Public Release Summary
on

Evaluation of the new active

SPINETORAM

in the product

DELEGATE INSECTICIDE

Australian Pesticides and Veterinary Medicines Authority

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FOREWORD

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority 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 Aging, Office of Chemical Safety (OCS), Department of the Environment, Water, Heritage and the Arts (DEWHA), and State Departments of Primary Industry.

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 all products containing new active ingredients and for all proposed extensions of use for existing products.

The information and technical data required by the APVMA to assess the safety of new chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in the APVMA's Manual of Requirements and Guidelines - *The Manual of Requirements and Guidelines - MORAG for Agricultural and Veterinary Chemicals [Ag MORAG & Vet MORAG]*.

This Public Release Summary is intended as a brief overview of the assessment that has been completed by the APVMA and 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.

More detailed technical assessment reports on all aspects of the evaluation of this chemical can be obtained by completing the order form in the back of this publication and submitting with payment to the APVMA. Alternatively, the reports can be viewed at the APVMA Library, 18 Wormald Street, Symonston, ACT.

The APVMA welcomes comment on the usefulness of this publication and suggestions for further improvement. Comments should be submitted to the Pesticides Program Manager, Australian Pesticides and Veterinary Medicines Authority, PO Box 6182, Kingston ACT 2604.

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LIST OF ABBREVIATIONS AND ACRONYMS

ABBREVIATIONS

Time	
d	Day
h	Hour
Min	Minute
Mo	Month
Wk	Week
S	Second
Yr	Year

Weight	
bw	Body weight
g	Gram
kg	Kilogram
µg	Microgram
mg	Milligram
ng	Nanogram
wt	Weight

Length	
cm	Centimetre
M	Metre
µm	Micrometre
mm	Millimetre
Nm	Nanometre

Volume/Area	
ha	hectare
vmd	volume median diameter
µL	Microlitre
L	Litre
mL	Millilitre

Dosing	
id	Intradermal
im	Intramuscular
inh	Inhalation
ip	Intraperitoneal
iv	Intravenous
po	Oral
sc	Subcutaneous
mg/kg bw/d	mg/kg bodyweight/day

Concentration	
m	Molar
ppb	Parts per billion
ppm	Parts per million

Clinical chemistry, haematology, toxicology	
A/G	Albumin/globulin ratio
ALT	Alanine aminotransferase (SGPT)
AP	Alkaline phosphatase
AST	Aspartate aminotransferase (SGOT)
AUC	Area under curve
BUN	Blood urea nitrogen
ChE	Cholinesterase
CHO/HGPRT	Chinese hamster ovary/hypoxanthin-guanine-phosphoribosyl transferase (assay)
CPK	Creatine phosphatase (phosphokinase)
GGT	Gamma-glutamyl transferase
Hb	Haemoglobin
Hct	Haematocrit
LDH	Lactate dehydrogenase
LH	Luteinising hormone
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
NTE	Neurotoxic target esterase
PCV	Packed cell volume (Haematocrit)
PT	Prothrombin time
RBC	Red blood cell/erythrocyte
T_3	Triiodothyroxine
T_4	Thyroxine
TSH	Thyroid stimulating hormone (thyrotropin)
WBC	White blood cell/leucocyte
WBC-DC	White blood cells – differential count

Anatomy	
CNS	Central nervous system
GIT	Gastro-intestinal tract
in vitro	outside the living body and in an artificial environment

in vivo	inside the living body of a plant or animal

Chemistry

GC	Gas chromatography
GLC	Gas liquid chromatography
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
LC-MS/MS	Liquid chromatography, mass spectroscopy
MS	Mass spectrometry
RIA	Radioimmunoassay
TGAC	Technical grade active constituent
TLC	Thin layer chromatography

Terminology

ac	active constituent
ADI	Acceptable Daily Intake
ai	active ingredient
AOEL	Acceptable Operator Exposure Level
ARfD	Acute Reference Dose
bw	bodyweight
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
DT_{90}	Time taken for 90% of the concentration to dissipate
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
Fo	original parent generation
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
IPM	Integrated Pest Management
K_{oc}	Organic carbon partitioning coefficient
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
LOEL	Lowest Observed Effect Level
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
MRL	Maximum Residue Limit or Level
MSDS	Material Safety Data Sheet
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
NOEC/NOEL	No Observable Effect Concentration/Level
OP	Organophosphorus pesticide
OC	Organic Carbon
OM	Organic Matter
PPE	Personal Protective Equipment
Q-value	Quotient-value
SC	Suspension Concentrate
TRR	Total Radioactive Residues
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
WG	Water Dispersible Granule
WHP	Withholding Period

Organisations & publications

AGCS	Advisory Group on Chemical Safety

AHMAC	Australian Health Ministers Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
CAC	Codex Alimentarius Commission
DEW	Department of the Environment and Water Resources
ECETOC	European Chemical Industry Ecology and Toxicology Centre
FAO	Food and Agriculture Organisation of the UN
FAISD	First Aid Instructions & Safety Directions
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
JECFA	FAO/WHO Joint Expert Committee on Food Additives
JMPR	Joint Meeting on Pesticide Residues
NCI	National Cancer Institute
NDPSC	National Drugs and Poisons Scheduling Committee
NHMRC	National Health and Medical Research Council
NOHSC	National Occupational Health & Safety Commission
NTP	National Toxicology Program
OCS	Office of Chemical Safety
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
US EPA	United States Environmental Protection Agency
WHO	World Health Organisation

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of *DELEGATE* Insecticide (*DELEGATE*), which contains the new active constituent spinetoram. The product is proposed for use in pome and stone fruit.

The purpose of this summary is to inform the public of the proposed registration and invite comment on this proposal.

Responses to this Public Release Summary will be considered prior to registration of the product. They 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.

Copies of full technical evaluation reports on spinetoram, covering toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA on request (see order form on last page of this document). They can also be viewed at the APVMA library located at the APVMA offices, 18 Wormald St, Symonston, ACT 2609.

Written comments should be received by the APVMA by 1 September 2008. They should be addressed to:

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Applicant
Dow AgroSciences Australia Limited

Details of Product
It is proposed to register *DELEGATE INSECTICIDE (DELEGATE),* containing spinetoram at 250g/kg, as a water dispersible granule formulation.

Spinetoram is a new active constituent from the spinosyn group of insecticides. It is also known as a spinosoid which is a synthetically modified spinosyn. Spinosyns are naturally derived fermentation products for arthropod pest control, which are produced by the soil organism *Saccharopolyspora spinosa*, a novel bacterium of the order Actinomycetales. Spinetoram is prepared from a mixture of two natural spinosyns, spinosyns J and L, produced by *S. spinosa*. Spinosyns are nicotinic acetylcholine receptor agonists (allosteric) in Group 5A for Insecticides Resistance Management, which act through contact or ingestion and are particularly effective against lepidopteran pests.

DELEGATE is proposed for use in pome and stone fruit for the control of codling moth, lightbrown apple moth and oriental fruit moth.

