Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active Fluensulfone in the Product NIMITZ 480 EC NEMATICIDE

APVMA Product Number P66678

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

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PREFACE

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

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

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

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

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

About this document

This is a Public Release Summary.

It indicates that the 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 NIMITZ 480 EC NEMATICIDE 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 28 July 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
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

Phone: +61 2 6210 4701
Fax: +61 2 6210 4741
Email: enquiries@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

1.1 Purpose of application

ADAMA AUSTRALIA PTY LTD has applied to the APVMA for registration of the new product NIMITZ 480 EC NEMATICIDE containing the new active constituent fluensulfone (480 g/L) as an emulsifiable concentrate formulation. This submission has been assessed under a joint review arrangement where registrations for the same formulation and similar uses have been submitted concurrently in Australia, Canada and the USA.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of NIMITZ 480 EC NEMATICIDE, containing the new active constituent, fluensulfone.

1.2 Mode of action

Fluensulfone is a pyrazole nematicide and is the first nematicide in the fluoroalkenyl class. It targets root-knot (*Meloidogyne* spp.) nematodes. The effects of fluensulfone are generally slow in onset and include cessation of feeding, effects on motility, and developmental arrest through egg retention. Eggs laid on treated substrate show concentration dependent inhibition of development. The severity of effects is dependent on the dose applied and the duration of exposure.

1.3 Product claims and use pattern

Nimitz 480 EC Nematicide (the product) is intended for control of Root-knot nematode in transplanted vegetable crops; including Cucurbits, Tomatoes (not for processing), Capsicum, Chilli, Eggplant and Okra. The product is intended to be used at a rate of 4–8 L in Queensland only. Use of the low rate is recommended in less susceptible crops and/or under low Root-knot nematode pressure and use of the high rate is recommended in more susceptible crops and/or under moderate to high Root-know nematode pressure.

1.4 Overseas registration

Products containing fluensulfone are currently registered overseas including in the USA.

2 CHEMISTRY AND MANUFACTURE

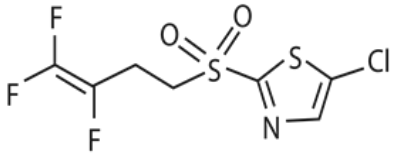
2.1 Active constituent

Fluensulfone is a new active constituent to be used as a nematicide in Cucurbits, Tomatoes (not for processing), Capsicum, Chilli, Eggplant and Okra. Fluensulfone belongs to the chemical family Heterocyclic fluoroalkenyl sulfones.

Manufacturing site

The active constituent fluensulfone is manufactured by Makhteshim Chemical Works Ltd, Israel.

Chemical Characteristics of the Active Constituent fluensulfone

COMMON NAME (ISO):	Fluensulfone
IUPAC NAME	5-Chloro-2-(3,4,4-trifluorobut-3-en-1-ylsulfonyl)-1,3-thiazole
CAS NAME:	5-Chloro-2-[(3,4,4-trifluoro-3-buten-1-yl)sulfonyl]thiazole
CAS REGISTRY NUMBER:	318290-98-1
MINIMUM PURITY:	957 g/kg
MOLECULAR FORMULA:	$C_7H_5NO_2S_2ClF_3$
MOLECULAR WEIGHT:	291.7
STRUCTURE:	
CHEMICAL FAMILY	Heterocyclic fluoroalkenyl sulfones

APVMA ACTIVE CONSTITUENT STANDARD FOR FLUENSULFONE ACTIVE CONSTITUENT

CONSTITUENT	SPECIFICATION	LEVEL
Fluensulfone	Fluensulfone	Not less than 957 g/kg

PHYSICAL AND CHEMICAL CHARACTERISTICS OF PURE ACTIVE CONSTITUENT

ODOUR:	Specific odour
PHYSICAL STATE:	White to off white fine crystalline powder (Purified active*) Yellow, resin like solid (Technical active#)
MELTING POINT:	34.4 °C (purified active); 34.8 °C (technical active)
RELATIVE DENSITY (20°C):	1.876 g/cm^3 (Purified active)
PH OF 1% AQUEOUS MIXTURE	5.11 at 21°C
OCTANOL/WATER PARTITION COEFFICIENT (P_{OW}):	logP_{ow} = 1.96 (Purified active, using HPLC method)
SOLUBILITY IN WATER:	545.3 mg/L at 20°C
VAPOUR PRESSURE:	3.0×10^{-2} Pa @25°C 1.3×10^{-1} Pa @35°C 3.4×10^{-1} Pa @45°C
FLAMMABILITY	Not a flammable solid
AUTO-FLAMMABILITY	No self-ignition temperature was observed up to 400°C
EXPLOSIVE PROPERTIES	Not explosive
OXIDISING PROPERTIES	No oxidizing properties

*: The purity of the purified active was 99.1% w/w

#: The purity of the technical active was 96.75% w/w

2.2 Formulated product

The product NIMITZ 480 EC NEMATICIDE will be packaged in 500 mL to 1000 L HDPE containers.

NIMITZ 480 EC NEMATICIDE

DISTIGUISHING NAME:	NIMITZ 480 EC NEMATICIDE
FORMULATION TYPE:	Emulsifiable Concentrate (EC)
ACTIVE CONSITUENT CONCENTRATION:	Fluensulfone (480 g/L)

PHYSICAL AND CHEMICAL PROPERTIES OF THE FORMULATED PRODUCT

APPEARANCE:	Clear amber liquid with specific odour
ACTIVE CONSTITUENT CONCENTRATION:	Fluensulfone (480 g/L)
PH OF A 1% AQUEOUS DILUTION:	5.2
RELATIVE DENSITY:	1.1978 g/cm3
SURFACE TENSION:	49.3 nM/m undiluted @ 19.5 °C
EXPLOSIVE PROPERTIES:	Not explosive
FLAMMABILITY:	Not flammable
CORROSIVE HAZARD:	Not corrosive to HDPE containers
PERSISTANT FOAM:	38 mL (after 1 min)
FLASH POINT:	101.5°C
OXIDISING PROPERTIES:	No oxidising properties
PRODUCT STABILITY:	The product should remain within specifications for at least 2 years under normal conditions in HDPE packaging.

2.1 Conclusion

The APVMA is satisfied that the chemistry and manufacture data requirements necessary for the registration of Nimitz *480 EC Nematicide* is supported and approval of its active constituent, fluensulfone, have been met.

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

A comprehensive toxicology and public health dataset was submitted for registration of the active constituent fluensulfone and associated product in the United States of America, Canada and Australia as part of a Global Joint Review. The toxicology assessment of fluensulfone was conducted jointly by scientists from the United States (US EPA), Canada (PMRA), and Australia (OCS, Office of Chemical Safety). The US EPA and PMRA were the primary reviewers with the OCS the secondary reviewers.

Fluensulfone is a new chemical class of nematicide whose mechanism of action is still under investigation. The product, Nimitz 480EC Nematicide an emulsifiable concentrate formulation containing 480 g/L fluensulfone, is a commercial use nematicide and is to be applied to bare soil pre-planting of seedlings and immature plants, including cucurbits and fruiting vegetables. The product will be available in high density polyethylene (HDPE) containers of 500 mL to 1000 L and will be applied at a label rate of 4–8 L/ha as a coarse spray using conventional broadcast spray application equipment or by ground application through band application or drip irrigation methods. The maximum proposed application rate is a single application of 3.84 kg a.i. per hectare.

Fluensulfone was found to be of low acute oral, acute dermal and acute inhalational toxicity in rats. A slight skin irritant in rabbits but not an eye irritant and a skin sensitiser in guinea pigs (Guinea Pig Maximisation Test, GPMT).

The systemic toxicity of fluensulfone in dietary studies consisted primarily of decreased body weight and body weight gain, and changes in haematology parameters. This systemic toxicity profile was observed in short-term, sub chronic and chronic toxicity studies in rats, mice and dogs, with the available data indicating that rats and dogs were more sensitive than mice. No treatment related effects were observed upon short term dermal administration of fluensulfone up to 400 mg/kg bw/day in rats. In a 90–day inhalational study in rats (nose only), effects were seen at the lowest concentration tested of 40 mg/m^3 (decreased weight gain, increased prothrombin time, decreased thymus weight and histopathology in the epiglottis).

In a dietary carcinogenicity study in mice, an increase was seen in the incidence of alveolar/bronchiolar adenomas and alveolar/bronchiolar adenomas and carcinomas combined in female mice. The increased tumour incidence in female mice was investigated in Mode of Action studies, but the available data were insufficient to rule out the human relevance of what may be a species (mouse) specific mechanism. Importantly, there was no increase in the incidence of tumours in male mice, or male and female rats in a 2– year dietary study.

Fluensulfone was a neurotoxicant producing neurobehavioural changes following administration of a bolus (i.e. gavage) dose, but such findings were not seen for dietary administration.

Fluensulfone was not an *in vivo* genotoxicant, a reproductive or teratogenic toxicant, or an immunotoxicant, and studies on metabolites provided no data that indicates that the observed level of these metabolites and their limited toxicity profile presents a toxicological concern.

The product Nimitz 480EC Nematicide was found to be of low acute oral, dermal and inhalational toxicity in rats, a moderate skin and eye irritant in rabbits, and a skin sensitiser in guinea pigs (GPMT). Additionally, NIMITZ 480EC Nematicide is considered to be an aspiration hazard based on the formulated products toxicological profile.

Based on an assessment of the toxicology, it was considered that there should be no adverse effects on human health from the use of Nimitz 480EC Nematicide when used in accordance with the label directions.

3.2 Evaluation of toxicology

The toxicology assessment of fluensulfone was conducted as part of a Global Joint Review (GJR) by scientists from the United States Environmental Protection Agency (US EPA), Health Canada Pest Management Regulatory Agency (PMRA) and the Office of Chemical Safety (OCS) within the Department of Health and Ageing. Since the assessment report relies significantly on international assessment collaboration between the agency partners, the OCS has adopted the no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) approach with scientific justification for the adoption of these NOAEL/LOAEL positions.

