduced for the majority of the study in females at the two highest doses (3200 and 16000 ppm), while the males at the highest dose showed a similar trend without statistical significance. Minor changes in clinical chemistry, haematology and urinary pH were not considered to be test material related. In a 78 week mouse carcinogenicity study, there was no effect of treatment on mortality, though decreased bodyweight gain was noted at doses above the limit dose. No effects of treatment were seen in haematology or at interim and terminal sacrifices. There was no carcinogenic potential identified in mice treated with dinotefuran.

In a two year combined toxicity/carcinogenicity study in rats there was no effect of treatment on survival. Female body weights and body weight gain were affected by treatment at the highest dose tested (20000 ppm). Haematology, clinical chemistry and urinalysis were unaffected by treatment. At interim sacrifices, absolute liver weights were significantly decreased in high dose females; however, this was not seen at terminal sacrifice. From the pooled data on all animals there was evidence of increases in several neoplasms at the highest dose. These included benign endometrial stromal polyps and mammary carcinomas in females, and thyroid C-cell adenomas and testicular (benign) interstitial cell tumours in males. These differences, while statistically significantly increased over those of the respective controls, were within the historical control range for the performing laboratory, were considered to be relatively common neoplasms and were not considered to indicate an increased carcinogenic potential in rats from exposure to dinotefuran.

Reproductive and developmental studies

A two generation reproductive study in rats identified body weight decreases in males and females in the first parental generation at the highest dose tested (10000 ppm), clear evidence of treatment-related toxicity was noted in parental animals at 10000 ppm, with decreased body weight gain seen in P_0 males and females.

Additionally at 10000 ppm, both males and females had reduced organ weights without associated histopathological changes. There were no effects on reproductive parameters in the P_0 females, or of F_1 offspring development parameters, including behavioural assessments. For the second generation (P_1 parents) evidence of treatment-related toxicity was restricted to decreased body weight gain seen in males and females at 10000 ppm. While an increased proportion of stationary and decreased motile sperm was noted at 10000 ppm, this was considered unlikely to be a treatment-related effect noting the lack of dose consistency and other sperm changes. No absolute organ weights were affected in males, with changes restricted to thyroid absolute and relative weights in females at the highest dose. There were no effects on reproductive parameters in the P_1 females. Beyond decreases in body weight gains of F_2 offspring during lactation there were no effects on development parameters. F_2 pups showed decreases in absolute organ weights in brain, thymus and spleen weights at terminal sacrifice along with corresponding changes in relative ratios with both body weight and brain weights at the highest dose level. Overall, dinotefuran was not a reproductive toxicant to rats.

Dinotefuran was not a developmental toxicant in rats up to the limit dose, while in rabbits, maternotoxicity was noted as reduction in body weight gains at 300 mg/kg bw/d, though there were no effects seen on kits. Dinotefuran was not a developmental toxicant in rabbits.

Neurotoxicity

Dinotefuran was not acutely neurotoxic to rats at 1500 mg/kg bw and was not neurotoxic at doses exceeding the limit dose in a subchronic dietary study. Developmental neurotoxicity was not observed.

Immunotoxicity

In Guideline-compliant immunotoxicity studies in mice and rats, no effects were seen from treatment with dinotefuran. Dinotefuran is not considered to pose any immunotoxicity risk.

Genotoxicity

Dinotefuran was not mutagenic or genotoxic with and without metabolic activation in a standard suite of *in vitro* studies, and was not genotoxic in an *in vivo* mouse micronucleus assay.

Metabolites DN, UF and N-Methyl-N'-Nitroguanidine (MNG)

DN phosphate and UF were tested for acute oral toxicity and bacterial reverse mutation potential. Both compounds were low acute oral toxicants in mice (LD_{50} > 5000 mg/kg bw) and not genotoxic. MNG was examined for acute oral toxicity, skin and eye irritation, skin sensitisation and for *in vitro* and *in vivo* genotoxic potential. MNG has a mouse acute oral LD_{50} >1000 mg/kg bw, was a slight eye irritant but not a skin irritant or a skin sensitiser. MNG did not show genotoxic potential.

The hazard posed by the metabolites was generally lower than that of the parent compound dinotefuran. Uncertainty regarding the acute oral toxicity of MNG relative to dinotefuran was noted, as MNG was only tested up to 1000 mg/kg bw, though no deaths were identified at this dose.

Formulated product

The product Starkle 200 SG Insecticide has low acute toxicity by oral, dermal and inhalational routes in rats. Starkle 200 SG Insecticide was a moderate skin irritant and eye irritant in rabbits. It is a non-skin sensitiser by the Buehler method in the guinea pig.

3.3 PUBLIC HEALTH STANDARDS

Poisons Scheduling

Dinotefuran and Starkle 200 SG Insecticide were referred to the Delegate of the Secretary of the Department of Health for scheduling consideration. The Delegate considered the application and published a Delegate-only decision for dinotefuran on 23 July 2015. In his final decision, the Delegate noted the following:

"*Dinotefuran is an insecticide in the neonicotinoid class. While other members of this class have a primary listing in Schedule 6 (with some product exemptions to Schedule 5), the toxicological profile of dinotefuran is clearly consistent with SPF guidance for inclusion in Schedule 5. Evidence of mild/moderate skin/eye irritancy for the formulated product means that is inappropriate to provide a schedule exemption for the formulated product considered in the application."*

The Delegate also confirmed an implementation date of 1 October 2015.

ADI

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

The OCS has established an ADI for dinotefuran, noting its proposed use in cotton.

The critical effect of dinotefuran identified from chronic toxicity studies is reduced body weights and/or body weight gains. Dogs appeared to be the most sensitive species for dinotefuran, with a decrease in body weights observed in females at 108 mg/kg bw/d. The corresponding NOEL was 22 mg/kg bw/d.

A 100-fold safety factor, consisting of factors of 10 for intraspecies and interspecies variation, was considered appropriate. The toxicological database for dinotefuran included several long-term oral studies and carcinogenicity studies in the mouse and rat, and was considered complete. Since no sensitive population groups were identified during the course of this evaluation no additional safety factor is required at this time. A safety factor of 100–fold safety factor was therefore applied to the relevant NOEL for the determination of an ADI. Therefore, an ADI of 0.22 mg/kg bw/d is established, based on a NOEL of 22 mg/kg bw/d in a 52–week oral study in beagle dogs, using a 100–fold safety factor.

ARfD

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

An acute reference dose (ARfD) was established since dinotefuran was considered likely to present an acute hazard to humans. Adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. The following criteria were used for the determination of an ARfD (Solecki *et al*., 2005):

Significant treatment-related findings in the acute, short-term, 2–generation reproduction or developmental toxicity studies or in the acute or subchronic neurotoxicity studies to indicate a concern for acute dietary risk at doses up to 500 mg/kg bw/d.

Treatment-related mortalities observed at doses up to 1000 mg/kg bw in single dose oral studies.

The acute, short-term, 2–generation reproduction and neurotoxicity database for dinotefuran does not contain studies that meet the criteria recommended for the establishment of an ARfD. However the developmental study in rabbits does meet these requirements, as administration of 300 mg/kg bw/d did elicit the treatment-related findings of concern, (reduced body weight gain). The NOEL of this study was established at 125 mg/kg bw/d. OCS considers that a default safety factor of 100, consisting of factors of 10 for intraspecies and interspecies variation, was considered appropriate. Since no sensitive population groups were identified during the course of this evaluation no additional safety factor is required at this time.