Spinetoram formulations are relatively new to the world insecticide market. Registrations for *DELEGATE* have been granted in Canada and USA, and in New Zealand for use on pome fruit.

CHEMISTRY AND MANUFACTURE

Active Constituent

Spinetoram is a new active constituent. Spinetoram belongs to the spinosyn chemical class of insecticides and is derived through the fermentation of a naturally occurring organism (*Saccharopolyspora spinosa*) followed by chemical modifications.

Manufacturing Sites

The active constituent spinetoram is manufactured by ChemDesign Products, Inc., 2 Stanton St, Marinette, WI 54143, USA.

Chemical Characteristics of the Active Constituent

Common Name: Spinetoram

Major Component (J form – spinosyn J (ethyl-spinosyn J)):

IUPAC Name: (2*R*,3a*R*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-13-{[(2*S*,5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl]oxy}-9-ethyl-14-methyl-7,15-dioxo-2,3,3a,4,5,5a,5b,6,9,10,11,12,13,14,16a,16b-hexadecahydro-1*H*-as-indaceno[3,2-*d*] oxacyclododecin-2-yl 6-deoxy-3-*O*-ethyl-2,4-di-*O*-methyl-*α*-*L*-mannopyranoside

and

Minor Component (L form – spinosyn L (ethyl-spinosyn L)):

IUPAC Name: (2*S*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*S*)-13-{[(2*S*,5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl]oxy}-9-ethyl-4,14-dimethyl-7,15-dioxo-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-1*H*-as-indaceno[3,2-*d*] oxacyclododecin-2-yl 6-deoxy-3-*O*-ethyl-2,4-di-*O*-methyl-α-*L*-mannopyranoside

Major Component (J form):

CAS Name: (2*R*,3a*R*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-3-*O*-ethyl-2,4-di-*O*-methyl-α-L-mannopyranosyloxy)-13-[(2*R*,5*S*,6*R*)-5-(dimethylamino)tetrahydro-6-methylpyran-2-yloxy]-9-ethyl-2,3,3a,4,5,5a,5b,6,9,10,11,12,13,14,16a,16b-hexadecahydro-14-methyl-1*H*-*as*-indaceno[3,2-*d*]oxacyclododecine-7,15-dione

and

Minor Component (L form):

CAS Name: (2*R*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*S*)-2-(6-deoxy-3-*O*-ethyl-2,4-di-*O*-methyl-α-L-mannopyranosyloxy)-13-[(2*R*,5*S*,6*R*)-5-(dimethylamino)tetrahydro-6-methylpyran-2-yloxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-

	dimethyl-1*H-as*-indaceno[3,2-*d*]oxacyclododecine-7,15-dione
CAS Number:	*Major Component*: 187166-40-1; *Minor Component*: 187166-15-0
Manufacturer's Codes:	*Major Component*: XDE-175-J; *Minor Component*: XDE-175-L
Molecular Formula:	*Major Component*: $C_{42}H_{69}NO_{10}$; *Minor Component*: $C_{43}H_{69}NO_{10}$
Molecular Weight:	*Major Component*: 748.02 g/mol; *Minor Component*: 760.03 g/mol

Major Component– XDE-175-J

Minor Component – XDE-175-L

APVMA Active Constituent Standard for Spinetoram Active Constituent

Constituent	Specification	Level
Spinetoram	Spinetoram	Not less than 820 g/kg
Major Component (*J form*)	Major Component	Not less than 50 % Not more than 95 %
Minor Component (*L form*)	Minor Component	Not less than 5 % Not more than 50%

Physical and Chemical Properties of Pure Active Constituent and Technical Material

Colour	Off-white
Physical state	Solid
Odour	Musty
Melting point	XDE-175-J: 143.4 °C XDE-175-L: 70.8 °C
Boiling point	XDE-175-J: Decomposes before boiling at 297.8 °C XDE-175-L: Decomposes before boiling at 290.7 °C
Density @ 20 °C	1.1485 g/mL

Bulk density @ 22.8 ^{o}C	0.24 g/mL
Water Solubility @ 20 ^{o}C	XDE-175-J: Unbuffered: 10 mg/L pH 5: 423 mg/L pH 7: 11.3 mg/L pH 9: 8 mg/L pH 10: 6.27 mg/L XDE-175-L: Unbuffered: 31.9 mg/L pH 5: 1.63 mg/L pH 7: 46.7 mg/L pH 9: 1.98 mg/L pH 10: 0.706 mg/L
Solubility in Organic Solvents @ 20 ^{o}C	XDE-175 Technical (XDE-175-J:XDE-175-L=3:1) Methanol: > 250 g/L Acetone: > 250 g/L *n*-Octanol: 132 g/L Ethyl acetate: > 250 g/L 1,2-Dichloroethane: > 250 g/L Xylene: > 250 g/L Heptane: 61 g/L
Vapour Pressure @ 20 ^{o}C	XDE-175-J: 5.3 x 10^{-5} Pa XDE-175-L: 2.1 x 10^{-5} Pa
Dissociation Constant (pK_a)	XDE-175-J: 7.86 XDE-175-L: 7.59
Partition Co-efficient (1-octanol/water) @ 19 ^{o}C	XDE-175-J: pH 5: log P_{ow} = 2.44 pH 7: log P_{ow} = 4.09 pH 9: log P_{ow} = 4.22 XDE-175-L: pH 5: log P_{ow} = 2.94 pH 7: log P_{ow} = 4.49 pH 9: log P_{ow} = 4.82
UV/Vis absorption spectrum	XDE-175-J: Neutral: 245 nm; ε = 12200 $Lmol^{-1}cm^{-1}$ Basic (pH 12.6): 246 nm; ε = 11700 $Lmol^{-1}cm^{-1}$ Acidic (pH 1.04): 247 nm; ε = 12400 $Lmol^{-1}cm^{-1}$ XDE-175-L: Neutral: 243 nm; ε = 11100 $Lmol^{-1}cm^{-1}$ Basic (pH 12.6): 244 nm; ε = 11200 $Lmol^{-1}cm^{-1}$ Acidic (pH 1.04): 202 nm; ε = 9800 $Lmol^{-1}cm^{-1}$ & 245 nm; ε = 11400 $Lmol^{-1}cm^{-1}$
Vapour pressure at 20°C	XDE-175-J: 5.3 x 10^{-5} Pa XDE-175-L: 2.1 x 10^{-5} Pa

Formulated Product

Distinguishing name: **Delegate Insecticide**
Formulation type: Water dispersible granule
Active constituent concentration: Spinetoram 250 g/kg

Physical and Chemical Properties of the Product

Colour	Tan
Physical state @ 23.2 ^{o}C	Granules
Odour	Musty
pH @ 22.6 ^{o}C diluted (1% aqueous)	8.66
Bulk density @ 21.8 ^{o}C	0.50 g/mL
Oxidising/Reducing action	No temperature change was greater than 5 ^{o}C. The addition of ammonium phosphate solidified the mixture. No reactivity or colour change was observed for zinc or water. Also subjected to potassium permanganate: colour changed from opaque tan to opaque brown
Thermal explodability	A melting point endotherm @ 121 ^{o}C was observed. In addition, 2 endotherms were present beginning @ 209 & 261 ^{o}C along with a non-quantifiable exotherm at 336 ^{o}C
Impact explodability	Not impact sensitive

Recommendation
Based on a review of the chemistry and manufacturing details provided by the applicant, registration of Delegate Insecticide is supported, pending the approval of the active constituent, spinetoram.