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

Chemical class

Fluensulfone is a new chemical class of nematicide. The effects of fluensulfone are generally slow in onset and include cessation of feeding, weak effects on motility, and developmental arrest through egg retention. Eggs laid on treated substrate show concentration dependent inhibition of development. The severity of effects is dependent on the dose applied and the duration of exposure.

Toxicokinetics and metabolism

The kinetic parameters for males and female rats following oral administration of fluensulfone were generally similar for the butene radiolabel, while for the thiazole label male rats demonstrated a slightly higher absorption based on AUC values.

Fluensulfone administered orally at nominal doses of either 5 mg/kg bw or 500 mg/kg bw was rapidly absorbed. The recovery of radioactivity was 91.3–97.3% of the applied dose for all groups of rats.

Following single oral administration of fluensulfone (thiazole- and butene-^{14}C) at either a low (5 mg/kg bw) or high (500 mg/kg bw) nominal dose to male and female rats, residues in organs and tissues were generally similar in both sexes for each of the three sacrifice intervals (Cmax, DT_{50} and DT_{90}). For both labels and both dose levels, the gastrointestinal tract, liver and kidney were among the tissues containing the highest radioactivity levels at Cmax for both sexes. Other tissues with high levels of radioactivity at Cmax (as a percentage of the administered dose) included the pancreas (in males administered the low dose of the thiazole label, in females administered the high dose of the thiazole label, and in both sexes administered the low dose of the butene label), the lung (in females administered the high dose of the thiazole label and in both sexes administered the low dose of the butene label), and the thyroid gland (in both sexes administered the high dose of the thiazole label). At DT_{90}, the levels of radioactivity remaining in the tissues accounted for ≤ 3% of the administered dose.

Fluensulfone administered orally to rats at nominal doses of either 5 mg/kg bw or 500 mg/kg bw is rapidly metabolised. The disposition and excretion of radiolabel were generally similar between males and females. There was no indication that the metabolic elimination processes were saturated by the 100–fold increase in dose level, as levels of radiolabel in urine, cage wash, faeces, carcass, and GI tract were similar between the low and high dose groups.

Following single dose administration, urine was the major route of excretion for both radiolabel positions and the only source of metabolites at ≥5% of the administered radiolabel for both radiolabel positions. The cage wash contained relatively high levels of radiolabeled metabolites and analysis showed that those metabolites in cage wash and urine were similar. Low amounts of thiazole sulfonic acid were found in faeces, but no other faecal metabolites were ≥5% of the administered dose.

Un-metabolised fluensulfone was not detected as a significant residue in either urine or faeces. The parent compound probably reacts with glutathione to displace butene sulfinic acid, the major urinary metabolite. This sulfinic acid is unstable to oxidation and is converted to butene sulfonic acid. The glutathione adduct of the thiazole ring is cleaved to the cysteine conjugate that ultimately is acetylated to the mercapturate as a major urinary product. The glutathione adduct is also cleaved to thiazole thiol (not detected) that is either oxidised to thiazole sulfonic acid or conjugated with glucuronic acid to give thiazole glucuronides (MW327-I and MW327-II). The two thiazole glucuronides are probably α- and ß-isomers at anomeric C-1 of the glucuronic acid moiety. The recovery of $^{14}CO_2$ indicates that a portion of both radiolabels is extensively degraded.

Comparison to residues from rats treated with a single oral dose from another study showed similar residues in tissues, urine and faeces in rats administered repeated doses in this study.

The dermal absorption of fluensulfone formulated as emulsifiable concentrate was low, with an estimated human *in vivo* dermal absorption of 1.18% for the concentrate and 43.42% for the aqueous suspension.

Acute toxicity

Fluensulfone was found to be of low acute toxicity via the oral (LD_{50} 671 mg/kg bw), dermal (LD_{50} >2000 mg/kg bw) and inhalational (4–hr LC_{50} >5.1 mg/L) routes in rats. It was a slight skin irritant in rabbits, but not an eye irritant in the same species. Fluensulfone was a skin sensitiser in guinea pigs.

Nimitz 480 EC Nematicide has low acute oral (LD_{50} >2000 mg/kg bw), dermal (LD_{50} >2000 mg/kg bw) and inhalational (4–hr LC_{50} >6.0 mg/L) toxicity in rats, is a moderate skin and eye irritant in rabbits and a skin sensitiser in guinea pigs. Nimitz 480 EC Nematicide is considered to be an aspiration hazard.

Systemic toxicity

In short term/sub-chronic and long term oral studies fluensulfone is generally of moderate to high toxicity. Dogs and rats were more sensitive than mice to fluensulfone mediated toxicity, particularly for liver and thyroid related effects (increased TSH levels) in the dog. The major systemic effects in addition to general toxicity (decreased body weight and body weight gain) included haematological changes (all species) and clinical chemistry (all species). These were not indicative of severe organ dysfunction (e.g. the observed haematology changes were not associated with decreased bone marrow production of blood cells). In long term oral toxicity studies, major systemic effects included an increased incidence of bronchiolisation of the alveoli (mice), interstitial inflammation in the lungs (rats) and alterations in haematological parameters (with no associated effect on bone marrow) and organ weights (male dogs only).

No treatment related effects were observed upon short term dermal administration of fluensulfone up to 400 mg/kg bw/day in rats. In a sub-chronic 90–day inhalational study in rats (nose only), the major systemic effects were haematological (with no associated effect on bone marrow) and organ weight changes, along with histopathological changes to the respiratory tract.

Genotoxicity and carcinogenicity

The available data indicates that fluensulfone was not mutagenic or genotoxic with and without metabolic activation *in vitro*. Additionally, fluensulfone was not genotoxic *in vivo*.

No carcinogenic potential was seen following dietary administration of fluensulfone in male mice (18–month study) and male and female rats (2–year study). In female mice (dietary 18–month study) an increase in the incidence of alveolar/bronchiolar adenomas and combined alveolar/bronchiolar adenomas and carcinomas was seen in mice (females only).

In relation to the adenoma findings in female mice it is noted that:

- Although the incidence of adenomas in females was outside the historical control range at 200 and 1200 ppm (28% and 18% respectively) and statistically significant by the Fisher exact test a dose response relationship was not evident.
- The onset of adenomas in female mice at 200 ppm (which produced the greatest incidence) was only slightly lower than that seen for the controls and 30 ppm female mice (78 weeks compared to 79 and 80 weeks respectively).

- While the onset of adenomas in female mice at 1200 ppm was reduced when compared to controls this was largely due to the early onset of 3/9 adenomas at week 56, 66 and 70.

In relation to the carcinoma findings in female mice it is noted that:

- Although the onset of carcinomas in females at 1200 ppm was reduced (69 weeks) compared to controls (79 weeks), due to 2/4 carcinoma findings at week 50 and 66, the incidence was within the historical control range.

In relation to the combined adenoma and carcinoma findings in mice it is noted that:

- A clear dose response relationship in the incidence of adenomas and carcinomas combined was not observed in female mice at 200 and 1200 ppm, though it is acknowledged that statistical significance was seen by the Peto trend test.
- The incidence of adenomas and carcinomas combined in female mice was not statistically significant by the Fisher exact test.

It is also noted that fluensulfone was not an *in vivo* genotoxicant.

Thus, overall, it is considered that fluensulfone exhibits a weak carcinogenic potential in female mice at 200 ppm and greater for adenomas and 1200 ppm for combined adenoma and carcinoma data. This carcinogenic potential is considered to be weak as: (1) no evidence of a dose response in females at the mid and high dose although statistical significance was attained in the high dose (Peto Trend Test), however not statistically significant using Fisher's Exact Test (one-sided and pairwise); and (2) combined adenomas and carcinomas in males at the high dose was comparable to the control group.

Additional mechanistic studies were provided to assist in the interpretation of the observed lung tumours in female mice, and on the available data a MOA was proposed for the development of these tumours, which involved extensive metabolism of fluensulfone by the mouse lung (predominantly by the mouse-specific enzyme Cyp2f2) leading to the production of reactive metabolites, increased proliferation of Clara cells resulting in alveolar/bronchiolar hyperplasia, and subsequent progression to adenomas and carcinomas. It was also proposed that since metabolic activation by fluensulfone is not likely in humans as such, the increased Clara cell proliferation, alveolar/bronchiolar hyperplasia and adenoma are unlikely to occur in humans.

The evidence to support the proposed MoA is currently insufficient due to uncertainties, inconsistencies and gaps in the currently available data. These include: (1) the inconsistent reporting of hyperplasia versus bronchiolisation; (ii) the inadequate demonstration of the specificity of the Cyp2f2 in the postulated MoA; (3) the lack of information supporting dose-response relationships; (iv) the lack of evidence for a temporal association of the key events; and (v) the inconsistencies in the evidence that indicate that fluensulfone and other chemicals operate via a similar MoA for the development of lung tumours in mice. It is important to note that there was no increase in the incidence of tumours in male mice, or male and female rats in a 2–year dietary study.

Reproductive and developmental toxicity

Fluensulfone was not a reproductive toxicant in rats in a dietary 2–generation study. In both rat and rabbit (oral gavage) developmental toxicity studies while reduced foetal body weight was observed, it was seen at doses levels that were maternotoxic and considered a secondary non-specific consequence. Thus, fluensulfone was not a developmental toxicant in rats and rabbits.

Neurotoxicity

Neurobehavioural signs of toxicity were seen in an acute neurotoxicity study in male and female rats following administration of a bolus (i.e. gavage) dose. In contrast no treatment related neurobehavioural signs, effect on functional observational battery (FOB) parameters or neuropathological changes were seen in rats in a dietary subchronic dietary study at doses greater than those producing neurobehavioral signs in the acute neurotoxicity study. It is considered that while the available data demonstrates a neurotoxic potential in rats, this is only seen at high doses when fluensulfone is administered as a gavage bolus dose.

Immunotoxicity

Fluensulfone was not immunotoxic to mice. No evidence of immunotoxicity was seen in the 28–day dietary studies in mice and rats which included immunotoxicity endpoints.

Toxicity of metabolites

Acute oral toxicity and genotoxicity studies on fluensulfone metabolites thiazole sulfonic acid, methylsulfone and butane sulfonic acid were indicative of low acute oral toxicity and were not *in vitro* or *in vivo* mutagens and/or genotoxins and, thus, unlikely to be toxicologically significant when considered in the context of the fluensulfone hazard profile.