Therefore, the ARfD for dinotefuran is established at 1.25 mg/kg bw using a default safety factor of 100.

4 RESIDUES ASSESSMENT

4.1 Introduction

Starkle 200 SG Insecticide contains the new active constituent dinotefuran (Figure 1) and is proposed for use on cotton. Two applications of *Starkle 200 SG Insecticide* will be made to cotton at a maximum rate of 375 g product/ha (75 g ai/ha) with a 14 day re-treatment interval. The proposed harvest withholding period is 14 days while 'DO NOT graze treated cotton crops or cut for stockfeed' and 'DO NOT feed cotton trash to livestock' grazing restraints are proposed. As part of the residue assessment for dinotefuran, plant and animal metabolism studies, supervised residue trials and trade aspects were considered.

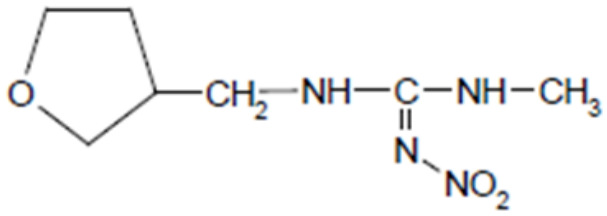


Figure 1: Dinotefuran

4.2 Metabolism

Plants

For rape, one foliar application of ^{14}C-dinotefuran was made at 100, 200 or 1000 g ai/ha. Samples of seeds, foliage and roots were collected at maturity (65–70 day PHI). The TRR in seeds were 0.055, 0.127 and 0.696 mg eq/kg for the 100, 200 and 1000 g ai/ha treatments respectively. The TRR in foliage were 0.259, 0.650 and 2.351 mg eq/kg for the 100, 200 and 1000 g ai/ha treatments respectively. Parent dinotefuran was found to be the major component (10.6 – 18.7 % TRR) of the oilseed rape (seed and forage). The metabolite 1-methyl-3-(tetrahydro-3- furylmethyl)guanidium dihydrogen (DN) was found to be a significant component in rape forage (13.45–17.36 % TRR).

For potato, one foliar application of ^{14}C-dinotefuran was made at 100, 200 or 1000 g ai/ha. Potato tubers were collected at a 54 or 75 day PHI. The TRR in whole tubers were 0.706–1.035, 0.499–0.664 and 3.014 mg eq/kg for the 100, 200 and 1000 g ai/ha treatments respectively. Parent dinotefuran was found to be the major component in potato tuber (8.5–14.5 % TRR).

For rice, one foliar or one soil application of ^{14}C-dinotefuran at 400 g ai/ha was made at either 5 or 20 days after bolting. Grain and straw samples were collected at maturity. The TRR in whole seeds were 0.245–0.396 and 5.096–5.845 mg eq/kg following a soil and foliar application respectively. The TRR in straw were 1.347–1.822 and 7.570–8.146 mg eq/kg following the soil or foliar application respectively. Parent dinotefuran was found to be the major component in rice whole grain and straw (35.9–66% TRR). The

metabolite 1-methyl-3-(tetrahydro-3-furylmethyl)urea (UF) was found to be a significant component in whole rice (5.6–17.2 % TRR) and rice straw (8.1–15.9% TRR).

For rotational crops, one application of ^{14}C-dinotefuran was made to bare soil at 608 g ai/ha. Following a 30 or 120 day Plant Back Interval (PBI), radishes, lettuces and cereals (sorghum or wheat) were planted. Total radioactive residue levels above 0.010 mg eq/kg plant part were detected in the plants originating from the 30–day field plot. However, the total radioactive residue was below 0.010 mg eq/ kg for all plant parts originating from the plants grown in the 120–day field plot, except for the radish leaf which had residues of 0.035 ppm and 0.026 mg eq/kg for immature and mature leaf samples, respectively. Analyses of the samples of the 120–day field plot showed that no radioactive component exceeded 0.006 mg eq/kg (DN). Parent dinotefuran and its MNG, UF, BCDN and DN metabolites were significant components in rotational crops.

The proposed metabolic pathway for dinotefuran in plants is presented below.

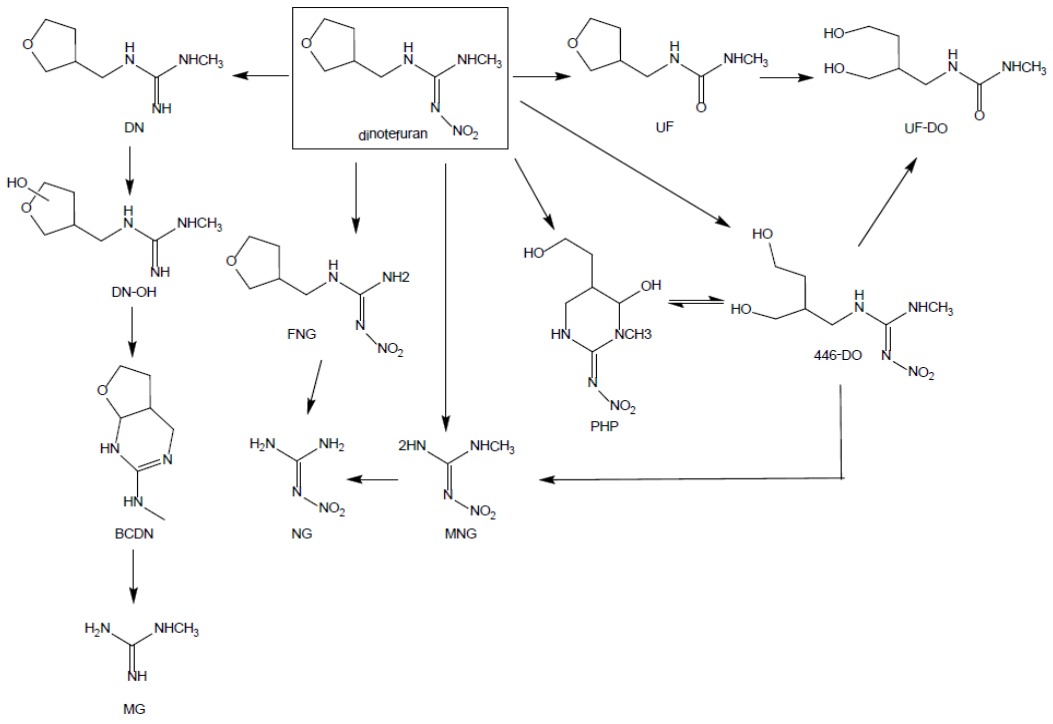


Figure 2: The Proposed metabolic pathway for dinotefuran in plants

Animals

For lactating goats, ^{14}C-dinotefuran was orally administered daily for 5 consecutive days at an actual dose of 8.8 ppm in the feed. TRR levels in goat milk, muscle, fat, liver and kidney were low (0.012–0.272 mg eq/kg), with the majority of the TRR being detected in urine and faeces (7.15 and 3.02 mg eq/kg respectively on day 5). Residue levels in milk were similar on each day. The major residues present in goat matrices were parent MTI-446 (40.1 % TRR in milk, 41.3% TRR in muscle, 20.0% TRR in fat, 12.1% in liver and 12.7% in kidney) and UF (8.7% TRR in milk, 14.6% TRR in muscle, 7.4% TRR in fat, 6.8% TRR in liver and 5.0% TRR in kidney).