TOXICOLOGICAL ASSESSMENT

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

Toxicokinetics and Metabolism

The absorption, distribution, metabolism and elimination of the two spinosyns that make up spinetoram (spinosyn J and spinosyn L) were determined separately.

In rats, orally administered spinosyn J and spinosyn L were rapidly absorbed from the gastrointestinal tract without any apparent lag time. The level of absorption was 70% and ≥ 70% for spinosyn J and spinosyn L respectively.

The plasma AUCs were approximately dose proportional; high dose AUCs were approximately 14-fold and 20-fold greater than low dose AUCs for spinosyn J and spinosyn L respectively.

In the case of spinosyn J, the radioactivity remaining in tissues and carcasses at 7 days after a single dose averaged 0.6% and 1.4% for rats dosed with 10 and 100 mg/kg, respectively; a similar amount (0.6%) remained in the tissues and carcasses of multiple dosed rats 7 days after a single dose. With spinosyn L, the residue radioactivity remaining in tissues and carcasses 7 days after dosing averaged 3.3% and 7.0% for rats dosed at 10 and 100 mg/kg, respectively; a similar amount (~3.1%) remained in the tissues and carcasses of multiple dosed rats 7 days after dosing.

Faeces represented the major route of elimination of spinosyn J and spinosyn L. Over 7 days post dosing, an average of 86% and 85% of the administered doses of spinosyn J and spinosyn L respectively were eliminated in faeces compared to 4% and 3% respectively in the urine of orally dosed rats.

Spinosyn J and spinosyn L were extensively metabolized with ~86% and ~85% respectively of the administered doses eliminated in the faeces of orally-dosed animals. The major metabolic pathway for the test substance was glutathione conjugation of the parent compound and metabolites arising from N-demethylation, O-deethylation and hydroxylation of the parent compound.

Rates of faecal and urinary elimination were similar regardless of dose level, gender, single vs. multiple dose, or route of administration.

Acute Studies

Based on the findings of toxicological studies provided, spinetoram and Delegate Insecticide have no significant acute toxicity *via* the oral, dermal, and inhalation routes of exposure. The LD_{50} for oral and dermal acute exposure to both spinetoram and the product is > 5000 mg/kg bw and the LC_{50} for acute inhalation exposure is > 5280 mg/m^3. Spinetoram is a slight irritant of the eye and showed a weak capacity for skin sensitisation. The product is a slight irritant of the eye.

Short term studies

Fischer 344 rats (10/sex/dose) were dermally exposed at a semi-occluded skin test site to 0, 100, 500, or 1000 mg spinetoram (XDE-175) per kilogram body weight for six hours per day for 28 consecutive days. There was no systemic toxicity in males or females at any dose level. The only treatment related change was a minimal, localized, microscopic skin effect at the site of XDE-175 application which consisted of very slight or slight epidermal hyperplasia variably accompanied by very slight hyperkeratosis in the majority of males and females given 500 or 1000 mg/kg/day and in some males and females given 100 mg/kg/day. This minimal epidermal alteration of the skin at the test site was interpreted to be a protective adaptational change to repeated exposures to a low level irritant. The NOEL for systemic effects was 1000 mg/kg bw/day CD-1 mice (5/sex/dose) were given test diets that contained 0, 0.005, 0.015, 0.045, or 0.12% XDE-175 Technical (0/0, 8.3/10.6, 25/31, 75/96 or 183/226 mg/kg bw/day for males/females respectively) for 28 days to evaluate systemic toxicity and serum concentrations.

At 0.12% XDE-175 (and to a lesser extent at 0.45%) the primary effect was cytoplasmic vacuolation of the parenchymal cells, epithelial cells, macrophages and fibroblasts of various organs. There was a slight microcytic anaemia. All males and one of five females showed splenic extramedullary haematopoiesis, elevated hepatobiliary enzyme activity and a decrease in albumin associated with decreased feed consumption. At these concentrations an inflammatory response was noted. Other effects included hyperplasia of the glandular mucosa of the stomach, degeneration with regeneration of skeletal muscle fibres and very slight hypertrophy of zona fasciculata in adrenal glands.

The body weight gain of mice given 0.12% XDE-175 was 50% (male) and 83% (female) that of controls. Decreases in feed consumption also occurred at this concentration. Increases in absolute and relative liver and spleen weights occurred. Increases in absolute and relative adrenal weights occurred in males ≥ 0.045%. XDE-175 Technical contained 64% XDE-175-J and 31% XDE-175-L for this trial, yet systemic bioavailability of XDE-175-L was 4-44% higher than XDE-175-J in all groups, except females given 0.12% for which bioavailability was 16% lower, suggesting preferential absorption of XDE-175-L or faster elimination/first-pass metabolism of XDE-175-J. Although females were exposed to more test substance than males due to higher feed consumption relative to body weight, test substance serum levels in females were mostly lower than males suggesting lower systemic bioavailability, especially for XDE-175-L. Systemic bioavailability became nonlinear at the highest dose suggesting nonlinear absorption (saturation), which was pronounced for XDE-175-L in females.

The NOEL in mice was at 0.015% in the diet (25 mg/kg bw/day). Toxic effects at the next dose level for males, 0.045% in diet (75 mg/kg bw/day), were decreases in haemaglobin and haematocrit increases in neutrophils and monocytes, increases in absolute and relative adrenal gland weight, very slight multifocal epididymal epithelial vacuolation, very slight multifocal renal tubule epithelial vacuolation, very slight multifocal aggregation of macrophages and vacuolation of alveolar epithelium and in mesenteric lymph node (among similar findings in many other tissues). For females at 0.045% in diet (96 mg/kg bw/day), the effects were increases in monocytes and histopathological findings similar to those described for males.

Fischer 344 rats (5/sex/dose) were given test diets formulated with 0%, 0.012%, 0.05%, or 0.15% (females only) or 0.2% (males only) XDE-175 Technical (0/0, 11/12 or 48/48 mg/kg bw/day for males and females respectively and 142 mg/kg bw/day for females and 185 mg/kg bw/day for males, for at least 28 days.

At the high dose levels in males and females (and to lesser extent at 0.05%) light vacuolation of the follicular epithelial cells of the thyroid and a very slight vacuolation of the renal tubular epithelial cells occurred. There were slight accumulations of macrophages (histiocytes) in the cortex of mesenteric lymph nodes and within the white pulp of the spleen.

Males given the high-dose level of XDE-175 Technical had decreases in body weight gain (8.6%) and feed consumption. Females had an increase in spleen weight.