3.3 Public health standards

Poisons sheduling

On 14 April 2014, the chemicals delegate to the Secretary of the Department of Health and Ageing made a delegate only decision on fluensulfone. The Secretary's delegate recommended that fluensulfone be included in Schedule 6 of the Standard for the Uniform Scheduling of Medicines and Poisons with no cut-off, along with an implementation date of 1st June 2014.

NOAEL/Acceptable daily intake

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

The critical effect of fluensulfone identified in chronic toxicity studies across all three species (mouse, rat and dog) is decreases in body weight and body weight gain, and effect on haematology parameters. Dogs and rats appeared to be the more sensitive species for fluensulfone than mice, and the toxicological database for fluensulfone included long-term oral or carcinogenicity studies in the mouse, rat and dog, and was considered complete. The most sensitive NOAEL to establish an ADI is 1.5 mg/kg bw/day in female dogs in a 52–week oral study based on decreased body weight and body weight gain. A default 100–fold safety factor, 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.

Consequently, an ADI value of 0.015 mg/kg bw/d is established based on a NOAEL of 1.5 mg/kg bw/d for decreased body weight and body weight gain in female beagle dogs in a 52–week oral study, using a default 100–fold safety factor. The ADI value was supported by a similar NOAEL of 1.7 mg/kg bw/d in female rats in a 2–year dietary study based on reductions in body weight and body weight gain.

Acute reference dose

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 1 meal or during 1 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 fluensulfone 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:

a) 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.

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

For fluensulfone, the critical adverse finding for establishing an ARfD was the observance of an increase in post-natal pup loss between days 0 and 4 in the F1 and F2 offspring in the dietary 2–generation study in rats. The offspring NOAEL for this finding is 250 ppm (16.2 mg/kg bw/day in males and 23.0 mg/kg bw/day in females). The end point of post-natal loss was considered to be relevant to an acute exposure scenario and has been used for the establishment of the ARfD which covers other acute toxicological endpoints of concern.

Consequently, the ARfD for fluensulfone was established at 0.15 mg/kg bw (rounding down) from a dietary 2–generation reproduction study, based on a NOAEL of 16.2 mg/kg bw in female offspring to take account of post natal loss, at 169.1 mg/kg bw in females and applying a default 100–fold safety factor to account for potential interspecies and intraspecies variation.

3.4 Conclusion

The APVMA is satisfied that the proposed use of Nimitz 480 EC Nematicide, containing the active constituent fluensulfone, is not likely to be harmful to human beings if used according to the proposed label instructions.

4 RESIDUES ASSESSMENT

4.1 Introduction

Nimitz 480 EC Nematicide contains the new active constituent fluensulfone (Figure 1) and is proposed for use on tomatoes, capsicums, chilli, eggplant and cucurbits in Queensland only. Nimitz will be applied to bare soil pre-planting of seedlings or immature plants. As part of the residues assessment for fluensulfone, plant and animal metabolism studies, supervised residue trials and trade aspects were considered.

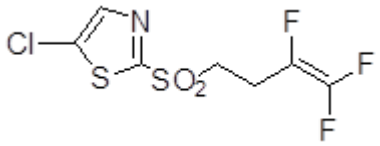


Figure 1: Fluensulfone

4.2 Metabolism

Plants

The metabolism of fluensulfone has been investigated in tomato, potato and lettuce using compound radio-labelled in either the thiazole ring or butene side chain. A confined rotational crop study on radish, lettuce and wheat has also been presented.

The major residues in the plant metabolism studies were thiazole sulfonic acid (TSA) and butene sulfonic acid (BSA). In target crops, BSA ranged from 0.071–1.24 mg/kg (43.6–68.1% TRR, butane label) and TSA ranged from 0.17–4.75 mg/kg (66.6–85.3% TRR, thiazole label). Trace amounts of parent were detected in the potato and lettuce study, however in the potato study this could not be confirmed by TLC. Trace amounts of parent were detected in some samples from the confined rotational crop study, but mainly at the shorter plant back interval (PBI). The major residues in the confined rotational study were TSA and BSA, with TSA detected in all rotational crop matrices at all PBIs. BSA was not detected after the longest PBI (360/390 days). The metabolism of fluensulfone in plants is summarised below in Figure 2.

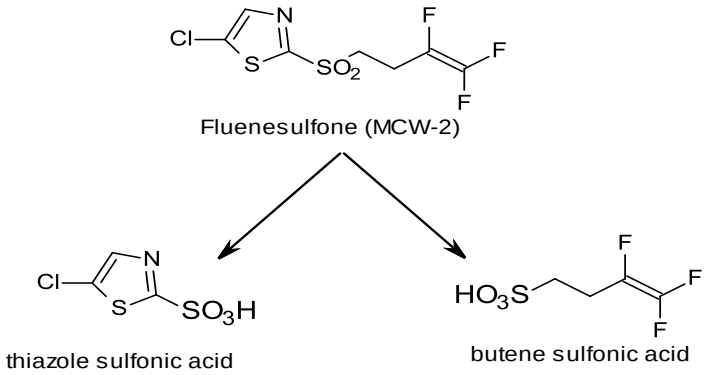


Figure 2: Proposed metabolic pathway of fluensulfone in plants

Livestock

The metabolism of fluensulfone has been investigated in lactating goats and laying hens using compound radio-labelled in either the thiazole ring or butene side chain. Parent fluensulfone was only detected in fat in the poultry metabolism study (up to 0.041 mg/kg, 54.7% TRR in sub-cutaneous fat, thiazole label). However, based on the plant metabolism studies and residue trials there is unlikely to be any parent compound in any animal feed commodities.

The only metabolite observed in tissues, milk or eggs in the goat and poultry metabolism studies was thiazole sulfonic acid in hen liver (0.016 mg/kg, 2.7% TRR). The majority of the residue was incorporated into natural products.

4.3 Analytical methods

Plant material

In the Australian residue trials provided in support of the application residues of fluensulfone, TSA, BSA and a methyl sulfone metabolite were extracted with acetonitrile/water. Extracts were filtered and analysed for parent and the methyl sulfone metabolite by liquid chromatography with detection by tandem mass spectrometry (APCI or electrospray ionisation in positive mode). For analysis of BSA and TSA, a solid phase extraction clean up step was used in some studies prior to analysis by liquid chromatography with detection by tandem mass spectrometry (electrospray ionisation in negative mode).

The LOQ for each of fluensulfone and the metabolites was 0.01 mg/kg as individual analytes. Recoveries of fluensulfone and its metabolites from fortified control samples of fruiting vegetables using these methods were within acceptable limits. Average method recoveries in Australian trials ranged from 79–98% for fluensulfone, 86–102% for BSA and 87–101% for TSA.

Animal commodities

A method for analysis of fluensulfone and its metabolites in commodities of animal origin (liver, kidney, meat, eggs, milk and fat) has been provided. Residues were extracted with acetonitrile / water (or just acetonitrile for analysis of BSA and TSA from eggs and milk, water was then added to the supernatant after centrifuging).

For BSA and TSA the supernatant from the extract was cleaned up by solid phase extraction prior to analysis by HPLC with detection by tandem mass spectrometry (electrospray ionisation in negative mode).

For fluensulfone and the methyl sulfone metabolite, sodium chloride was added to the extract. The organic phase was dried over magnesium sulphate and partitioned with hexane. The aqueous phase was evaporated and re-dissolved in acetonitrile water prior to analysis by liquid chromatography with detection by tandem mass spectrometry (APCI in positive mode).

The LOQ was determined to be 0.01 mg/kg for each analyte and matrix. Recoveries of fluensulfone and metabolites from fortified control samples of animal matrices were within acceptable limits. Average method

recoveries across all matrices ranged from 71–109% for fluensulfone, 76–110% for BSA and 71–108% for TSA.

Stability of pesticide residues in stored analytical samples

Studies on the storage stability of fluensulfone and its metabolites have been performed on a range of commodities including tomato, pepper, cucumber, melon, tomato paste and tomato purée.

Residues of fluensulfone, BSA and TSA were found to be stable during frozen storage for at least 15 months in tomatoes and for at least 16 months in peppers at -20°C.

Residues of fluensulfone, BSA, TSA and methyl sulfone were found to be stable in tomato paste and puree for at least 6 months of frozen storage (< -12°C).

4.4 Residue definition

As BSA and TSA were the major components of the residues in plants both should be considered for the residue definition. As adding BSA and TSA together will approximate to a conversion to parent equivalents, a simple definition will be proposed as the sum of parent + BSA + TSA. This definition is suitable for both risk assessment and enforcement.

The recommended residue definition is the sum of fluensulfone, 3,4,4-trifluorobut-3-ene-1-sulfonic acid (BSA) and 5-chloro-thiazole-2-sulfonic acid (TSA).

4.5 Residue trials

Australian residue trials on tomato (6), capsicum (3), rockmelon (6), cucumber (3) and zucchini (3) are supported by North American trials on tomato, pepper, rockmelon, cucumber and squash and EU trials on melons. The Australian and North American trials also include information on tomato processing.

Tomatoes

Highest residues of fluensulfone (Parent + TSA + BSA) in tomatoes in the Australian and North American trials after a pre-planting application at approximately 4 kg ai/ha were <0.03 (2), 0.03, 0.04 (6), 0.05 (3), 0.06, 0.07, 0.085, 0.09, 0.105, 0.11, 0.15, 0.16, 0.18 (2), 0.19, 0.20, 0.21, 0.33, 0.35, 0.36, 0.37 and 0.47 (2) mg/kg.

Peppers

Highest residues of fluensulfone (Parent + TSA + BSA) in capsicums in the Australian trials and in Bell and non-Bell peppers in the North American trials after a pre-planting application at approximately 4 kg ai/ha were <0.03 (2), 0.03, 0.04, 0.055, 0.09, 0.10, 0.11 (2), 0.20 (2), 0.23, 0.28, 0.30, 0.34, 0.35, 0.41, 0.44 and 0.53 mg/kg.