The proposed metabolic pathway for dinotefuran in lactating goat is presented below.

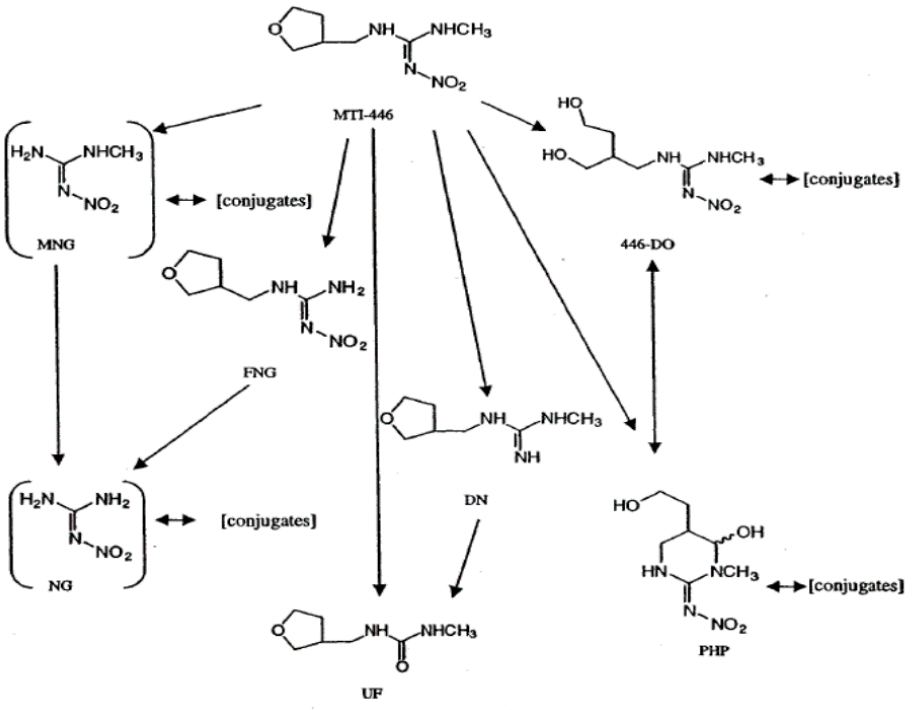


Figure 3: The proposed metabolic pathway for dinotefuran in lactating goats

For laying hens, ^{4}C-dinotefuran was orally administered daily for 5 consecutive days at an actual dose of 9.9 ppm in the feed. TRR levels in hen eggs (yolk and whites), meat, fat and liver were low (0.020–0.134 mg eq/kg). Residues in egg whites were similar from day 2–5 and residues in egg yolks were similar from day 3–5. The major residue present in hen matrices was parent MTI-446 (57.9% TRR in egg whites, 44.2% TRR in egg yolks, 9.1% TRR in muscle, 10.8% TRR in fat and 9.3% TRR in liver).

The proposed metabolic pathway for dinotefuran in laying hen is presented below.

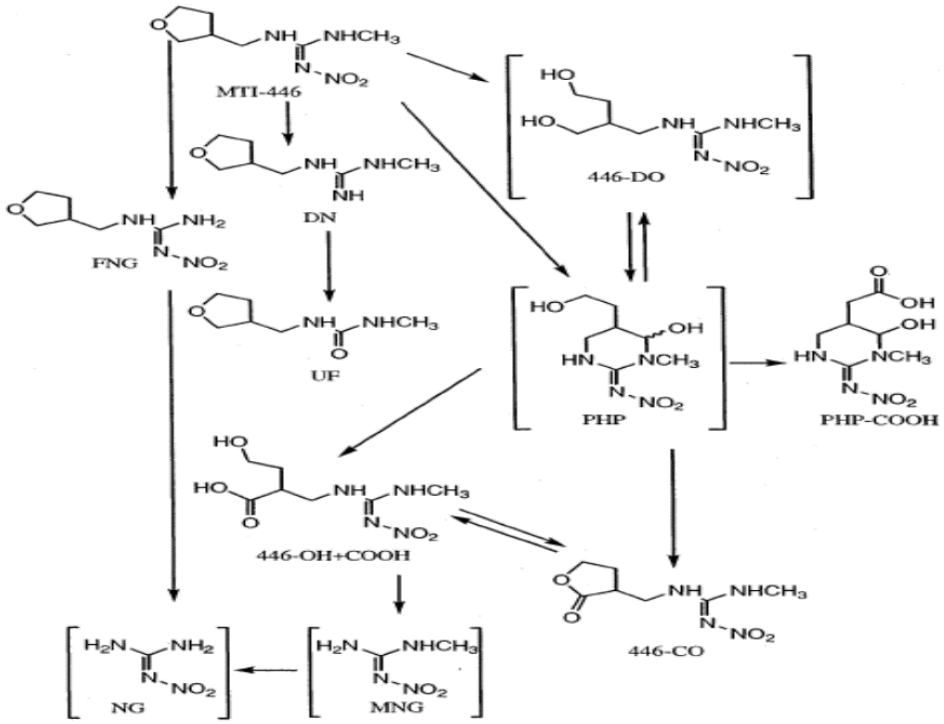


Figure 4: The proposed metabolic pathway for dinotefuran in laying hens

For rats, the majority of the radioactivity was excreted as the unchanged parent compound and dinotefuran was the major radioactive component in most examined tissues. The metabolism of dinotefuran in rats is therefore similar to that observed in goats and hens.

4.3 Analytical Methods

Plants

Residues of dinotefuran and its metabolites were extracted with acidified acetonitrile/water and the extract was then cleaned up with hexane. HPLC/MS/MS was used for analysis and different instrumental parameters are required for DN as to parent dinotefuran and DF. The LOD and LOQ were 0.02 and 0.05 mg/kg respectively for each analyte and the recovery of dinotefuran, UF and DN were with acceptable limits.

Animals

Residues of dinotefuran and its metabolites were extracted with acidified acetonitrile/water. Clean up was by liquid:liquid partition with hexane and solid phase extraction using C18 cartridge. Quantitation was by liquid chromatography using tandem mass spectrometric detection (LC-MS/MS). The LOQ was 0.01 mg/kg for each analyte. This methodology was validated in bovine liver, kidney, muscle, fat, milk, cream and hen eggs and the recovery of dinotefuran, UF and DN in the residue studies was acceptable.

4.4 Stability of the Pesticide in Stored Analytical Samples

The storage stability of parent dinotefuran (metabolites were not tested) in lettuce (leaf), cotton (seed), apple (fruit), tomato (fruit) and potato (tuber) following frozen storage (-20^{o}C) for up to 12 months was within acceptable limits.

4.5 Residue Definition

Based on the results of the metabolism and residue studies, it is recommended that the residue definition for dinotefuran in plant commodities be parent dinotefuran only for enforcement. Toxicological studies did not discount the toxicity of the UF and DN metabolites so the sum of parent dinotefuran, UF and DN (expressed as parent) for the dietary exposure assessment definition for plant commodities is proposed. It is recommended that both parent dinotefuran and the UF metabolite be included in the residue definition for animal commodities (for both enforcement and dietary risk assessment).