A higher than dose proportional increase in serum concentrations for both components of the test substance at the two higher doses, was observed. This was more pronounced for XDE-175-J than for XDE-175-L. Higher than expected serum concentration ratios between doses is an indication of saturation of elimination at high doses or more efficient first-pass elimination at low doses with absorption of the test substance from the gastrointestinal tract appearing to be unaffected.

A similar trend was observed among doses for the steady-state 24 hour area-under-the-plasma-concentration-time-curve (AUC 24 hour) determined from 3 blood samples collected at 5 am, 10 am, and 5 pm, 24 days after study initiation. The elimination rate of both of the components decreased with increasing dose, corresponding to plasma elimination half-lives of 7 and 9, 10 and 12, and 32 and 16 hours for XDE-175-J and XDE-175-L at the low, middle and high doses, respectively.

The NOEL in rats was 0.012% in the diet (11 mg/kg bw/day). There were no toxic effects in males at the next dose level, 0.05% (48 mg/kg bw/day). At 0.2% (185 mg/kg bw/day) the effects were decreased body weight gain, decreased feed consumption, slight thyroid vacuolation, very slight kidney vacuolation, slight splenic histiocytosis and very slight lymph node histiocytosis. For females at 0.05% (48 mg/kg bw/day), the effects were very slight kidney vacuolation and slight splenic histiocytosis.

Beagle dogs (two/sex/dose) were fed diets formulated to contain 0, 200, 900, or 2000 ppm XDE-175 Technical (0/0, 5.9/8.1, 31/35 or 65/62 mg/kg bw/day for males and females respectively) for 28 days.

Very slight or slight vacuolization of macrophages within lymphoid tissue occurred at 900 or 2000 ppm. Extramedullary hematopoiesis of the spleen was noted and was interpreted to be a response to the bone marrow necrosis and anaemia occurring at these dose levels. Very slight or slight hyperplasia and hypertrophy of Kupffer cells in liver occurred. Kupffer cells showed cytoplasmic vacuolization. Also observed were aggregates of alveolar macrophages in the lungs.

At these concentrations, alterations in red blood cell, white blood cell, and platelet parameters reflective of a non-regenerative anaemia, and increases in alanine aminotransferase and/or aspartate aminotransferase activities occurred.

Three dogs lost bodyweight over the duration of the study. There were decreases in absolute and relative thymus weights. The lower thymic weights corresponded to the microscopic alteration of atrophy of the thymic cortex in the affected females.

The NOEL in dogs was 200 ppm in the diet (6.0 mg/kg bw/day). Toxic effects at the next dose level for males, 900 ppm (31 mg/kg bw/day), were increased monocytes, increased absolute and relative liver weight, decreased absolute and relative thymus weight, widespread occurrence in organs of vacuolization of macrophages and other tissues, very slight multifocal necrosis of bone marrow, very slight hyperplasia and hypertrophy of liver. For females at 900 ppm (35.1 mg/kg bw/day) the effects were decreased body weight gain, increased absolute and relative liver weight, decreased absolute and relative thymus weight and similar histopathological changes as occurred in males.

Subchronic Studies

CD-1 mice (10/sex/dose) were given test diets formulated with 0, 0.005, 0.015, or 0.045% (0, 50, 150, or 450 ppm, respectively) XDE-175 (0/0, 7.5/10, 23/30 or 70/90 mg/kg bw/day for males and females respectively) for at least 90 days.

At 450 ppm cytoplasmic vacuolation of parenchymal cells, epithelial cells, macrophages and fibroblasts in numerous organs was noted. Observations also included hyperplasia of the glandular mucosa of stomach, multifocal degeneration and regeneration of skeletal muscle fibres and renal tubular epithelium, and a slight increase in splenic extramedullary haematopoiesis. Males at 150 ppm, showed a vacuolation of the tubules of the head of the epididymis.

At 450 ppm, a microcytic hypochromic anaemia was observed. Females given 150 or 450 ppm had increases in white blood cell counts. There was an increase in the activity of aspartate aminotransferase (and alanine aminotransferase in females) which may have been associated with subclinical hepatic effects or skeletal muscle degeneration.

The body weight gains of males at 450 ppm were substantially lower than controls throughout the study, with a 24% reduction by study termination. They also experienced decreases in feed consumption of up to 11%. Males and females had increases in mean absolute and relative spleen weights. The increase in spleen weight was attributed to splenic extramedullary hematopoiesis. Males and females also showed increases in mean absolute and relative liver weights.

The NOEL for the 90-day mice study was 50 ppm in the diet (7.5 mg/kg bw/day). Toxic effects at the next dose level for males, 150 ppm (23 mg/kg bw/day), were multifocal vacuolization of the epithelium of the epididymides. For females at 150 ppm (30 mg/kg bw/day), the effects were increased white blood cell count.

Fischer 344 rats (10/sex/dose up to 2000 ppm; 10 females at 4000 ppm) were given test diets containing 0, 120, 500, 1000, 2000 ppm for males and females respectively and 4000 ppm for females only XDE-175 Technical (0/0, 7.9/9.5, 32/40 or 66/79 mg/kg bw/day for males and females respectively and 311 mg/kg bw/day for females only), for at least 90 days.

Additional groups of the same size were given either 0 or 1000 ppm XDE-175 for 90 days, and were maintained on control feed for an additional four weeks to assess the potential reversibility of treatment related effects.

At 1000 ppm or higher in males and at 500 ppm or higher in females, aggregates of macrophages (histiocytes) occurred in lymphoid tissues. Vacuolation of parenchymal cells occurred in the thyroid gland and kidney, and skeletal muscle degeneration involved multiple muscles. Females at 4000 ppm had vacuoles within tubular epithelial cells that contained a flocculent material or membranous whorls. These effects were consistent with those observed in animals given agents known to be cationic amphiphilic drugs and establish XDE-175 as a cationic amphiphilic compound.

Females given 2000 or 4000 ppm had decreases in red blood cell parameters and higher reticulocyte counts. The white blood cell counts of females given 1000 ppm or higher dose were also higher than the controls. Males given 2000 ppm and females given 2000 ppm or a higher dose, had higher liver enzyme levels (alanine aminotransferase – males; aspartate aminotransferase – males and females). The triglyceride levels of females given 500 ppm or a higher doses were lower than the controls and dose related. Females given 4000 ppm also had a slightly higher alkaline phosphatase activity. Females given 2000 or 4000 ppm had lower triiodothyroinine levels and females given 500, 1000 or 2000 ppm had lower tetraiodothyroinine levels than the control, concomitant with increased liver weights (1000 ppm or higher), and a slight degree of vacuolation of the thyroid follicular epithelium (500 ppm or higher). A decreased amount of colloid was also observed in females given 1000 ppm or higher doses.

Males given 2000 ppm and females given 2000 or 4000 ppm showed decreases in bodyweight gain at the end of the dosing phase. Feed consumption of males given 2000 ppm and females given 4000 ppm were also lower than the controls.