Melons

Highest residues of fluensulfone (Parent + TSA + BSA) in rock melon whole fruit from the Australian trials, cantaloupe whole fruit from the North American trials and melon whole fruit from the European trials after a pre-planting application at approximately 4 kg ai/ha were <0.03 (3), 0.03 (6), 0.04, 0.055, 0.065, 0.07 (2), 0.08, 0.10, 0.14, 0.20, 0.22, 0.23, 0.36, 0.37, 0.52 and 0.62 mg/kg.

Cucumber

Highest residues of fluensulfone (Parent + TSA + BSA) in cucumber fruit in the Australian and North American trials after a pre-planting application at approximately 4 kg ai/ha were <0.03 (2), 0.03 (2), 0.04, 0.06, 0.08, 0.09, 0.10, 0.12, 0.15, 0.30, 0.54, 0.70 and 0.84 mg/kg.

Zucchini/squash

Highest residues of fluensulfone (Parent + TSA + BSA) in zucchini/summer squash fruit in the Australian and North American trials after a pre-planting application at approximately 4 kg ai/ha were 0.04 (2), 0.05, 0.06, 0.065, 0.11, 0.12, 0.17, 0.20, 0.48, 0.51, 0.69 and 0.91 mg/kg.

MRL determination

Based on a highest residue of 0.47 mg/kg in tomatoes and 0.53 mg/kg in peppers from an MRL of 1 mg/kg is recommended for fluensulfone on VO 0050 Fruiting vegetables, other than Cucurbits.

Based on highest residues of 0.62 mg/kg in melons, 0.84 mg/kg in cucumber and 0.91 mg/kg in summer squash (zucchini) an MRL of 2 mg/kg is recommended for fluensulfone on VC 0045 Fruiting vegetables, Cucurbits.

Rotational crops

The confined rotational crop study indicates that detectable residues may occur in rotational crops when fluensulfone is used as directed. The following rotational crop restrictions have been proposed:

Growers applying Nimitz must observe the following plantback (recropping) intervals:

CROP	PLANTBACK INTERVAL
Cucurbits, Capsicums, Chilli, Eggplant, Tomatoes (not for processing)	No restriction
Cover crops (green manure crops) not used for stock food or grazing	No restriction
Lettuce	180 days
Leafy vegetables (except lettuce), vegetable brassicas, Onions, Bananas	365 days
Sugarcane, All other crops	2 years

Additionally registration will be restricted to Queensland only and no significant animal feeds will be grown in rotation with the primary crops.

No plant back restrictions are required for crops that are already on the label as the primary use, or for cover crops that will only be used as green manure and will not be grazed. The MRLs for the primary crops are conservative and should cover any additional residues arising from from rotational situations.

For lettuce, a 180 day plant back interval has been proposed. In an interim field rotational crop study, combined residues of parent + TSA + BSA in lettuce grown after a 180 day plant back interval were 0.03 and 0.05 mg/kg. However, given the higher residues observed in radish leaves after a 365 day plant back interval (see below) conservative MRLs of 1 mg/kg would be considered more appropriate for lettuce and by extrapolation other leafy vegetables for which a 365 day plant back interval is recommended (a 180 day plant back interval remains appropriate for lettuce).

A 365 day plant back interval has been proposed for vegetable brassicas, onions and bananas. In the field rotational study, the highest residue of parent + TSA + BSA in vegetable crops grown after a 365 day plant back interval was 0.85 mg/kg in radish leaves. MRLs of 1 mg/kg would be appropriate for fluensulfone on VB 0040 Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead brassicas and VA 0385 Onion, Bulb to cover potential residues in these crops when they are grown in rotation on soil previously treated with fluensulfone.

Given the potential for residues to occur in rotational crops depending on the plant back interval observed, an MRL of 1 mg/kg will be established for fluensulfone on ‘All other foods’.

4.6 Processing studies

The processing component of the Australian tomato trials indicated that total fluensulfone residues are expected to concentrate in dry tomato pomace (average processing factor = 6.5×). However, as the draft label indicates that fluensulfone should not be used on tomatoes destined for processing, a Table 4 entry for tomato pomace will not be established at this time.

4.7 Animal commodity MRLs

Animal transfer studies for fluensulfone and the TSA and BSA metabolites are not currently available. With the exception of tomato pomace, none of the other commodities associated with fruiting vegetables are significant feeds for cattle or poultry. The applicant has proposed a registration on tomatoes that will not be used for processing. However, waste tomatoes may be fed to livestock or fresh tomatoes damaged by rain may be sent for processing. Based on a HR in tomatoes of 0.47 mg/kg and a moisture content of 90%, if waste tomatoes were fed at 5% of the diet the exposure would be 0.24 ppm (based on the recommended residue definition) which is considerably less than the 10.5 ppm feeding level of parent in the goat metabolism study which did not cause any residues in tissues or milk (noting that the metabolism of parent in animals is thought to proceed through formation of TSA and BSA). The risk of residues in animal commodities through the feeding of waste tomato products is considered to be low.

The applicant has also proposed that registration will initially be restricted to Queensland only and that there will be restrictions on the crops that can be grown in rotation with the primary crops on the label to prevent residues of the fluensulfone metabolites occurring in significant animal feeds. As there is not expected to be any exposure of livestock to residues of fluensulfone or its metabolites based on the restricted registration, animal commodity MRLs for fluensulfone will be established at the combined LOQ of the analytical methods provided by the applicant.

It is noted that the applicant has committed to undertake a dairy cattle animal transfer study involving dosing with both the TSA and BSA metabolites to allow future use in areas where the primary crops on the label may be grown in rotation with crops that can be used as animal feeds.

4.8 Estimated dietary intake

The chronic dietary exposure to fluensulfone 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 fluensulfone is equivalent to approximately 55% of the ADI.

It is concluded that the chronic dietary exposure of fluensulfone is acceptable.

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

The NESTIs for fluensulfone are acceptable at <30% of the acute reference dose for children (2–6 years) and the general population (2+ years).

4.9 Bioaccumulation potential

The Log P_{ow} for fluensulfone is 1.96. The Log P_{ow} for thiazole sulfonic acid is -3.5, while butene sulfonic acid has a Log P_{ow} of -2.5. The potential for bioaccumulation of fluensulfone and its metabolites is considered to be low.

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

4.10 Spray drift

For broadcast applications the draft label indicates that the product should not be applied with spray droplets smaller than a coarse spray droplet size category according to nozzle manufacturer specifications that refer to the ASAE S572 Standard or the BCPC Guideline.

In the goat metabolism study, dosing with fluensulfone at 10.5 ppm in the diet did not result in detectable residues of parent or relevant metabolites in tissues or milk. Assuming pasture consists of 1500 kg DM/ha the acceptable drift is 15.75 g ai/ha to give a maximum feeding level of 10.5 ppm. Consideration of exposure to parent is considered suitably conservative at this time.

Considering the average deposition over a 300 metre field downwind from the application area, and using the standard scenario for ground application (high boom, coarse droplets) the average deposition from 1– 300 metres downwind from the application area is 0.0038× the field rate or 14.6 g ai/ha. This level of deposition from spray drift is not expected to give significant residues in animal commodities.

A no-spray zone is not required for ground broadcast application of fluensulfone for protection of international trade.

4.11 Recommendations

The following amendments are proposed to the MRL Standard:

Table 1

COMPOUND		FOOD	MRL (mg/kg)
ADD:			
FLUENSULFONE			
		All other foods	1
MO	0105	Edible offal (Mammalian)	*0.03
PE	0112	Eggs	*0.03
VC	0045	Fruiting vegetables, Cucurbits	2
VO	0050	Fruiting vegetables, other than Cucurbits	1
MM	0095	Meat [mammalian]	*0.03
ML	0106	Milks	*0.03
PO	0111	Poultry, Edible offal of	*0.03
PM	0110	Poultry meat	*0.03

Table 3

COMPOUND	RESIDUE
ADD:	
FLUENSULFONE	Sum of fluensulfone, 3,4,4-trifluorobut-3-ene-1-sulfonic acid (M-3627) and 5-chloro-thiazole-2-sulfonic acid (M-3625).

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

Harvest: Not required when used as directed.

Grazing: Do not graze treated crop, or feed treated crop commodities to livestock.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Fruiting vegetables, including cucurbits are not considered major export commodities[3] and the overall risk to export trade is considered to be low.

There is potential for residues of fluensulfone to occur in rotational crops, however the initial registration will be restricted to Queensland only, which together with the proposed plant back intervals appropriately mitigate the risk of residues of fluensulfone metabolites occurring in rotational crops that are major export commodities or can be used as animal feeds. For sugarcane, a 2 year plant back interval and also the processing of sugar reduces the risk.

MRLs for fluensulfone have been established in the USA at 0.5 mg/kg for Vegetables, cucurbits, group 9 and also at 0.5 mg/kg for Vegetables, fruiting, group 8–10. No animal commodity MRLs for fluensulfone have been established.

Codex MRLs have not been established, but fluensulfone has been considered by the 2014 JMPR and MRLs of 0.3 mg/kg proposed for Fruiting vegetables, cucurbits and also at 0.3 mg/kg for Fruiting vegetables, other than cucurbits except sweet corn and mushroom. The 2014 JMPR proposed an MRL of 2.1 mg/kg for peppers chilli, dried and 0.5 mg/kg for both tomato paste and tomato, dried.

[3] Part 5B of the Vet Requirements Series and Ag Requirements Series, Overseas Trade Aspects of Residues in Food Commodities, August 2004.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Summary

The product will be used for commercial use situations, and 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 (or connecting containers during chemigation and cleaning up spills and equipment). The main route of exposure to the product/spray will be dermal and inhalation, with limited occupational exposure possible during mixing/loading and application.

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide was used to estimate exposure. Exposure to the product by the stated application methods was at an acceptable level when a single layer of clothing (cotton overalls or equivalent clothing) and elbow-length chemical resistant gloves are worn.

Based on the risk assessment, First Aid Instruction, Safety Directions and a Warning statement have been recommended for the product label.