4.6 Residue Trials

The Australian cotton trials (n=8) found that two application made 14 days apart at the maximum proposed application rate of 75 g ai/ha resulted in parent dinotefuran residue levels of <0.05 mg/kg (n=8) and total residues (expressed as dinotefuran) of <0.18 (n=7) and 0.21 mg/kg in cotton seed at the proposed withholding period of 14 days (or later if higher). Following the 2X rate of 150 g ai/ha, parent dinotefuran residue levels of <0.05 (n=7) and 0.16 mg/kg and total residues (expressed as dinotefuran) of <0.18 (n=7) and 0.49 mg/kg were observed in cotton seed at the proposed withholding period of 14 days.

The US cotton trials (n=13) found that two application made 14 days apart at 150 g ai/ha (2X the maximum rate proposed) resulted in parent dinotefuran residue levels of <0.05 (n=8), 0.07 (n=2), 0.08, 0.10, 0.17 mg/kg and total residues (expressed as dinotefuran) of <0.18 (n=8), 0.20 (n=2), 0.21, 0.23, 0.31 mg/kg in cotton seed at the proposed withholding period of 14 days (or later if higher).

The combined dataset from the 8 Australian and 13 US trials for parent dinotefuran residues suitable for MRL estimation (including scaled data) is, in rank order, <0.05 mg/kg (n= 18), 0.05, 0.08 and 0.085mg/kg (n=21) in cotton seed. It is noted that the 0.08 mg/kg result is a scaled residue from the 2X treatment in one Australian trial and it was used in the MRL estimation. The STMR was <0.05 mg/kg and the OECD MRL calculator estimates an MRL of 0.09 mg/kg. A dinotefuran MRL at 0.1 mg/kg for SO 0691 Cotton seed is supported by the available data. The scaled STMR and HR for total residues (expressed as parent) is <0.18 and 0.25 mg/kg respectively and this information will be considered during the dietary exposure estimates.

Cotton seed meal and hulls are both considered to be animal feed commodities. The processing study found that parent dinotefuran (the residue definition for enforcement) should not concentrate into cotton seed meal but may concentrate slightly into cotton seed hulls (PF = 1.4X for parent dinotefuran). The calculated HR-P for cotton seed hulls is 0.12 mg/kg, which is higher than the proposed MRL for cotton seed (0.1 mg/kg). It is therefore recommended that an MRL for ‘Cotton seed hulls’ be established at 0.2 mg/kg in Table 4 of the MRL standard.

4.7 Animal Commodity MRLs

The applicant has proposed that the grazing restraints ‘DO NOT feed cotton trash to livestock’ and ‘DO NOT graze treated cotton crops or cut for stockfeed’ be included on the product label. Consideration to the exposure of dinotefuran through the consumption of cotton forage (no data) or cotton gin trash is not required at this time. According to OECD guidelines, cotton seed, cotton seed meal and cotton seed hull can be consumed by cattle and cotton seed meal can be consumed by poultry.

The potential exposure to dinotefuran for beef and dairy cattle in Australia is calculated to be equal to 0.128 and 0.074 mg/kg respectively, which is significantly lower than the lowest feeding level included in the lactating cow feeding study (5.73 ppm in the feed). The highest estimated ‘sum of dinotefuran and UF, expressed as dinotefuran’ residue that may result in beef and dairy cattle commodities following consumption of foodstuffs (cotton seed, meal and hull) that may be treated with the dinotefuran, was 0.0005 mg/kg (in milk) and it is recommended that mammalian animal commodity (meat, milk and offal) MRLs be established at *0.02 mg/kg.

The potential exposure to dinotefuran for poultry in Australia is calculated to be equal to 0.02 mg/kg, which is significantly lower than the lowest feeding level included in the laying hen metabolism study (10 ppm in the feed). The highest estimated ‘sum of dinotefuran and UF, expressed as dinotefuran’ residue that may result in poultry commodities following consumption of foodstuffs (cotton seed meal) that may be treated with the dinotefuran, was 0.00004 mg/kg (in liver) and it is recommended that poultry commodity (meat, eggs and offal) MRLs be established at *0.02 mg/kg

4.8 Estimated Dietary Intake

The chronic dietary exposure to dinotefuran is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived primarily from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for dinotefuran is equivalent to <1% of the ADI. It is concluded that the chronic dietary exposure to dinotefuran is acceptable.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived primarily 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 highest acute dietary intake was estimated at <1% of the ARfD. It is concluded that the acute dietary exposure is acceptable.

4.9 Bioaccumulation Potential

The octanol-water partition coefficient ($\log_{10}K_{OW}$) for dinotefuran is -0.644 (pH 7) indicating that dinotefuran has a low potential for fat solubility and bioaccumulation. The cotton seed processing study found that dinotefuran residues did not concentrate in cotton seed oil and the animal transfer study and animal metabolism studies found that dinotefuran residues did not concentrate in fat. Potential for bioaccumulation is considered to be low.

4.10 Spray Drift

Spray drift modelling, using APVMA spray drift standard application scenarios, shows that with respect to no-spray zones (using an application rate of 75 g ai/ha), for a ‘broadacre high ground boom—medium’ application, a downwind buffer of 3 m is required. For an ‘aerial agricultural fixed wing—Large application—ASAE medium droplet’ application, a downwind buffer of 0 m is required for an 8 km/h wind speed, 2 m is required for a 14 km/h wind speed and 6 m is required for a 20 km/h wind speed.

Due to the insignificant size of the calculated buffers, it is considered that a no-spray zone should not be required for the protection of international trade.

4.11 Recommendations

The following amendments are proposed to the MRL standard:

TABLE 1

COMPOUND		FOOD	MRL (mg/kg)
ADD:			
DINOTEFURAN			
SO	0691	Cotton seed	0.1
MO	0105	Edible offal (Mammalian)	*0.02
PE	0112	Eggs	*0.02
MM	0095	Meat [mammalian]	*0.02
ML	0106	Milks	*0.02
PO	0111	Poultry, Edible offal of	*0.02
PM	0110	Poultry meat	*0.02

TABLE 3

COMPOUND	RESIDUE
ADD:	
DINOTEFURAN	Commodities of plant origin for enforcement: Dinotefuran Commodities of plant origin for dietary exposure assessment: Sum of dinotefuran, 1-methyl-3-(tetrahydro-3-furylmethyl) urea (UF) and 1-methyl-3-(tetrahydro-3-furylmethyl) guanidium dihydrogen (DN) expressed as dinotefuran Commodities of animal origin: Sum of Dinotefuran and 1-methyl-3-(tetrahydro-3-furylmethyl) urea (UF) expressed as dinotefuran

TABLE 4

COMPOUND	ANIMAL FEED COMMODITY	MRL (mg/kg)
ADD:		
DINOTEFURAN		
	Cotton seed hulls	0.2

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

- Harvest: DO NOT harvest for 14 days after application.
- Grazing: DO NOT graze treated cotton crops or cut for stockfeed.

  DO NOT feed cotton trash to livestock

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Cotton seed (including derived oils and meals) is exported along with animals that have been fed feeds containing residues arising from the proposed use.