The potential to recover from the effects induced by XDE-175 Technical was demonstrated. Variable degrees of recovery occurred during the 28-day recovery phase. Complete recovery was noted for a number of effects including: lower triglycerides, higher relative liver weights, higher relative heart weight, and microscopic effects involving the ileum (males), jejunum (males), kidney (females), liver (males), spleen (males), skeletal muscle and thymus. Partial recovery occurred in relative spleen weights and microscopic effects involving the kidneys (males), spleen (females), mesenteric and mediastinal lymph nodes, jejunum (females), ileum (females), liver (females) and thyroid glands. Recovery was not demonstrated in males given 1000 ppm for the elevated alanine aminotransferase activity.

The NOEL was 120 ppm in diet (8 mg/kg bw/day). There were no toxic effects in males at the next dose level, 500 ppm (32 mg/kg bw/day). At 1000 ppm (66 g/kg bw/day), toxic effects were focal or multifocal aggregates of macrophages in mediastinal and mesenteric lymph nodes and spleen and thymus. For females at 500 ppm (40 mg/kg bw/day), the effects were decreases in serum triglyceride levels, decreases in serum tetraiodothyronine (T4), the presence of focal or multifocal aggregates of macrophages (histiocytes) in mesenteric lymph nodes, spleen and bone marrow and vacuolation of thyroid follicular epithelial cells.

Beagle dogs (four/sex/dose) were fed diets formulated to contain 0, 150, 300, or 900 ppm XDE-175 Technical (0/0, 5.7/5.0, 9.8/10 or 27/31 mg/kg bw/day for males and females respectively) for 90 days.

At 300 and 900 ppm very slight or slight vacuolization of macrophages occurred within lymphoid tissue. Very slight vacuolization of macrophages within lymphoid tissue also occurred in males given 150 ppm.

At the two high doses, very slight, slight or moderate arteritis or perivascular inflammation occurred in numerous tissues of some males and females. The more severe arteritis was frequently accompanied by necrosis of the arterial walls, with occasional associated haemorrhage. The arteritis was not observed in the mouse or rat and is believed to be a treatment related exacerbation of spontaneous arteritis to which Beagle dogs are genetically predisposed.

Very slight to moderate bone marrow necrosis was also noted at the two high doses. The concomitant extramedullary hematopoiesis of the spleen and liver in some females was interpreted to be a response to the bone marrow necrosis and/or anaemia at these dose levels. Very slight or slight hyperplasia and hypertrophy of Kupffer cells and vacuolization of Kupffer cells occurred in the liver of some males and females.
Also noted was a higher aspartate aminotransferase activity higher alkaline phosphatase activity, a lower albumin concentration and higher globulin concentration.

At the two high doses males and females showed lower mean body weights and body weights gains during the majority of the study. There were increases in absolute and relative liver weights and decreases in absolute and relative thymus weights.

A NOEL for dogs was not established. The LOEL was 150 ppm in diet (5.0 mg/kg bw/day). Toxic effects in males at the LOEL of 150 ppm (6 mg/kg bw/day) were very slight vacuolization of macrophages within lymphoid tissue, jejunum, nasal tissue and rectum of some males at the lowest dose. For females at 150 ppm (5.0 mg/kg bw/day) no effects were seen. For females at 300 ppm (10 mg/kg bw/day) the effects were increases in mean reticulocyte counts, vacuolization of macrophages, arteritis and perivascular inflammation.

Chronic toxicity
Crl:CD1(ICR) mice (50/sex/dose) were given diets formulated to provide 0 (controls), 25, 80, 150 or 300 ppm XDE-175 Technical (0/0, 3/4, 10/13, 19/24 or 37/47 mg/kg bw/day for males and females respectively) for up to 18 months.

At 300 ppm hyperplasia of the glandular mucosa of the stomach was noted with associated dilatation of mucosal glands and chronic inflammation of the glandular submucosa. In general, the stomach alterations were most prominent in the region of the glandular mucosa near the limiting ridge, and lessened in the pyloric area.

Also noted at this dose was an increase in the incidence of very slight or slight aggregates of alveolar macrophages in the lungs. The aggregates of macrophages were randomly distributed yet were most commonly located in subpleural regions of the lungs. Males at this dose showed an increase in the incidence and severity of cytoplasmic vacuolization of epithelial cells lining the ducts in the head of the epididymides.

There were no effects on bodyweight gain in males at any dose. Females given 300 ppm had periodic slight decreases in body weight gains throughout the study. They also showed concomitant periodic decreases in feed consumption.

No significant increase in neoplasms was observed in either male or female mice at any dose level indicating that XDE-175 Technical did not have an oncogenic potential under the conditions of this study.

The NOEL for mice was 150 ppm in the diet (19 mg/kg bw/day). Toxic effects at the next dose level, 300 ppm (37 mg/kg bw/day), for males were hyperplasia of the glandular mucosa of the

stomach, slight aggregation of macrophages in the alveolar tissue of the lung and cytoplasmic vacuolization of epithelial cells in the heads of the epididymides. For females at 300 ppm (46.62 ± 6.74 mg/kg bw/day), the effects were decreased body weight gain and hyperplasia of the glandular mucosa of the stomach.

Fischer 344 rats (65/sex/dose) were fed diets formulated to provide 0, 50, 250, 500, or 750 ppm XDE-175 Technical for up to two years. The chronic toxicity group (10 rats/sex/dose) and the chronic neurotoxicity group (10 rats/sex/dose) shared 5 rats/sex/dose. Ten rats/sex/dose were necropsied after one year of treatment. Five rats/sex/dose were also necropsied at this time for chronic neuropathology assessment, and the remaining 50 rats/sex/dose level were fed the respective diets for up to two years. Test substance intake at the 12 month mark was 0/0, 2.4/2.9, 12/15, 24/30 or 37/44 mg/kg bw/day for males and females respectively and at the 24 month mark was 0/0, 2.1/2.6, 11/13, 22/27 or 33/40 mg/kg bw/day for males and females respectively).

After 12 months, vacuolation of thyroid follicular cells at 500 and 750 ppm in males and females was noted. There were also increased heart and liver weights for females at these doses.

After 24 months the observed effects in males and females at 500 and 750 ppm were vacuolation of thyroid follicular cells and aggregates of macrophages (histiocytes) in the mesenteric lymph nodes. Females given these two doses also had aggregates of macrophages (histiocytes) in the mediastinal lymph nodes and Peyer's patches of the ileum and the spleen. Females given 750 ppm had aggregates of alveolar macrophages in the lung, and retinal degeneration/vacuolation. Females given 750 ppm showed increased heart weights.

After 24 months there was no statistically significant difference in the incidence of neoplasms in any of the treatment groups compared with the controls ($p < 0.05$).

The neurotoxicity subgroup was evaluated pre-exposure, and at 1, 3, 6, 9, and 12 months of exposure using an automated test of motor activity, a functional observational battery (FOB), determinations of grip performance, rectal temperature, and landing foot splay. Following 12 months of exposure, five rats/sex/dose were perfused, and tissues from the central and peripheral nervous system of the control and high-dose groups were submitted for neuropathologic examination.