6.2 Health hazards

Fluensulfone (CAS: 318290-98-1) is not listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2014). Based on the available toxicology information, classification of the active constituent fluensulfone as a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following human health risk phrases is warranted:

Xn; R22	Harmful if swallowed
Xi; R43	May cause sensitisation by skin contact
Xn; R40	Limited evidence of a carcinogenic effect

The following cut-off concentrations apply for fluensulfone:

Conc. $\geq$ 25 %	Xn; R40 (Carc. Cat. 3), R22, R43
1 % $\leq$ Conc. < 25 %	Xn; R40 (Carc. Cat. 3), R43

Based on the product toxicology information and/or concentration of fluensulfone and other ingredients in the product, Nimitz 480EC Nematicide containing fluensulfone at 480 g/L is classified as a hazardous substance in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following human health risk phrase warranted:

Xi; R36	Irritating to eyes
Xi; R38	Irritating to skin
Xi; R43	May cause sensitisation by skin contact
Xn; R65	Harmful: may cause lung damage if swallowed
Xn; R40	Limited evidence of a carcinogenic effect

6.3 Formulation, packaging, transport, storage and retailing

The active constituent fluensulfone will be manufactured overseas. Nimitz 480 EC will be marketed in high density polyethylene (HDPE) containers of 500 mL to 1000 L for commercial use.

6.4 Use pattern

The product Nimitz 480 EC Nematicide is an emulsifiable concentrate containing 480 g/L of fluensulfone. It is intended for commercial use situations, and is to be applied to bare soil pre-planting of seedlings and immature plants, including cucurbits and fruiting vegetables.

Nimitz 480EC Nematicide will be marketed in high density polyethylene (HDPE) containers of 500 mL to 1000 L and will be applied at a label rate of 4–8 L/ha as a coarse spray using conventional broadcast spray application equipment or by ground application through band application or drip irrigation methods. The maximum proposed application rate is a single application of 3.84 kg a.i. per hectare.

6.5 Exposure during use

Nimitz 480EC Nematicide is to be used commercially. The product is intended to be applied by drip irrigation, banded groundboom spray or broadcast spray applicators.

Application of Nimitz 480 EC Nematicide by groundboom methods may lead to unintended bystander exposure *via* chemical spray drift. This may be in the form of a single random exposure or repeat exposures of residents who reside adjacent to areas being treated with the product. Parameters for assessing bystander exposure have not been finalised by APVMA, though good agricultural practices are expected to be followed.

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 (or connecting containers during chemigation and

cleaning up spills and equipment). The main route of exposure to the product/spray will be dermal and inhalation, with limited occupational exposure possible during mixing/loading and application.

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide was used to estimate exposure. The toxic endpoint of concern and identified NOAEL is derived from repeat dose study in animals, and in this instance a margin of exposure (MOE) of 100 for dermal exposure and 1000 for inhalational exposure are considered to be acceptable. The MOE takes into account both interspecies extrapolation, intraspecies variability and the seriousness of the critical health effect of concern. The estimated MOEs for dermal and inhalational exposures are both considered acceptable when the user is wearing a single layer of clothing (cotton overalls or equivalent) and chemical resistant gloves.

6.6 Exposure during re-entry

As the product is expected to be as a pre-planting treatment, and that the product will also be incorporated into the soil at a 15–20 cm depth, post-application exposure for agricultural crops is expected to be minimal and not require a quantitative post-application exposure determination.

6.7 Recommendations for safe use

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

6.8 Conclusion

The registration of Nimitz 480 EC Nematicide containing fluensulfone at 480 g/L, a nematicide to be applied to bare soil pre-planting of seedlings and immature plants, including cucurbits and fruiting vegetables for commercial use, is supported.

Nimitz 480 EC Nematicide 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

The product is formulated as an emulsifiable concentrate (EC) and contains 480 g ac/L and it is to be used as a nematicide prior to transplanting cucurbits and fruiting vegetable crops. As it is a new product containing a new active constituent an environmental risk assessment has been conducted based on the proposed use pattern.

7.2 Environmental fate

Behaviour in soil

The metabolism of fluensulfone was investigated in 7 soils (6 EU; aerobic and 1 US; aerobic/anaerobic) and the pathway was shown to be the same in all soils. Fluensulfone was degraded to three major radioactive fractions. High mineralisation was observed, reaching 29% to 56% AR for the butene label and reaching 11%–30% AR for the thiazole label by the end of the study (120 day incubation period). The bound radioactivity increased to a maximum 11%–15% and 29%–49% for the thiazole and butene-label treated samples, respectively. The microbial degradation of the thiazole label showed two metabolites thiazole sulfonic acid (TSA) and methyl sulfone (MS), whereas the butene label showed only butene sulfonic acid (BSA) as a metabolite. These metabolites were detected in all soils. TSA and BSA were the major metabolites reaching maximum amounts of 77% and 31% AR, respectively. The MS metabolite was a minor metabolite and exceeded 5% for only in two intervals in one soil, with its maximum level of 8% of applied radioactivity.

Laboratory DT50 values for fluensulfone were calculated to be 7–17 days (n=6). BSA (M-3627) and MS (M- 3626) metabolites were shown to rapidly further degrade in the laboratory with DT50 values of 18–26 (n = 5) and 23–35 days (n = 3), respectively. However, TSA showed very slow degradation with calculated DT50 values of 174–471 days (n = 3) (at pF2).

A terrestrial field dissipation study of fluensulfone was conducted in bare soils representative of the proposed use areas at four sites in the U.S. and Canada. Fluensulfone dissipated relatively rapidly with a mean and a median DT50 of approximately 11 days. Fluensulfone formed three metabolites in soil from all four sites, namely, methyl sulfone (MS), thiazole sulfonic acid (TSA) and butene sulfonic acid (BSA). TSA and BSA were most predominant whereas MS was produced in minor amounts. The single first-order half-life of TSA averaged 83 days in two of the four soils where accurate kinetic endpoints could be calculated. BSA dissipated more rapidly in soil than TSA. The highest TSA and BSA residues were found in the surface soil at all four sites although low concentrations were found at lower soil depths. TSA, in particular, was found at the lowest portion of the soil profile (75–90 cm) at three of the four sites. Dissipation of fluensulfone in this field study was consistent with the conceptual model developed from the relevant laboratory physico-chemical and environmental fate studies.

After about 25 days (approximate time to reach the DT50) of aerobic incubation using a US soil, the samples were further incubated under anaerobic conditions. Fluensulfone as well as its major metabolites (BSA and TSA) were shown to be stable in soil under anaerobic flooding conditions, (however, a significant

degradation was observed in the water sediment study under anaerobic conditions with a DT50 of 26–28 days). Fluensulfone photodegraded moderately in soil when exposed to artificial sunlight, with calculated half-lives of 10–16 days (corresponding to 22–36 days natural sunlight at latitude 38ºN). The observed degradation of fluensulfone in dark control samples was slower (DT50 of 123 days).

The adsorption and desorption of fluensulfone and its soil metabolites was studied in at least 5 soils using the batch equilibrium method. Adsorption Koc mean values for fluensulfone (KFOC = 187; 1/n = 1.041), MS (KFOC = 23.4; 1/n = 1.08), TSA (Koc = 7.8) and BSA (Koc = 6.1) were determined.

On the basis of its vapour pressure (2.25 x 10-4 mm Hg at 25 °C), fluensulfone would be classified as non-volatile to slightly volatile according to EPA pesticide volatility classifications. However, fluensulfone is applied to bare soil and then immediately incorporated (either mechanically or by drip irrigation) to a depth of 15–20 cm (6–8 inches). In studies investigating the rate and route of degradation in soil, which were conducted under continuous aeration, no significant volatilisation of fluensulfone was observed. Therefore, significant volatilisation of fluensulfone from soil is not expected.

Fate and behaviour in aquatic systems

Fluensulfone is stable to hydrolysis. However, fluensulfone was rapidly photodegraded in water by light with a half-life of about 1 day midsummer sunlight at latitude 30 to 50°N. Fluensulfone was photodegraded to a very high number of minor degradates, which were further degraded to very polar fractions containing multiple components, probably acids of small molecular weight or polymers.

In aquatic systems, the degradation of fluensulfone was quite significant in both water as well as sediment under both aerobic and anaerobic conditions. Under both aerobic and anaerobic conditions in both river and lake systems treated with thiazole- and butene-labelled fluensulfone, mean non-extractable radioactivity reached a maximum of 29–33% of applied radioactivity. Under both aerobic and anaerobic conditions in both river and lake systems, mean mineralisation to 14CO2 reached 13–19% of applied radioactivity for the butene labelled fluensulfone and 3–6.2% for the thiazole labelled fluensulfone. DT50 values of 38–45 days in water and 49–50 days in the whole system were calculated under aerobic conditions. DT50 values of 26–28 days in the whole system were calculated under anaerobic conditions. Fluensulfone is cleaved to butene sulfinic acid and presumably to a thiazole adduct. Butene sulfinic acid is unstable to oxidation, but under anaerobic conditions it becomes a major metabolite. Under aerobic conditions butene sulfinic acid is readily oxidized to butene sulfonic acid. The thiazole adduct is mainly oxidised to thiazole sulfonic acid under aerobic conditions or methylated to thiazole methyl sulfone under anaerobic conditions. Another significant route of degradation is the dechlorination of fluensulfone to form deschloro-fluensulfone, which further degraded via a route similar to that of fluensulfone.

7.3 Environmental effects

Avian

Acute oral toxicity studies with the technical active substance have been conducted on northern bobwhite quail and canary. The study on northern bobwhite demonstrates fluensulfone to be only slightly toxic to this species (LD50 = 1506 mg ac/kg bw). An endpoint could not be determined from the study conducted with

canary due to regurgitation at all dose levels. In terms of short-term dietary toxicity, studies conducted on northern bobwhite quail and mallard demonstrate fluensulfone to be practically non-toxic when administered in the diet (LC50 for both species > 5620 ppm diet). The reproductive studies on these species resulted in NOECs of 1000 ppm and 500 ppm diet for northern bobwhite quail and mallard, respectively.