5.2 Destination of exports

Australian exports of cotton seed grain in 2013–14[2] totalled 464 kt (value $168 million), with the major export destinations being the United States (181 kt), the Republic of Korea (88 kt) and Japan (78 kt). Australian exports of cotton seed meal in 2013–14 totalled 36 kt, with the major export destinations being the New Zealand (22 kt) and the Republic of Korea (14 kt). Export figures for cotton seed oil for 2013–14 are not available, but only 3.7 kt of cotton seed oil were exported in 2012–2013[3].

The significant export markets for Australian beef, sheep, pig meat and offals are listed in the APVMA Regulatory Guidelines—Data Guidelines: Agricultural—Overseas trade (Part 5B).

Total exports of dairy products in 2013–14 were worth $2.73 billion, with key export destinations including Japan, Singapore, China, Indonesia, Malaysia, Thailand, the Philippines, Korea, Russia, and the USA (Australian Commodity Statistics 2014).

[2] Australian Commodity Statistics 2014

[3] Australian Commodity Statistics 2013

5.3 Proposed use pattern

Starkle 200 SG Insecticide (200 g/kg dinotefuran)

Restraints:
DO NOT apply when wind speed is less than 3 or more than 20 km/h at the application site.
DO NOT apply with smaller than MEDIUM spray droplets according to ASAE S572 definition for standard nozzles.
DO NOT apply during surface temperature inversion conditions at the application site.
Users of this product MUST make an accurate written record of the details of each spray application within 24 hours following application and KEEP this record for a minimum of 2 years.

Crop	Pest	Rate	Critical Comments
Cotton	Silverleaf whitefly (*Bemisia tabaci*)	250 g to 375 g/ha ***(50 – 75 g ai/ha)***	Ensure thorough coverage. Monitor crops and commence applications once local thresholds are reached. Use the higher rate when longer residual control is required or during periods of high pest pressure or rapid crop growth or when crops are well advanced. Continue to monitor crops and make a subsequent application as necessary. Performance can be reduced in stressed crops (eg drought affected dryland cotton) or when senescing late season. **Do not apply more than 2 applications per crop. Do not reapply within 14 days of a previous Starkle application.** Use in accordance with the current Insecticide Resistance Management Strategies.
	Green mirid (*Creontiades dilutus*)	90 g/ha ***(18 g ai/ha)***	

Withholding periods:
Harvest: DO NOT harvest for 14 days after application.
Grazing: DO NOT graze treated cotton crops or cut for stockfeed.
DO NOT feed cotton trash to livestock

Mixing and application:
Mixing: Partially fill the spray tank with clean water and add the required quantity of product to the water surface. Allow the product to submerge before agitating. Top up the tank with clean water to the required volume.
Ground rig Application: Apply as a blanket spray or banded spray ensuring thorough coverage is achieved. Apply in a minimum of 80 L/ha water. Use only medium spray droplets according to specifications of the nozzle manufacturer that refer to the ASAE S572 Standard or BCPC guideline.

5.4 Overseas registration and approved label instructions

The applicant has stated that the following use pattern is registered for use on cotton in the USA.

COUNTRY	REGISTERED COTTON USE PATTERN
USA	Two applications at a rate of 98.5–150 g ai/ha, with a 14 day PHI.

5.5 Comparison of Australian MRLs with Codex and International 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. Dinotefuran has been considered by Codex, the USA, Japan and Korea. Dinotefuran has not been approved for use by the EU, Canada and New Zealand and has not been approved for use on relevant commodities by Korea. The following relevant Codex and international MRLs have been established for dinotefuran:

Australian and overseas MRLs/tolerances for dinotefuran in cotton commodities

COMMODITY	TOLERANCE FOR RESIDUES ARISING FROM THE USE OF DINOTEFURAN (mg/kg)			
	AUSTRALIA	CODEX[4]	JAPAN[5]	USA[6]
Residue Definition (for enforcement)	Dinotefuran (proposed)	Dinotefuran	Dinotefuran	Dinotefuran plus UF and DN, expressed as dinotefuran
Cotton seed	0.1 (proposed)	0.2	0.4	0.4
Cotton, gin byproducts	-	-	-	8.0

[4] www.codexalimentarius.net

[5] www.m5.ws001.squarestart.ne.jp

[6] www.ecfr.gov

Australian and overseas MRLs/tolerances for dinotefuran in animal commodities

COMMODITY	TOLERANCE FOR RESIDUES ARISING FROM THE USE OF DINOTEFURAN (mg/kg)			
	AUSTRALIA	CODEX	JAPAN	USA
Residue Definition	Dinotefuran plus UF, expressed as dinotefuran (proposed)	Dinotefuran plus UF, expressed as dinotefuran	Dinotefuran	Dinotefuran
Meat (mammalian)	*0.02 (proposed)	0.1	0.05	0.05
Fat (mammalian)	-	-	0.05	0.05
Offal (mammalian)	*0.02 (proposed)	0.1	0.05	0.05
Milk	*0.02 (proposed)	0.1	0.05	0.05

5.6 Potential Risk to Trade

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

Available residue data found the STMR and HR for parent dinotefuran for the proposed use to be <0.05 and 0.085 mg/kg respectively in cotton seed and a dinotefuran MRL at 0.1 mg/kg for cotton seed is proposed. The STMR and HR for total residues (expressed as parent) is <0.18 and 0.245 mg/kg respectively. Residues are therefore expected be lower than the tolerance set by Codex (0.2 mg/kg for parent dinotefuran), Japan (0.4 mg/kg for parent dinotefuran) and the US (0.4 mg/kg for total residues, expressed as dinotefuran). Korea, which is a major export destination for Australian cotton seed and cotton seed meal, has not established relevant dinotefuran MRLs.

Given the STMR was below the LOQ of 0.05 mg/kg and cotton seed is subject to bulking and blending during the ginning process, the potential risk to the trade of cotton seed is considered to be low.

Residues of dinotefuran and the UF metabolite above the LOQ are not expected in animal commodities as a result of the proposed use on cotton. An MRL at *0.02 mg/kg is recommended for mammalian meat, milk and offal, which is lower than that established by codex (0.1 mg/kg on a parent dinotefuran plus UF basis) and the US and Japan (0.05 mg/kg on a parent dinotefuran only basis). As residues above the LOQ are not expected in animal commodities, the potential risk to trade of animal commodities is considered to be negligible.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Health hazards

Dinotefuran (CAS: 165252-70-0) is currently not listed on the Safe Work Australia Hazardous Substances Information System (HSIS) Database (SWA, 2015). With the available toxicology information, OCS has not classified the active constituent dinotefuran as a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

However based on the product toxicology information, Starkle 200 SG Insceticide is classified as a hazardous substance in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004) with the following risk phrases:

R38	Irritating to skin

Formulation, packaging, transport, storage and retailing

The active constituent dinotefuran and the product Starkle 200 SG Insecticide will be manufactured overseas. The product will be available in pack sizes of 1 to 20 kg individual polyethylene lined bags or HDPE containers.

Use pattern of the product

Starkle 200 SG Insecticide is proposed for registration for the control of silverleaf whitefly and green mirid in cotton crops. Starkle 200 SG Insecticide will be applied by various ground boom or aerial application methods up to a maximum of two times per cotton season. The maximum used rate proposed is 375 g product/ha, equivalent to 75 g a.i./ha. Re-entry into treated crops may be required to scope the insect load on the crop and to harvest the crop.