There was no effect on grip performance, landing foot splay, rectal temperature, or motor activity at any time. For the ranked and categorical FOB, there were no observations that could be attributed to treatment. There were no gross or histopathologic findings in either the central or peripheral nervous system following 12 months of dietary exposure.

There were no effects of XDE-175 on any parameter that suggested a neurotoxic effect.

The 12 month NOEL was 250 ppm in diet (11.0 mg/kg bw/day). Toxic effects at the next dose level for males, 500 ppm (24.4 ± 8.7 mg/kg bw/day) were decreased body weight gain and vacuolation of follicular epithelium of the thyroid gland. For females at 500 ppm (29.6 ± 7.3 mg/kg bw/day), the effects were vacuolation of follicular epithelium of the thyroid gland.

The 24 month NOEL was 250 ppm in diet (11.0 mg/kg bw/day). Toxic effects at the next dose level for males, 500 ppm (21.6 ± 8.1 mg/kg bw/day), were decreased body weight gain and vacuolation of follicular epithelium of the thyroid gland. For females at 500 ppm (26.6 ± 7.2 mg/kg bw/day), the effects were vacuolation of follicular epithelium of the thyroid gland, increased aggregation of macrophages/histiocytes in mesenteric lymph nodes, mediastinal lymph

nodes, Peyer's patches in the ileum, alveoli of the lung and white pulp of the spleen and decreased foci of basophilic cellular alteration in the liver.

In mice the NOEL for neurotoxicity was 750 ppm in the diet (37 mg/kg bw/day), the highest dose given.

Beagle dogs (four/sex/dose) were fed diets formulated to contain 0, 50, 100, or 200 ppm XDE-175 Technical (0/0, 1.6/1.3, 3.0/2.5 or 5.4/5.8 mg/kg bw/day in males and females respectively), for up to one year.

Arteritis in one male and one female given 200 ppm was the only histopathologic effect noted. Arteritis occurred bilaterally in the epididymides of one male given 200 ppm and in the thymus, thyroid, larynx, and urinary bladder of one female given 200 ppm. The arteritis was accompanied by necrosis of the arterial walls in all of the affected dogs and was interpreted to represent a treatment related exacerbation of spontaneous arteritis in genetically predisposed Beagle dogs.

There occurred increases in mean absolute and relative liver weights of males given 200 ppm. The higher liver weights were interpreted to be treatment related, but of minimal toxicological significance due to the lack of any clinical pathologic or microscopic changes.

In dogs the NOEL was 100 ppm in the diet (2.5 mg/kg bw/day). Toxic effects at the next dose level in males, 200 ppm (5.36 ± 0.88 mg/kg bw/day), were bilateral arteritis in the epididymides. For females at 200 ppm (5.83 ± 0.90 mg/kg bw/day), the effects were arteritis in larynx, thymus, thyroid and urinary bladder.

Genetic toxicity

XDE-175 Technical was negative (with or without metabolic activation) in the following *in vitro* assays: reverse bacterial mutation, chromosome aberration, gene mutation (CHO/HGPRT) and in an *in vivo* mouse bone marrow micronucleus test.

Based on the available studies, spinetoram has no potential for genotoxicity.

Developmental toxicity

Time-mated female CD rats (26/dose) were administered XDE-175 Technical (suspended in 0.5% methylcellulose) by oral gavage at targeted dose levels of 0, 30, 100, or 300 mg/kg/day on gestation days (GD) 6 to 20 inclusive.

Maternal body weight decreases (43.5% below controls) in the interval GD 6-12 and decreases (up to 15.4%) in food consumption over GD 6-15 were noted at 300 mg/kg bw/day. No treatment-related embryo/foetal toxicity or teratogenicity was observed at dose levels up to and including 300 mg/kg/day, the highest dose tested.

In rats, the NOEL for maternal toxicity was 100 mg/kg bw/day and the NOEL for embryo/foetal toxicity/teratogenicity was 300 mg/kg bw/day, the highest dose tested.
Time-mated female New Zealand White rabbits (25-26/dose) were administered XDE-175 Technical by oral gavage on gestation days (GD) 7-27 inclusive at targeted dose levels of 0, 2.5, 10, or 60 mg/kg/day.

At 60 mg/kg bw/day there were decreases in body weight gain, feed consumption and increased mean absolute and relative liver weights. In addition, one dam given 60 mg/kg/day was

euthanized on GD 21 due to inanition and subsequent weight loss. There was no developmental toxicity at any dose level.

In rabbits, the NOEL for maternal toxicity was 10 mg/kg bw/day and the NOEL for embryo/foetal toxicity/teratogenicity was 60 mg/kg bw/day, the highest dose tested.

PUBLIC HEALTH STANDARDS

Poisons Scheduling

The National Drugs and Poisons Schedule Committee (NDPSC) considered the toxicity of spinetoram and assessed the necessary controls to be implemented under States' poisons regulations to prevent the occurrence of poisoning.

At its 52nd meeting in February 2008 the NDPSC created a new entry for Spinetoram in Schedule 5 of the SUSDP.

NOEL/ADI

The Acceptable Daily Intake is that quantity of an agricultural compound which can safely be consumed on a daily basis for a lifetime and is based on the lowest NOEL obtained in the most sensitive species. This NOEL is then divided by a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

The ADI for spinetoram was established at 0.06 mg/kg bw/day based on a NOEL of 6 mg/kg bw/day in a 28 day dietary study in dogs and using a 100-fold safety factor.

Acute Reference Dose (ARfD)

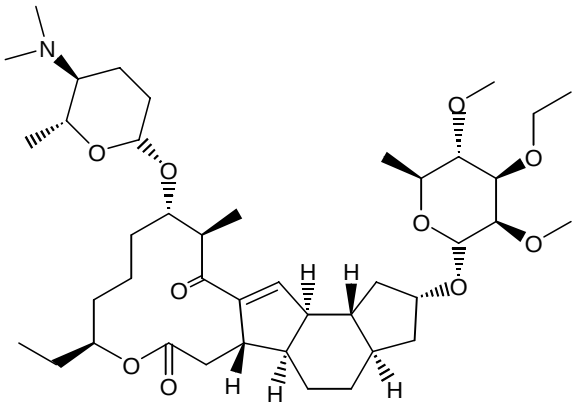
The acute reference dose is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated, event. The ARfD is derived from the lowest single or short term dose which causes no effect in the most sensitive species of experimental animal tested, together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

No ARfD has been established for spinetoram and no data were submitted to enable an ARfD to be set

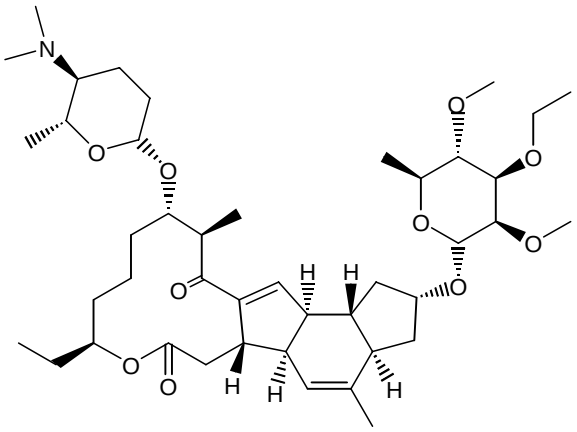
RESIDUES ASSESSMENT

Introduction

Delegate Insecticide contains the new active constituent spinetoram (consisting of XDE-175-J or Ethyl-spinosyn-J and XDE-175-L or Ethyl-spinosyn-L in a ~3:1 ratio) and is to be used for the control of codling moth, lightbrown apple moth and oriental fruit moth in pome and stone fruit. As part of the residues assessment for spinetoram, plant and animal metabolism studies, supervised residue trials, trade aspects, environmental fate and chemistry were considered. Details are provided below.