Effects on aquatic organisms

Fish

An acute toxicity studies with the technical active substance have been conducted on four species of fish: rainbow trout, common carp, sheepshead minnow, bluegill and fathead. The endpoints from these studies were all comparable, ranging from 13 to 41 mg ac/L and demonstrate fluensulfone to be only slightly toxic to fish. Testing on 3 of the species showed the formulation to be more toxic, with LC50 ranging from 5.56 mg/L (2.38 mg ac/L) for bluegill to 13 mg/L (5.51 mg ac/L) for sheepshead minnow.

As bluegill was the most sensitive species to the technical active substance, the three major surface water metabolites (thiazole sulfonic acid (TSA), butene sulfonic (BSA) acid and methyl sulfone (MS)) were tested on this species. The results of these studies demonstrated the former two metabolites to be practically non-toxic to fish (LC50 > 121 and > 122 mg/L, respectively), while methyl sulfone was demonstrated to be slightly toxic to fish (LC50 = 35 mg/L).

A 33 day early life stage study on fathead minnow was also conducted with fluensulfone technical, which resulted in an overall NOEC of 0.63 mg ac/L.

Given the LogPow = 1.96 and it is less than 3, the substance is not expected to bioaccumulate hence bioaccumulation studies were not conducted.

Aquatic invertebrates

Acute toxicity study with the technical active substance conducted on Daphnia magna resulted in an EC50 of 29 mg ac/L, demonstrating fluensulfone to be slightly toxic to this species. Acute toxicity studies on the Eastern oyster and the saltwater mysid showed fluensulfone to be of moderate toxicity to these species (EC50 = 6.4 mg ac/L and LC50 = 1.0 mg ac/L, respectively).

As the saltwater mysid was the most sensitive species to the technical active substance, the three major surface water metabolites (TSA, BSA and MS), were tested on this species. The results of these studies demonstrated TSA and BSA to be practically non-toxic to mysid (LC50 > 123 and > 114 mg/L, respectively), while MS was demonstrated to be slightly toxic to mysid (LC50 = 18 mg/L).

A 21 day chronic toxicity study is available on Daphnia magna, which resulted in a NOEC of 0.39 mg ac/L. In addition, a chronic toxicity study on the saltwater mysid (38 day study) gave overall NOECs of 0.37 mg ac/L.

The toxicity of the formulation was further studied as follows. For Daphnia magna, the 48-hour EC50 value was determined to be 0.83 mg product (0.35 mg ac)/L. For the saltwater mysids the 96-hour LC50 value was determined to be 0.53 mg product (0.22 mg ac)/L. For the Eastern oysters, based on inhibition of shell deposition, the 96-hour EC50 value was 0.23 mg product (0.11 mg ac)/L.

According to the US EPA classification, the formulations would be classified as highly toxic to aquatic invertebrate, on an acute exposure basis.

Algae and aquatic plants

The technical active substance was tested on five different species of algae. Studies on Anabaena flos-aquae (freshwater blue-green algae), Navicula pelliculosa (freshwater diatom) and Skeletonema costatum (marine diatom) resulted in broadly comparable results, and demonstrated fluensulfone to be of slight to moderate toxicity to these species (72 and 96 hour EC50 values were in the range 2.0–23 mg/L).

The freshwater green algal species (Pseudokirchneriella subcapitata, and Scenedesmus subspicatus) were approximately one hundred times more sensitive than the other species tested, demonstrating fluensulfone to be very highly toxic to fresh water green algae. The 72 h ErC50 was around 40 µg ac/L.

As P. subcapitata was the most sensitive of all algal species tested with the technical active substance, this species was tested with four surface water metabolites of fluensulfone (TSA, BSA, MS and deschloro-fluensulfone). The results of these studies demonstrated the 72 and 96 hours EC50 values for TSA, BSA and deschloro-fluensulfone to be greater than the highest tested concentration (> 4.4 or > 4.5 mg/L), and the ErC50 for MS to be 4.5 and 4.6 mg/L, after 72 and 96 hours, respectively, demonstrating the metabolites to be no greater than moderately toxic to green algae.

A Lemna toxicity study is available, which gave an overall 7day EC50 of 1.91 mg ac/L (based on biomass yield), demonstrating moderate toxicity of technical fluensulfone.

The toxicity of the formulation was studied using the freshwater green alga, P. subcapitata. The 72 and 96– hour ErC50 values were 44.1 and 44.9 µg ac/L, respectively.

Sediment dwelling organisms

A toxicity study on Chironomous tentans (10 day acute study) is available, which gave an overall NOEC of 4.0 mg/kg sediment.

Non-target arthropods

An acute oral and contact honeybee toxicity study was conducted with the technical active substance and the formulation, which demonstrates fluensulfone to be practically non-toxic to bees.

Tier I glass-plate studies on A. rhopalosiphi resulted in an LR50 of 16.2 g ac/ha and no adverse effects on reproduction were found at a rate of up to 9.6 g ac/ha. A similar study on T. pyri gave an LR50 of 1000 g ac/ha and demonstrated less than 50% effects on reproduction at this rate. In addition, the chronic study on the ground beetle showed it is the most sensitive species with a NOEC of 1.49 mg ac/kg soil dw.

Earthworms and soil arthropods

The chemical and its metabolites are slightly toxic to earthworms. Acute earthworm toxicity studies have been conducted with the technical active substance, its three major soil metabolites (TSA, BSA and MS) and the formulation. The LC50 for fluensulfone was determined to be 153 mg ac/kg soil dw and 136.7 mg

formulation/kg soil dw. The LC50 values for the metabolites were all greater than the maximum concentration tested, which was 300 mg/kg soil dw for TSA and BSA, and 50 mg/kg soil dw for MS.

A chronic earthworm toxicity study was conducted, which resulted in a NOEC of 10.5 mg ac/kg soil dw.

In addition, chronic toxicity studies were conducted on Folsomia candida (springtail) and Hypoaspis aculeifer (soil mite), which resulted in NOECs of 15.54 and 63.4 mg ac/kg soil dw, respectively.

Soil microbial activity

A standard study on the effects of the formulated product (MCW-2 480 EC) on the activity of soil microflora (nitrogen and carbon transformation test) is available. The test item showed no adverse effects (< 25% deviation from the control) on soil nitrogen transformation up to a concentration of 5.48 mg ac/kg soil dw and on carbon transformation up to a test concentration of 27.37 mg ac/kg soil dw, at the end of the tests, 98 and 28 days, respectively.

Terrestrial plants

In vegetative vigour tests, a pre-emergent application of the MCW-2 480 EC to the soil surface at a maximum label rate of 4000 g ac/ha resulted in no treatment related effects on any endpoint of eight of the ten terrestrial species tested 21 days after application. The lowest most reliable EC50 value was for cabbage (3190 g ac/ha, NOEC = 470 g ac/ha). In the seedling emergence and growth limit test only one out of the ten species tested showed effects of > 50%. This was Lolium perenne (ryegrass) which showed an 83% reduction in dry weight and a 70% reduction in height. However, in the Tier II rate response test no effects of >50% were observed in any of the ten species tested, which included L. perenne, up to the maximum tested rate of 4.0 kg ac/ha.

7.4 Risk assessment

A risk assessment was conducted for the active constituent and when necessary for metabolites, for birds, mammals, aquatic organisms and terrestrial non-target invertebrates likely to be exposed, as well as terrestrial plants and soil microbes.

The assessment showed an acceptable risk to birds and mammals.

The risk to aquatic organisms resulting from spray drift (ground application only), runoff and leaching into the groundwater was assessed. The risk from spray drift was considered to be acceptable with a downwind no spray zone of 50 m to neighbouring aquatic environments for a worst case scenario of broadcast application. However, for band application where, in practice, only half of the target field is treated, the no spray zone can be reduced to 20 m.

Use of the Department's screening model to determine risk from runoff shows that only for the worst case broadcast application (higher rate, lowest Koc, longest half-life) is the runoff risk likely to be unacceptable. Under the likely conditions fluensulfone is expected to be used (lower rate, banded application or drip irrigation, lower slopes and use of average Koc and half-lives) the runoff risk is often mitigable becoming

acceptable only at the bottom of the application range, with a slope ≤ 4% and in all cases if the treated area is covered in plastic. Therefore, an appropriate label warning is required to avoid runoff risk.

The assessment showed the risk to terrestrial non-target vegetation and to bees is acceptable without a downwind no spray zone.

Similarly, the risk to earthworms and soil microbes is acceptable. Risk assessment for soil dwelling arthropods showed an acceptable risk for band and chemigation application.

7.5 Conclusion

The APVMA is satisfied that the proposed use of NIMITZ 480 EC NEMATICIDE, containing 480 g/L fluensulfone, when used according to the product label instructions, would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed use pattern

Nimitz 480 EC Nematicide (the product) is intended for control of Root-knot nematode in the following transplanted crops: Cucurbits, Tomatoes (not for processing), Capsicum, Chilli, Eggplant and Okra. The product is intended to be used at a rate of 4–8L in Queensland only. Use of the low rate is recommended in less susceptible crops and/or under low Root-knot nematode pressure and use of the high rate is recommended in more susceptible crops and/or under moderate to high Root-know nematode pressure. Nimitz 480 EC Nematicide is to be applied a minimum of seven days before transplanting, Nimitz 480 EC Nematicide is to be applied no more than once per crop, and no more than 8 L/ha.

The product must be applied to moist soil either by broadcast spray, banded spray or via drip irrigation. All application of Nimitz 480 EC Nematicide require soil incorporation to a depth of 15–20cm, and followed with irrigation within 3–5 days of application.

8.2 Summary of evaluation of efficacy and crop safety

Data which was provided from a series of trials conducted in Australia were conducted to evaluate fluensulfone (NIMITZ) for the control of Root-knot nematode (RKN) (*Meloidogyne* spp.) in tomatoes, capsicums, cucurbits including rockmelon, watermelon, zucchini, squash and pumpkins. Application was made either by sub surface drip irrigation or by spraying a band to moist soil followed by rotary hoeing.

The data is supplemented by a major independent study undertaken in the USA and Canada in a range of vegetable crops including squash, cucumber, cantaloupe, bell pepper, potato, non-bell pepper and okra.

The aim of the studies was to evaluate the efficacy of NIMITZ for controlling nematodes in a range of vegetables as well as data on crop phytotoxicity and yield.