6.1 Exposure during use

Farmers and their employees will be the main users of the product. Workers may be exposed to the product when opening containers, mixing/loading, and cleaning up spills and equipment. The main route of exposure to the product/spray will be dermal and inhalational, with possible accidental exposure via the ocular route. The expected duration of possible exposure would be expected to be intermittent and/or short-term.

In the absence of product-specific exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used to estimate exposure.

The toxic endpoint of concern and identified NOEL for risk assessment is derived from a repeat dose study in animals, and in this instance a margin of exposure (MOE) of 100 or above is considered acceptable. The MOE takes into account both potential inter-species extrapolation and intra-species variability. Based on the risk assessment for workers conducting open mixing and loading or application for aerial applications, the margins of exposure are all considered to be acceptable. Open mixing and loading and ground boom

application also showed margins of exposure that were considered to be acceptable. While the MOE values estimated are high and suggest that the use of clothing PPE would not be necessary during the different phases of use based on risks from repeat exposure, the acute hazard profile of the product (being a moderate skin and eye irritant) identifies risks from use of the product that would require clothing PPE, particularly during mixing and loading operations where handling of unmixed/undiluted product would take place.

6.2 Exposure during re-entry

There are not expected to be re-entry risks associated with dermal contact with crops treated with Starkle 200 SG Insecticide after the spray has dried. Noting the high MOE estimated in the re-entry risk assessment, a NIL re-entry statement is considered appropriate.

6.3 Recommendations for safe use

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

6.4 Conclusion

The approval of the active constituent dinotefuran and registration of the product Starkle 200 SG Insecticide for the control of silverleaf whitefly and green mirid in cotton crops are supported.

Starkle 200 SG 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 Fate and behaviour in soil

Preliminary testing with five soils resulted in dissipaton half-lives from 20 days to 89 days under laboratory conditions. Full testing was undertaken on two soils at 20°C and resulted in half-lives of 9.9 days and 68 days (DT90 values corresponded to 33 days and 278 days respectively). Testing at a lower temperature (10°C with one of the soils) approximately doubled the half-life from 9.9 days to 20 days. The main route of degradation was via cleavage of the tetrahydromethyl portion of the molecule to MNG (1-methyl-2-nitroguanidine) with further de-methylation to NG (nitroguanidine). Mineralisation in the two full aerobic soil studies was extensive with between 42–52% CO_2 produced during the incubation periods.

Further laboratory testing with the main soil metabolite, MNG, in three different soils showed this compound to have half-lives between 45.4 days to 64.3 days, but relatively long DT90 values (234–709 days).

Field dissipation of dinotefuran to bare soil was assessed in three sites in the USA. All sites were classed as sandy loams in the top 15 cm soil layer. Dissipation half-lives were similar to those found in the laboratory, and ranged from 33 days to 58 days (DT90s of 180 days to 234 days when applying the full data set and no consideration of the slow phase only). MNG was found at maximum levels during these studies of 7.9% to 29%. Despite the properties of dinotefuran indicating it may be highly mobile in the environment, there was only very limited movement of either dinotefuran or MNG below the 0–15 cm soil layer.

In standard batch equilibrium studies, dinotefuran was tested in five soils with organic carbon concentrations ranging from 1.0% to 2.9%. Koc values ranged from 5.5 L/kg to 45 L/kg, and in all these soils, dinotefuran can be considered to be very highly mobile. Desorption coefficients in all soils were larger, indicating the in part irreversibility of the adsorption. In a further screening (adsorption only) study with four different Japanese soils containing between 1.2% OC and 3.3% OC, Koc values were all again <50 L/kg.

Batch equilibrium studies were undertaken on the two main metabolites, DN and MNG, in 5 different soils with organic carbon ranging from 0.71% to 2.9%. MNG was very highly mobile in all soils (Koc <50 L/kg), while DN had Koc values between 50–150 L/kg in two soils (high mobility), between 150–500 L/kg in two soils (medium mobility) and between 2000–5000 L/kg in one clay loam soil (slight mobility).

7.2 Fate and behaviour in water

Dinotefuran and its two main metabolites, MNG and DN, were stable to hydrolysis at pH 4, 7 and 9. Aqueous photolysis may provide an important degradation route for dinotefuran in the environment with a half-life in both natural river water and sterile water of 3.8 h. Quantum yield experiments indicated half-life values ranging from 1.8 days to 7.8 days at 40°N for the different seasons. While the major metabolite DN was stable, the minor aquatic metabolite MNG was estimated to have a photochemical degradation half-life in water of between 2.8 days to 12 days at 40°N for the different seasons.

In an aerobic water/sediment study testing degradation in two different systems, levels of dinotefuran decreased slowly. After 28 days of incubation the parent compound still accounted for 74% and 58% of the

applied radioactivity in the river and pond systems, respectively, and was detected until the end of incubation (320 days) amounting to 7.0% and 7.6% in the river and pond system, respectively.

The major degradate formed in both water and sediment was identified as DN (1-methyl-3-(tetrahydro-3-furylmethyl) guanidine). This metabolite was more significant in the sediment reaching maximum levels of 18% applied and 31% applied in the river and pond systems, respectively, compared to the water column where maximum levels in both systems were <10% applied.

The mineralization of the test item (formation of $^{14}CO_2$) accounted for a maximum of 35% and 20% of the applied radioactivity for river and pond systems, respectively, over the duration of the study. Half-lives for dinotefuran in the water layer were 23 days (pond) to 51 days (river) while those in the sediment compartment were 71 days (river) to 122 days (pond).

In an anaerobic study the degradation pattern appeared to be similar to that under aerobic conditions with DN being the main metabolite, found in sediment at a maximum 29% at the end of the incubation period of 120 days, and a maximum 4% in the water layer at the same time. The DT50 values for dinotefuran were determined to be 16 days in water and 70 days in sediment.

7.3 Fate and behaviour in air

Based on an average tropospheric hydroxyl radical concentration of 1.5 X $10^6/cm^3$, the estimated half-life for the degradation of dinotefuran by hydroxyl radicals was calculated to be 0.82 hours.

Effects on terrestrial vertebrates

Dinotefuran is considered practically non-toxic to terrestrial vertebrates based on avian, rat and mouse acute oral exposure studies (LD50 >2000 mg ac/kg bw) and avian dietary toxicity studies (LC50 >5000 mg/kg diet). The mallard duck was the most sensitive avian species in chronic (reproduction) studies; continuous exposure of dinotefuran in the diet resulted in a NOEC of 2000 mg/kg diet based on effects on egg viability and number of hatchlings at 5000 mg/kg diet. Risks of adverse effects on terrestrial vertebrates following dietary exposure of food items directly treated with two applications of 375g product/ha (75g ac/ha), with a 14–day interval between applications, were determined to be acceptable.

Effects on aquatic species

Dinotefuran is practically non-toxic on a short-term basis to fish (96h LC50 >100 mg/L), *Daphnia magna* (48h EC50 >100 mg/L; 21d NOEC 100 mg/L), Eastern oyster (96h EC50 >141 mg/L), algae (96h ErC50 >100 mg/L), and aquatic vascular plants (7d ErC50 >110 mg ac/L). However, dinotefuran was highly toxic to mysid shrimp (96h LC50 0.90 mg/L) and sediment-dwelling organisms (48h LC50 0.072 mg/L). As a result, protection statements are required indicating high toxicity to aquatic life.