XDE-175-J



XDE-175-L

Metabolism

Plants

Studies have been provided which investigate the metabolism of spinetoram in apples, lettuce and turnips.

Apples

Apples were treated separately with radio-labelled XDE-175-J and XDE-175-L and samples taken at 0, 1, 3, 7, and 14 days after treatment (DAT), while covered apples were also collected at 3 DAT. Much higher residues were present on leaves than apples and untreated samples (translocation samples) had negligible radioactivity. Greater than 96% of the apple residue was on the surface (rinses and peel), while the majority of the leaf residue was also on the surface. The major radioactive components present were the parent and the *N*-demethyl-175 (N-D) and *N*-formyl-175 (N-F) metabolites. For example, following application of XDE-175-J, parent XDE-175-J ranged from 82.2 % of the TRR at Day 0, to 22.2% at Day 30 in apples and from 80.2% at Day 0 to 19.9% at Day 30 in leaves, whilst N-D-J (up to 13.5% of the TRR in the Day 7 apple sample and 13.9% in the Day 3 leaves sample) and N-F-J (up to 4.9% of the TRR in Day 3 apples and 4.1% in Day 3 leaves) were present in lesser, though significant amounts. Similarly, parent XDE-175-L ranged from 42.6% of the TRR at Day 0 to 0.9% at Day 14 in apples and 26.8% at Day 0 to 0.2% at Day 30 in leaves. N-D-L was at a maximum at Day 0 (8.0% of the TRR) in apples and at Day 1 in leaves (3.2%). NF-L was at a maximum in apples in the Day 3 dark sample (covered apples) (2.7% of the TRR) and in leaves at Day 0 (2.5%). Other metabolites were observed in both apples and leaves and were identified in the leaves at low levels: 3-*O*-de-ethyl-175-J (a maximum of 3.4% of the TRR at Day 30), C9-pseudoaglycone-

175-J (a maximum of 4.6% at Day 30) and a demethylated *N*-formyl-175-J in XDE-175-J samples and hydroxylation of the macrolide portion of the molecule in the XDE-175-L samples.

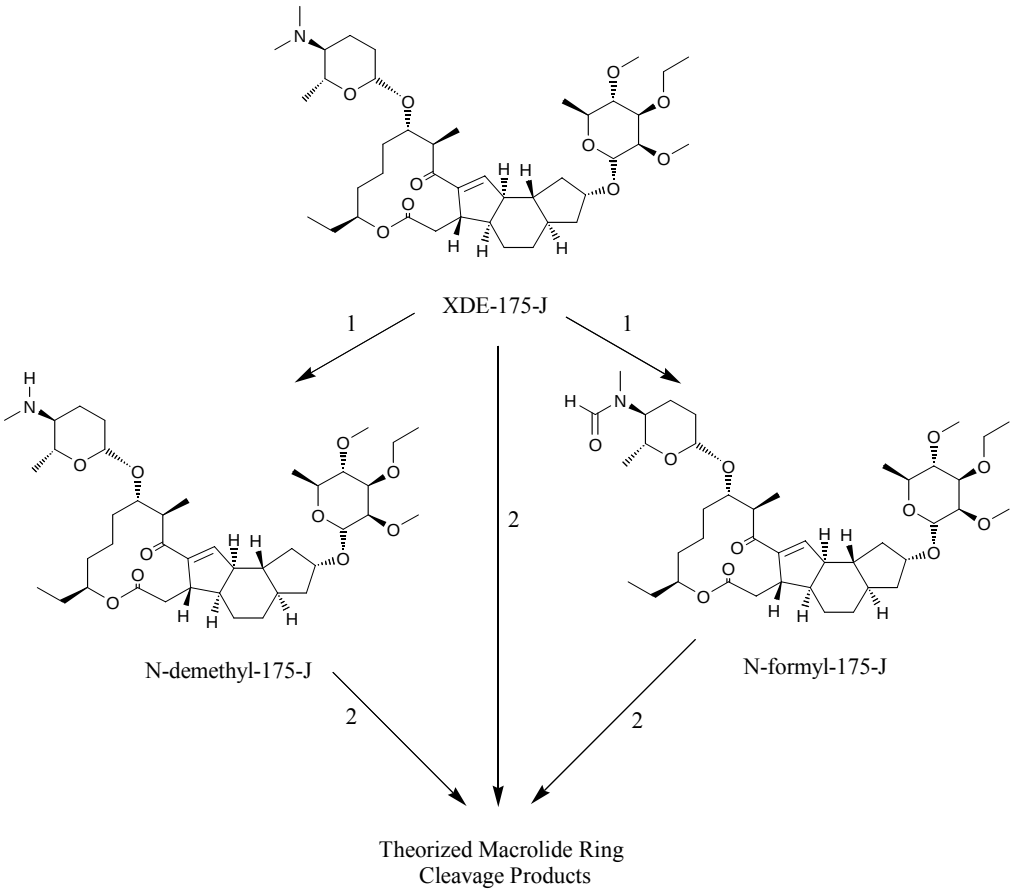
Turnips
For turnip tops treated with radiolabelled XDE-175-J, over 60% of the TRR in the 0.25 DAT sample was accounted for as XDE-175-J (35.7%) and the N-D-J (14.4%) and N-F-J (10.4%) metabolites; this decreased to 29% at 3 DAT (Single Application - SA) (XDE-175-J 9.4%; N-D-J 8.5%; and N-F-J 11.2%) and 20% (Multiple Applications - MA) (XDE-175-J 4.9%; N-D-J 4.1%; and N-formyl (N-F-J) 11.4%). In all samples there were varying levels of multi-component residues (maximum for a single component 2.6% of the TRR – 0.25 DAT Turnip Tops sample). These eluted in the more polar regions of the silica columns, as 5 - 6 fractions (up to 84 individual components) which increased over time, so that at 3 DAT (SA and MA) they represented over 50% of the TRR. For tops treated with XDE-175-L, the parent, N-D-L and N-F-L were present at lower levels than in XDE-175-J (27% at 0.25 DAT comprised of XDE-175-L 17.1%; N-D-L 7.4% and N-F-L 3.0% and 4.5 - 4.6% at 3 DAT SA (XDE-175-L 2.9%; N-D-L 1.0% and N-F-L 0.6%) and 3 DAT MA (XDE-175-L 3.0%; N-D-L 1.1%; and N-F-L 0.5%)). As observed for XDE-175-J, multi-component residues (maximum for a single component 0.9% of the TRR - 0.25 DAT Turnip Tops sample) accounted for most of the remainder of the residue (57.3% of the TRR at 0.25 DAT and 68.8 - 73.8% of the TRR at 3 DAT (SA and MA)).