NIMITZ was applied at a range of rates including 0.96, 1.92, 2.88, 3.84, and 7.68 kg ai/ha and compared to untreated control plants and plants treated with industry standards. Application of NIMITZ at the rate of 7.68 kg ai/ha is double the label rate and is included in the trial program for crop safety data.

Application was made prior to sowing of the range of vegetable crops, with one single application made a minimum of five to seven days before transplanting. The target nematode in the trials was Root Knot Nematode (*Meloidogyne* spp.) [RKN].

Performance of NIMITZ was measured by gall rating with galling rated according to the Zeck rating scale (Zeck, W.M. (1971) – A rating scheme for field evaluation of root-knot nematode infestations. Pflanzenschutz Nachrichten, Bayer, 24: 141–144.), nematode counts and gall counts per plant.

All treatments were replicated and a full statistical analysis was undertaken in all studies. Trials were laid out as Randomised Complete Blocks with up to 6 replicates. Plot size was generally very good with size being 5 to 10 metres by 1 row of the vegetable crop.

Overall NIMITZ provided equivalent levels of control as measured by galls/plant and Zeck ratings to the commercial industry standards. Root damage as measured by gall/plant and Zeck ratings was in most trials significantly reduced when compared to the untreated control.

Very good crop safety was observed in the target vegetable crops, with plants treated with NIMITZ often showing an increase in plant vigour, plant height and root development and yield when compared to the untreated control.

Symptoms of plant phytotoxicity were observed in a few trials at the highest rate of 7.68 kg ai/ha (double the proposed label rate) at early rating dates, however the plants grew out of this damage over time and there was no detrimental effect on quality and yields at harvest. In most studies where yield data was obtained the application of NIMITZ provided yields at least equal to or greater than the untreated control and equal to the commercial industry standards.

Forty eight USA and Canadian studies conducted by external bodies show the efficacy and crop safety of NIMITZ as a nematicide when applied pre-planting to a range of vegetables. The findings from these studies support the Australian studies in terms of NIMITZ efficacy and crop safety.

Efficacy was demonstrated for NIMITZ against nematodes through observations of reductions in root galling per plant and or a reduction in Zeck ratings over the growing season relative to untreated control plots. In the case of root knot nematodes, NIMITZ applications resulted in numerous instances of statistically significant levels of reductions in galling caused by *Meloidogyne* sp.

The data from the Australian and overseas trials on a range of vegetable crops show the efficacy of NIMITZ 480EC in controlling root knot nematodes in vegetables. Application of NIMITZ 480EC was generally equivalent to the industry standards in the series of Australian trials. Further the data shows that if Fluensulfone is applied in accordance with the proposed label it has very good crop safety to the vegetables in the trial programs.

8.3 General conclusions

The label claims and instructions proposed in the Claims for use statement and the Directions for use and other label instructions are consistent with the results of the trials and other information presented.

The APVMA is satisfied, based on the trial data submitted and the advice provided, that the product NIMITZ 480 EC NEMATICIDE is expected to be safe and efficacious when used as proposed.

9 LABELLING REQUIREMENTS

POISON

KEEP OUT OF REACH OF CHILDREN

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

NIMITZ 480 EC NEMATICIDE

ACTIVE CONSTITUENT: 480 g/L FLUENSULFONE

SOLVENT: 428 g/L HYDROCARBON LIQUID

For control of nematodes in selected vegetable crops, as per the Directions for Use

www.adama.com CONTENTS: 500 mL - 1000 L

DIRECTIONS FOR USE
Restraints
Use only before transplanting a crop, and not in conjunction with direct seeded crops.
DO NOT apply NIMITZ® to crops grown outside Queensland.
DO NOT plant any crops not specified on this label into treated land for 2 years after the last application unless otherwise stated in the rotational crop restriction table on this label.
DO NOT apply more than one application per crop, and no more than 8 L/ha per year.
DO NOT apply to tomato crops that are to be used for processing.
DO NOT irrigate to the point of runoff within 72 hours of application.
DO NOT apply if heavy rain has been forecast within 72 hours.

MANDATORY NO-SPRAY ZONES
Ground Application Only
Aquatic Environment
DO NOT apply if there are aquatic or wetland areas including aquacultural ponds within 50 metres downwind from the application area from broadcast application, or 20 metres from banded application.

CROP	PEST	STATE	RATE/ha	CRITICAL COMMENTS
Transplanted crops: **Cucurbits** **Tomatoes** (not for processing) **Capsicum** **Chilli** **Eggplant** **Okra**	Root-knot nematode	Qld only	4–8 L	Apply a minimum of seven (7) days before transplanting. **Rate selection** Use the low rate in less susceptible crops and/or under low Root-knot nematode pressure where soil counts or paddock history indicate the population density is close to the economic threshold and minor yield loss is expected. Use the high rate in more susceptible crops and/or under moderate to high Root-knot nematode pressure where soil counts or paddock history indicate that the population density is above the economic threshold and significant yield loss is expected. Apply a maximum of 8 L per hectare per year.

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

WITHHOLDING PERIOD

DO NOT GRAZE TREATED CROP, OR FEED TREATED CROP COMMODITIES TO LIVESTOCK

CROPS FOR EXPORT

Before using NIMITZ on crops destined for export it is essential to consult your exporter or ADAMA to ensure that an appropriate MRL is in place in the importing country.

ROTATIONAL CROP RESTRICTIONS

Growers applying NIMITZ must observe the following plant-back (re-cropping) intervals:

Table 1. Rotational crop restrictions after an application of NIMITZ

Crop	Plant-back interval
Cucurbits, Tomatoes (not for processing),Capsicum, Chilli, Eggplant, Okra	No restriction
Cover crops (green manure crops) not used for stock food or grazing	No restriction
Lettuce	180 days
Leafy vegetables (except lettuce), Vegetable brassicas, Onions, Bananas	365 days
Sugarcane, All other crops	2 years

GENERAL INSTRUCTIONS

Only use NIMITZ in accordance with applicable label directions.

NIMITZ can be used to control Root-knot nematode (*Meloidogyne* spp.) in transplanted crops specified in the Directions for Use table. A successful treatment with NIMITZ will control Root-knot nematodes present in the treated soil zone at the time of application. An application of NIMITZ does not provide season long control nor guarantee crops free from root galling at harvest.

NIMITZ will not eradicate nematode populations and does not control bacteria, insects, viruses, weeds or pathogens which attack plants in treated areas. Other management options will be required for control of these pests.

Do not make applications of NIMITZ when the soil temperature is below 16°C. Key species of Root-knot nematodes that are not active below 16°C, will not absorb NIMITZ at these temperatures and will not be controlled.

RESISTANCE MANAGEMENT

Although resistance in nematode populations has not been proven, repeated exclusive use of any product may lead to a reduction in control. Rotation with a nematicide with a different mode of action is recommended.

NIMITZ should be used as part of an Integrated Pest Management (IPM) program to control nematodes. IPM programs using cultural practices, farm hygiene, planting of resistant varieties to reduce infestations caused by nematodes, monitoring or other detection methods, proper pest identification and rotation of nematicides with different modes of action will help prevent economic pest damage.

APPLICATION

Always apply NIMITZ a minimum of seven (7) days before transplanting. Make soil applications only in accordance with directions and conditions of use described in this label. Do not apply by flood irrigation or overhead irrigation systems. Treated areas can be covered with plastic or left uncovered according to planting practices.

Uniform application and incorporation to moist well prepared soils is essential. If soils are not free of clods, debris and plant residues thoroughly incorporate them into the soil to prevent interference with application or control.

NIMITZ must always be applied to moist soil either by broadcast spray, banded spray or via drip irrigation. All applications of NIMITZ require soil incorporation to a depth of 15–20 cm, and followed with irrigation within 3–5 days of application as per the application specific requirements below.

Avoid application during rain or when heavy rain is forecast within the next 72 hours. Excessive moisture immediately after application may cause NIMITZ to move too quickly past the targeted zone.

Soil moisture management can have an influence on soil incorporation and efficacy of NIMITZ. For broadcast and banded spray applications, ensure soil moisture is adequate for uniform mechanical incorporation. If applied by drip irrigation, make sure the initial soil moisture is sufficient to allow the product to move uniformly from shoulder to shoulder and throughout the bed to a depth of 15–20 cm as it is being irrigated.

Refer to Table 3 for irrigation requirements following an application of NIMITZ.

Broadcast application

Conventional boom spray equipment can be used to apply Nimitz as a broadcast spray application to the soil surface. Use a minimum spray volume of 200 L/ha to obtain a uniform application. Flat fan nozzles are recommended. Select an appropriate nozzle and pressure to produce a coarse droplet spectrum according to nozzle manufacturer specifications that refer to the ASAE S572 Standard or the BCPC Guideline. Do not apply NIMITZ from a spray boom at a height greater than 50 cm above the soil surface to minimise spray drift into off-target areas.

After application, NIMITZ must be mechanically incorporated into the soil using a rotary implement to a depth of 15–20 cm as soon as possible i.e. the same day of application. Ensure soil moisture is adequate for uniform incorporation.

After application and prior to transplanting, irrigate according to the guidelines in Table 3 for broadcast application. Following transplanting, resume normal irrigation practices.

Banded spray application

Using banded spray equipment allows a targeted application of NIMITZ to only the beds where seedlings are to be transplanted, reducing the overall volume of product required. Rates should be applied based on the percentage of the area treated. Use Table 2 to determine the amount of product required based on bed width, length and use rate.

Use a minimum spray volume of 200 L/ha to obtain a uniform application. Even fan nozzles are recommended, where available, to ensure an even dose over the treated band. Select an appropriate nozzle and pressure to produce a coarse droplet spectrum according to nozzle manufacturer specifications that refer to the ASAE S572 Standard or the BCPC Guideline. Do not apply NIMITZ from a spray boom at a height greater than 50 cm above the soil surface to minimise spray drift into off-target areas.