No chronic toxicity was observed in fish or *Daphnia magna* at the highest doses tested (94d NOEC 10 mg/L and 21d NOEC 100 mg/L, respectively). Sediment dwelling organisms were very sensitive to dinotefuran on a chronic basis (27d EC10 0.0086 mg/L).

The major aquatic metabolite, DN, was practically non-toxic to fish, *Daphnia magna* or algae under acute exposure conditions (EC/LC50 >100 mg/L). No chronic toxicity of DN to sediment dwelling organisms was observed at the limit dose tested (27d NOEC 5 mg/kg sediment). The major soil metabolite, MNG, was not toxic to algae (EC50 >100 mg/L).

Dinotefuran has a log Pow of -0.549 and is not expected to bioaccumulate.

The key regulatory endpoint for assessing risk to aquatic species was based on acute toxicity to sediment dwelling organisms. Risks of spray drift and runoff following two applications of 375g product/ha (75g ac/ha), with a 14–day interval between applications, were determined to be acceptable provided a mandatory no-spray zone of 5 metres is observed and the slopes of treatment areas are restricted to 4% or less.

Effects on bees

Both dinotefuran and the formulated product are highly toxic to bees through both contact exposure (LD50 0.056 and 0.014 µg ac/bee, respectively) and oral exposure (LD50 0.023 and 0.0068 µg ac/bee, respectively). Further, residues on foliage were shown to remain toxic to bees up to 48 hours after application. However, full scale field testing with long-term observation of hives did not demonstrate effects in the field. Field testing closely resembled the proposed Australian use pattern with two applications to cotton crops, and the second application occurring during flowering. At the time of first sampling (5–7 days after the second application), peak residues in nectar and pollen of 0.115 mg/kg and 0.0099 mg/kg respectively were found. Residues in pollen were generally relatively low and seldom exceeded the limit of detection (LOD). Residues in nectar, based on three sampling times, appeared to decline exponentially. Residues from within the hive matrices (nectar, pollen, honey and beeswax) did not indicate accumulation within hives based on the results of this study, with measurements in honey and beeswax taken up to 71–85 days after the second application.

While bees were clearly exposed to dinotefuran based on residues found in nectar and honey, and residues later detected within the hive, it was apparent that they were not exposed to maximum likely residues due to the hives not being placed in the treated fields until at least 5 days following the final application. On the basis of this study, the risks were determined to be acceptable provided beehives are removed or covered during application and for 5 days after treatment.

Effects on other arthropods

Other beneficial (predatory and parasitic) arthropods are also very sensitive to dinotefuran. Glass plate tests provided LR50 values of 0.084 g ac/ha (*Aphidius rhopalosiphi*), 23 g ac/ha (*Typhlodromus pyri*) and 0.013 g ac/ha (*Orius laevigatus*).

A field study was subsequently conducted in cotton at five application of 18 or 75 g ac/ha in 7 to 14–day intervals. Significant adverse effects to the Coleoptera and thrip groups and to individual species (*D. bellalus* and *Trichogramma*) were observed. Although *Trichogramma* was the only Hymenoptera species to show a significant treatment-related response, the result of the toxic reference across this group as a whole was highly variable (+28.7% to -47.3%).

On the basis of the lab and field results, dinotefuran is not considered to be compatible with integrated pest management (IPM) programs that utilise beneficial arthropods. Furthermore there was not sufficient data to demonstrate recovery of sensitive populations within a reasonable period of time. For this reason, an advisory statement on the label is required to identify the product is not compatible with IPM programs and to minimise spray drift to reduce harmful effects on beneficial arthropods in non-crop areas.

Effects on earthworms and other soil organisms

Dinotefuran is considered to be toxic to earthworms (14d LC50 4.9 mg/kg soil; 56d NOEC 0.2 mg/kg soil). Risks of adverse effects on earthworms following direct exposure to soil treated with two applications of 375g product/ha (75g ac/ha), with a 14–day interval between applications, were determined to be acceptable.

Soil micro-organisms, as measured by carbon mineralisation or nitrogen transformation activities, were not affected by dinotefuran at concentrations up to 4.0 mg/kg soil (equivalent to 3000 g ac/ha). Therefore, risks to soil micro-organisms were also determine to be acceptable.

Effects on non-target terrestrial plants

Dinotefuran is not considered to be phytotoxic. In tier 1 toxicity testing with 10 standard plant test species, dinotefuran did not demonstrate toxicity at a single application rate of 600 g ac/ha. Risks of dinotefuran to non-target plants are considered to be acceptable.

8 EFFICACY AND SAFETY ASSESSMENT

Purpose of application

The application is for the registration of a new water-soluble granule (SG) product Starkle® 200 SG Insecticide, containing 200 g/kg dinotefuran, for use as an insecticide for the control of silverleaf whitefly, (*Bemisia tabaci* Biotype B) and green mirid, (*Creontiades dilutus*) in cotton.

The product is to be applied in cotton as a foliar spray, mid to late season (end-January to mid-March) coinciding with crop stages from early flowering through boll opening when the target pests are present.

8.1 Summary of Evaluation

Silverleaf whitefly

Data from five trials in cotton and one in eggplant were used. The trials were carried out in Northern New South Wales, Central Queensland and North Queensland.

All trials included treatments that encompassed the rates of Starkle proposed for registration (250–375 g/ha). In two trials Starkle was also assessed when mixed with oil.

At least one of the industry standards; (Pegasus, Movento + Hasten, Admiral) was included in each trial.

In all trials, Starkle at the rates proposed for registration, produced whitefly infestations significantly lower than in untreated plots. Although adult infestations were significantly reduced in only three trials, the lack of significance was due to very low numbers and/or movement between plots and influx from the adjacent crop.

Nymphs/pupae infestations were significantly reduced in all six trials.

The addition of oil showed no additional efficacy

In the six trials where Pegasus was used, control of silverleaf whitefly was variable, due to differing population structures and residual properties, but was generally similar to that provided by Starkle.

In the four trials where Movento was used, it tended to give slightly better control than Starkle at 250 and 375 g/ha. In the two trials where Admiral was used, Starkle at 250 and 375 g/ha provided better control.

None of the Starkle treatments, even at rates above the proposed registered rate, produced any evidence of phytotoxicity to the three different varieties of cotton assessed.

The data therefore show that Starkle at 250–375 g/ha, is safe and effective for the control of silverleaf whitefly in cotton.

Green Mirid

Data from three trials were provided. In one trial, no data was provided for Starkle, at the proposed registered rate, and it was therefore excluded.

The trials were carried out in Northern New South Wales. The trials included treatments that encompassed the rate of Starkle proposed for registration (90 g/ha). In both trials Starkle was used alone and also mixed with oil and compared with the industry standards Regent and Shield.

The generation of useful data was severely hampered by very low and variable insect numbers. However in both trials Starkle at 90 g/ha produced a significant reduction in green mirid infestations. Starkle performed as well as the industry standards.

No phytotoxicity was observed in either trial.

The data therefore show that Starkle at 90 g/ha, is safe and effective for the control of green mirid in cotton.