Table 2. Rate calculation for banded spray application or drip irrigation application

Bed width*	NIMITZ rate		
	4 L/ha	6 L/ha	8 L/ha
	Amount of product per 100 m of row		
60 cm	24 mL	36 mL	48 mL
75 cm	30 mL	45 mL	60 mL
100 cm	40 mL	60 mL	80 mL
125 cm	50 mL	75 mL	100 mL

* The guidelines in this table are based on treating the entire bed width

For example:

If planting on bed widths of 60 cm and there is a total of 2000 m of row (20 x 100 m) to be treated using the high rate of 8 L/ha, the required amount of NIMITZ is: 48 mL x 20 = 960 mL

After application, NIMITZ must be mechanically incorporated into the soil using a rotary implement to a depth of 15-20 cm as soon as possible i.e. the same day of application. Ensure soil moisture is adequate for uniform mechanical incorporation.

After incorporation and prior to transplanting, irrigate according to the guidelines in Table 3 for banded application. Following transplanting, resume normal irrigation practices.

Drip irrigation application

NIMITZ can be applied through low volume surface or subsurface drip irrigation systems.

Do not apply NIMITZ through any other type of irrigation system.

Due to the availability of various drip application systems, ADAMA recommend that users of NIMITZ follow the guidelines of the manufacturer of their chosen equipment which must meet the requirements below:

1. The injection pump is a critical component of the irrigation system and must be properly installed and maintained to ensure an even flow of the chemical solution to every emitter.

2. The system must contain a functional check valve, vacuum relief valve and low pressure drain appropriately located on the irrigation pipeline to prevent water source contamination from backflow.

3. The pesticide injection pipeline must contain a functional, automatic, quick-closing check valve to prevent the flow of fluid back toward the injection pump.

4. The pesticide injection pipeline must be configured to prevent fluid from being withdrawn from the supply tank when the irrigation system is either automatically or manually shut down.

5. The irrigation line or water pump must include a functional pressure switch which will stop the water pump motor when the water pressure decreases to the point where pesticide distribution is adversely affected.

6. Systems must use a metering pump designed and constructed of material that is compatible with NIMITZ.

It is recommended that NIMITZ is applied by a person knowledgeable and experienced with the operation of the system as described above.

NIMITZ should be applied with sufficient water and duration to uniformly wet the entire bed width and root zone (15 to 20 cm deep).

Calculate the amount of product required according to width of the planting bed and row length as per the guidelines in Table 2. Assume the wetting front is the same as the bed width for determining the rate to apply, or preferably use the actual wet area.

The amount of water needed for an application will depend upon the initial level of soil moisture, the soil type, % organic matter and condition, as well as the placement of the drip irrigation line, emitter spacing etc. The following steps are recommended when applying NIMITZ through drip irrigation systems:

1. Pre-irrigate the area in a manner to wet the planting bed from shoulder to shoulder. During the pre-irrigation process, the entire irrigation system including emitters must be checked to ensure the system is operating normally before injecting NIMITZ.

2. Introduce NIMITZ into the irrigation system to distribute the product evenly in the area being treated.

3. Flush the irrigation system with water to ensure no NIMITZ remains in the system. Do not over apply system rinse water and wash the NIMITZ from the root zone.

After application and prior to transplanting, irrigate according to the guidelines in Table 3 for broadcast application. Following transplanting, resume normal irrigation practices.

TRANSPLANTING GUIDELINES

Seedlings must have two true leaves at the time of transplanting to minimise any potential post-transplant stress that may result in slower crop establishment.

SOIL MOISTURE MANAGEMENT

The objectives of soil moisture management when applying NIMITZ are:

1. Ensure NIMITZ reaches the target treated soil zone (a depth of 15 to 20 cm) ensuring contact with Root-knot nematodes

2. Irrigate to ensure NIMITZ movement away from the target root zone prior to transplanting.

The amount of water required will vary with soil type and existing soil moisture.

Excessive moisture (as rainfall and/or irrigation) immediately after application may cause the product to move past the target soil zone of 15–20 cm.

Table 3 below denotes the amount of water required to achieve these objectives.

Table 3. Post-application irrigation requirements prior to transplanting

Application type	Irrigation type	Soil Clay %	Irrigation schedule (mm)		
			3 DAA	5 DAA	7 DAA
Broadcast or Banded Spray Application	Overhead sprinkler	<5%	8	-	-
		≥5%	8	8	-
	Surface drip*	<5%	6	-	-
		>5%	4	4	-
	Buried drip**	<5%	11	-	-
		>5%	11	5	-
Drip Application	Surface drip*	<5%	5	-	-
		>5%	5	5	-
	Buried drip**	<5%	7	-	-
		5%-15%	11	11	-
		>15%	11	5	5

DAA = Days after application.
^ These guidelines are calculated to deliver an effective irrigation to a depth 20 cm.
- No further irrigation required.
* Transplanting up to 10 cm from irrigation line.
** Transplanting up to 20 cm from irrigation line.

COMPATIBILITY

Do not apply NIMITZ in a mixture with other products or fertilisers unless the physical compatibility of the mixture has been confirmed. Contact ADAMA for further information regarding product compatibility with NIMITZ.

MIXING, LOADING AND HANDLING INSTRUCTIONS

Broadcast and banded spray applications

Fill the spray tank to 70% full, add the required amount of NIMITZ to the water in the spray tank and commence agitation while adding the balance of the water to the spray tank. Continue agitation during application.

If NIMITZ is to be mixed with other products or fertilisers, refer to the above section on compatibility prior to use.

NOTE: Thoroughly clean application equipment prior to use and before using for application of other pesticides.

Drip irrigation application

Ensure application equipment is clean after use and before using for application of other pesticides. NIMITZ should not be applied in conjunction with a drip line cleaning product as performance may be reduced.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product or used containers.

SAFETY DIRECTIONS

Harmful, may cause lung damage if swallowed. Will irritate the eyes and skin. Repeated exposure may cause allergic disorders. 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), elbow length chemical resistant gloves and face shield or goggles. Wash hands after use. After each day's use wash gloves and contaminated clothing.

STORAGE AND DISPOSAL

Store in the closed, original container in a cool, well-ventilated area. Do not store for prolonged periods in direct sunlight.

Triple or preferably pressure rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point.

If not recycling, break, crush or puncture and deliver empty packaging for appropriate disposal 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.

FIRST AID

If poisoning occurs contact a doctor or Poisons Information Centre. Phone 131 126.

MATERIAL SAFETY DATA SHEET

If additional hazard information is required refer to the Material Safety Data Sheet. A material safety data sheet for NIMITZ is available from ADAMA on request. Call Customer Service on (02) 9431 7800.

CONDITIONS OF SALE: The use of NIMITZ® 480 EC NEMATICIDE being beyond the control of the manufacturer, no warranty expressed or implied is given by ADAMA Australia Pty. Ltd., regarding its suitability, fitness or efficiency for any purposes for which it is used by the buyer, whether in accordance with the Directions for Use or not. ADAMA Australia Pty. Ltd. accepts no responsibility for any consequence whatsoever resulting from the use of this product.

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Barcode

Date of Manufacture

ABBREVIATIONS

AC/ac	Active constituent
ACN	Acetonitrile
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
APCI	Atmospheric pressure chemical ionisation
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
AUC	Area under the curve
BCPC	British Crop Production Council
BSA	Butane sulfonic acid
bw	bodyweight
^{o}C	Degrees Centigrade
^{14}C	Carbon 14
Cd-1	Cluster of differentiation 1
cm	Centimetre
CMAU	Case Management and Administration Unit
Cmax	Concentration maximum
d	Day
DAT	Days After Treatment
DM	Dry matter
DT_{50}	Time taken for 50% of the concentration to dissipate
DT_{90}	Time taken for 90% of the concentration to dissipate
dw	Dry weight
EA	Environment Australia
E_bC_{50}	Concentration at which the biomass of 50% of the test population is impacted

EC	Emulsion concentrate
EC_{50}	Concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
EGI	Export Grazing Interval
EI	Export Interval
EL_{50}	Effective Loading rate lethal to 50% of the test population
ER_{50}	Effect (sub-lethal) rate that cause 50% of maximal defined response in test population
E_rC_{50}	Concentration at which the rate of growth of 50% of the test population is impacted
ESI	Export slaughter index
EUP	End Use Product
F_0	Original parent generation
F_1	First generation
F_2	Second generation
FOB	Functional observational battery
g	Gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GI	Gastro Intestinal
GJR	Global Joint Review
GLP	Good Laboratory Practice
GPMT	Guinea Pig Maximisation Test
h	hour
ha	hectare
HCl	Hydrogen chloride
Hct	Heamatocrit
HDPE	High Density Polyethylene
Hg	Haemoglobin

HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HR	Highest residue
HR-P	Calculated highest residue – processed commodity
HSIS	Hazardous Substance Information System
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
JMPR	Joint FAO/WHO Meetings on Pesticide Residues
kg	kilogram
K_{oc}/K_{foc}	Organic carbon adsorption coefficient
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
LOAEL	Lowest Observable Adverse Effect Level
$logK_{ow}$	Octanol-Water Partition Coefficient
LR_{50}	Lethal rate required to kill half (50%) of the test population
m	metre
mg	milligram
min	minute
mL	millilitre

MoA	Mode of Action
MOE	Margin of Exposure
MRL	Maximum Residue Limit
MS	Methyl sulfone
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
nm	nanometres
NOAEL	No Observable Adverse Effect Level
NOHSC	National Occupational Health and Safety Commission
NOEC	No Observable Effect Concentration
OC	Organic Carbon
OCS	Office of Chemical Safety
OECD	Organisation for Economic Cooperation and Development
OM	Organic Matter
PBI	Plant back interval
PHED	Pesticide Handler Exposure Database
PMRA	Pest Management Regulatory Agency (Canada)
po	oral
P_{ow}	Octanol/water partition coefficient
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value

RBC	Red Blood Cell Count
RKN	Root-knot nematode
s	second
sc	subcutaneous
STMR	Supervised Trials Medium Residues
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SWA	Safe Work Australia
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
TLC	Thin layer chromatography
TRR	Total Radioactive Residue
TSA	Thiazole sulfonic acid
TSH	Thyroid-stimulating hormone
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
US EPA	U.S. Environmental Protection Agency
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 bioassays
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.