8.2 Conclusion

The claims on the proposed label that Starkle 200 SG Insecticide provides acceptable control of silverleaf whitefly and green mirid in cotton when used as directed is supported by the results from the Australian trials.

Acceptable crop safety is expected when the product is used as directed. The directions for use are appropriated and consistent with insecticide use in commercial agriculture in Australia.

The application by AgNova Technologies Pty Ltd for the registration of Starkle 200 SG Insecticide is supported on efficacy and crop safety grounds when used in accordance with label instructions.

9 LABELLING REQUIREMENTS

RELEVANT LABEL PARTICULARS (RLPs) Starkle® 200 SG Insecticide

Select appropriate:

☑ New Product (include all applicable RLPs) OR

☐ Variation (highlight instructions that are being varied). Approval No. of label being varied:

Signal Heading	CAUTION KEEP OUT OF REACH OF CHILDREN READ SAFETY DIRECTIONS BEFORE OPENING OR USING
Product Name	Starkle® 200 SG Insecticide
Active Constituent/s	200 g/kg DINOTEFURAN
Mode of Action	GROUP 4A INSECTICIDE
Statement of Claims	For the control of silverleaf whitefly and green mirid on cotton as per the Directions for Use Table.
Net Contents	1 kg – 20 kg
Name & Address	AgNova Technologies Pty Ltd, Suite 3, 935 Station Street Box Hill North Vic 3129 Australia Phone (03) 9899 8100
Directions for Use	DIRECTIONS FOR USE
Restraints	**RESTRAINTS** **DO NOT** apply by aircraft. **DO NOT** apply where the slope exceeds 4%. **SPRAY DRIFT RESTRAINTS** **DO NOT** apply with spray droplets smaller than a MEDIUM spray droplet size category according to nozzle manufacturer specifications that refer to the ASAE S572 Standard or the British Crop Production Council guideline. **DO NOT** apply when wind speed is less than 3 or more than 20 kilometres per hour, as measured at the application site. **DO NOT** apply during surface temperature inversion conditions at the application site. Users of this product **MUST make an accurate written record** of the details of each spray application within 24 hours following application and **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;

<table>
<tr><td></td><td>
4. amount of product used per hectare and number of hectares applied to;
5. crop/situation and weed/pest;
6. wind speed and direction during application;
7. air temperature and relative humidity during application;
8. nozzle brand, type, spray angle, nozzle capacity and spray system pressure measured during application;
9. name and address of person applying this product. (Additional record details may be required by the state or territory where this product is used.)
MANDATORY NO-SPRAY ZONES
DO NOT apply if there are aquatic and wetland areas including aquacultural ponds, surface streams and rivers within 5 metres downwind from the application area.
</td></tr>
<tr><td>Directions for Use</td><td>
<table>
<tr><th>CROP</th><th>PEST</th><th>RATE</th><th>CRITICAL COMMENTS</th></tr>
<tr><td rowspan="2">Cotton</td><td>Silverleaf whitefly (Bemisia tabaci)</td><td>250 g to 375 g/ha.
.</td><td rowspan="2">Ensure thorough coverage.
Monitor crops and commence applications once local thresholds are reached.
Use the higher rate when longer residual control is required or during periods of high pest pressure or rapid crop growth or when crops are well advanced.
When both pests are present always use silverleaf whitefly rate.
Continue to monitor crops and make a subsequent application as necessary.
Performance can be reduced in stressed crops (eg drought affected dryland cotton) or when senescing late season.
Do not apply more than 2 applications per crop. Do not reapply within 14 days of a previous Starkle application. Use in accordance with the current Insecticide Resistance Management Strategies.</td></tr>
<tr><td>Green mirid (Creontiades dilutus)
ONLY</td><td>90 g/ha</td></tr>
</table>
</td></tr>
<tr><td>“Not to be used…”</td><td>NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL UNLESS AUTHORISED UNDER APPRORIATE LEGISLATION.</td></tr>
<tr><td>Withholding Period/s</td><td>Cotton:
Harvest: DO NOT HARVEST FOR 14 DAYS AFTER APPLICATION.
Grazing: DO NOT GRAZE TREATED COTTON CROPS OR CUT FOR STOCKFEED.
DO NOT FEED COTTON TRASH TO LIVESTOCK.</td></tr>
<tr><td>General Instructions</td><td>MIXING/APPLICATION
Mixing
Partially fill the spray tank with clean water and add the required quantity of product to the water surface. Allow the product to submerge before agitating. Top up the tank with</td></tr>
</table>

	clean water to the required volume. **Ground Rig Application** Apply as a blanket spray or banded spray ensuring thorough coverage is achieved. Apply in a minimum of 80 L/ha water. Use only medium spray droplets according to specifications of the nozzle manufacturer that refer to the ASAE S572 Standard or BCPC guideline.
Resistance Warning	**INSECTICIDE RESISTANCE WARNING** **GROUP 4A INSECTICIDE** For insecticide resistance management Starkle® is a Group 4A insecticide. Some naturally occurring insect biotypes resistant to Starkle and other Group 4A insecticides may exist through normal genetic variability in any insect population. The resistant individuals can eventually dominate the insect population if Starkle or other Group 4A insecticides are used repeatedly. The effectiveness of Starkle on resistant individuals could be significantly reduced. Since the occurrence of resistant individuals is difficult to detect prior to use, AgNova Technologies Pty Ltd accepts no liability for any losses that may result from the failure of this product to control resistant insects. Starkle may be subject to specific resistance management strategies. For further information contact your local supplier, AgNova Technologies Pty Ltd representative or local agricultural department agronomist.
Precautions	**RE-ENTRY PERIOD** DO NOT allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length chemical resistant gloves. Clothing must be laundered after each day's use.
Protections	**PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT** Very toxic to aquatic life. DO NOT contaminate wetlands or water courses with this product or used containers. **PROTECTION OF HONEYBEES AND OTHER INSECT POLLINATORS** Highly toxic to bees and will kill bees foraging in a treated crop or in hives which are accidentally sprayed or contaminated by spray drift. Spray residues remain toxic to bees for 2-3 days after application. To protect long term viability of beehives, remove or cover beehives during application and for 5 days after treatment. **INTEGRATED PEST MANAGEMENT** Toxic to beneficial arthropods. Follow the Cotton Pest Management Guide when using this product. Minimise spray drift to reduce harmful effects on beneficial arthropods in non-crop areas.
Storage & Disposal	Store in the closed, original container in a cool, well-ventilated area. DO NOT store for prolonged periods in direct sunlight. Triple rinse containers or preferably pressure rinse before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and bury empty containers in a local authority landfill. If no landfill is available bury the containers below 500mm in a disposal pit specifically set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should not be burnt.
Safety Directions	Will irritate the eyes. Will irritate the skin. Avoid contact with eyes and skin. When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing). chemical resistant gloves and face shield or goggles. If product on skin, immediately wash area with soap and water. If product in eyes, wash

	it out immediately with water. Wash hands after use. After each day's use, wash gloves, face shield or goggles and contaminated clothing.
First Aid	If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26.

The following is for APVMA use only:

APVMA Approval No.	69398/60731

ABBREVIATIONS

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

HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
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
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	repels water
Leaching	Removal of a compound by use of a solvent
Log 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, *Registration and Permits, Data Guidelines* (2015), apvma.gov.au/registrations-and-permits/data-guidelines.