For the 3 DAT turnip root samples treated with XDE-175-J or XDE-175-L, residues of parent and the *N*-demethyl and *N*-formyl metabolites were 48.9% (XDE-175-J 22.3%; N-D-J 10.0%; and N-F-J 16.6%) and 17.8% (XDE-175-L 14.8% and N-F-L 3.0%) respectively. Multi-component residues accounted for 9.9% (no single component >1.2%) and 13.1% (no single component >1.6%) of the TRR respectively.

Lettuce
For lettuce treated with radiolabelled XDE-175-J, over 75% of the TRR in the 0 DAT sample was accounted for as XDE-175-J (63.6%) and the N-D-J (8.9%) and N-F-J (6.6%) metabolites; this decreased to 44.3% (SA –parent (17.6%), N-D-J (15.5%) and N-F-J (11.2%)) and 30.5% (MA – parent (8.5%), N-D-J (7.2%) and N-F-J (14.8%)) at 3 DAT. In all samples there were varying levels of multi-component residues (maximum 0.9% of the TRR at 0 Time (0.44 mg equiv./kg) and at 1 DAT (0.31 mg equiv./kg)) that eluted in the more polar regions of the silica columns as 5 - 6 fractions (>70 individual components in each) which increased over time. At 3 DAT (SA and MA) multi-component residues represented over 30-50% of the TRR.

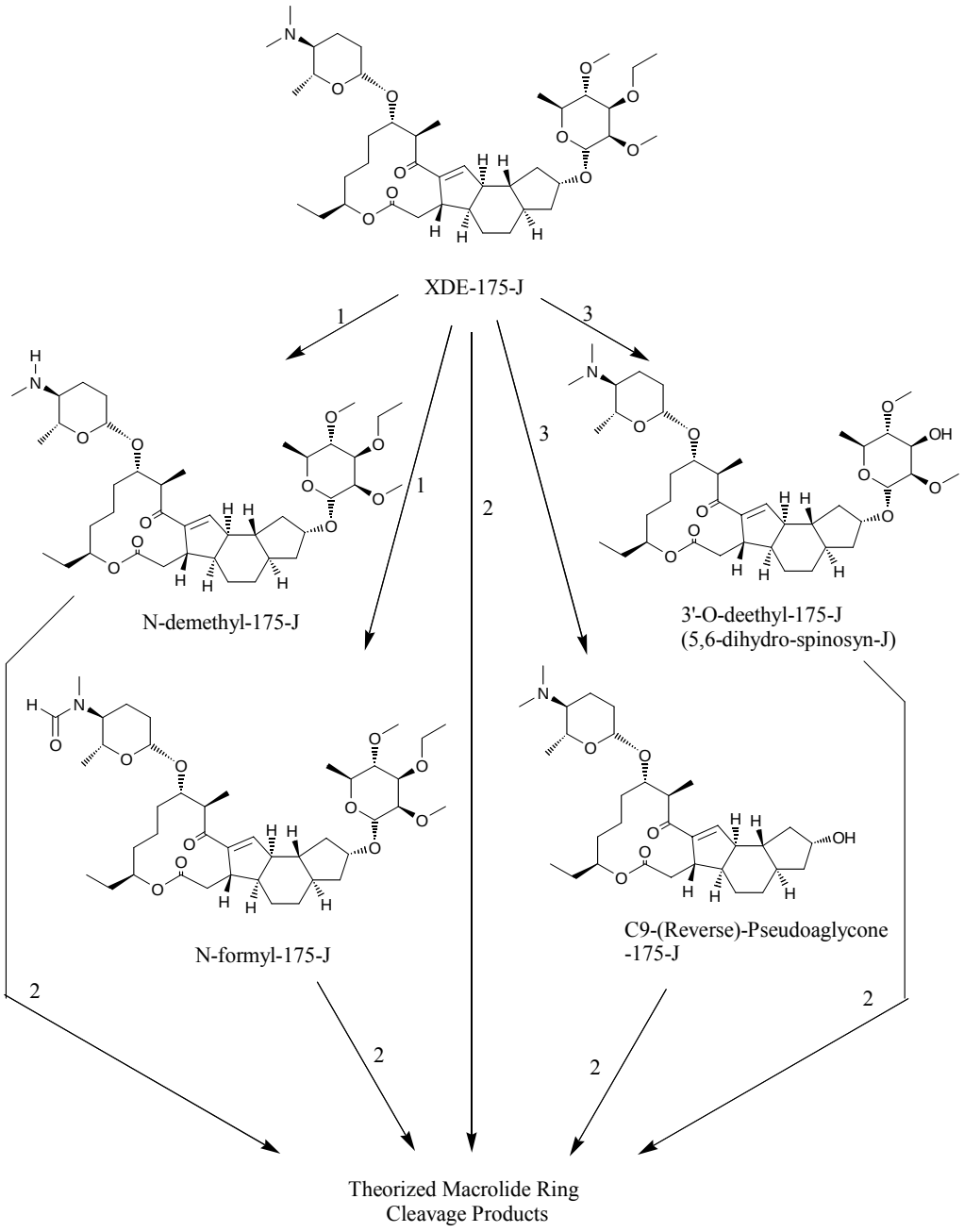
For lettuce treated with XDE-175-L, the parent and N-D-L and N-F-L were present at much lower levels than in XDE-175-J (75% at 0 Time (parent 52.4%; N-D-L 17.6% and N-F-L 5.9%) but 23.1% at 1 DAT (parent 11.9%; N-D-L 7.2% and N-F-L 4.0%) and 5-11% at 3 DAT (SA (parent 5.1%; N-D-L 3.5% and N-F-L 2.0%) and MA (parent 3.0%; N-D-L 1.5% and N-F-L 1.1%)). As observed for XDE-175-J, multi-component residues (maximum 2.9% of the TRR at 0.25 DAT) accounted for most of the remainder of the residue (>50% of the TRR at 1 DAT and >70% of the TRR at 3 DAT (SA and MA)).

Two pathways were proposed for the breakdown of XDE-175-J and XDE-175-L in turnips and lettuce and for the formation of the bulk of the residues in apples. A third minor pathway was also observed for the breakdown of XDE-175-J in apples. One pathway leads to alterations in the forosamine portion of the molecule with the *N*-demethyl-175 and *N*-formyl-175 metabolites being the primary components formed.



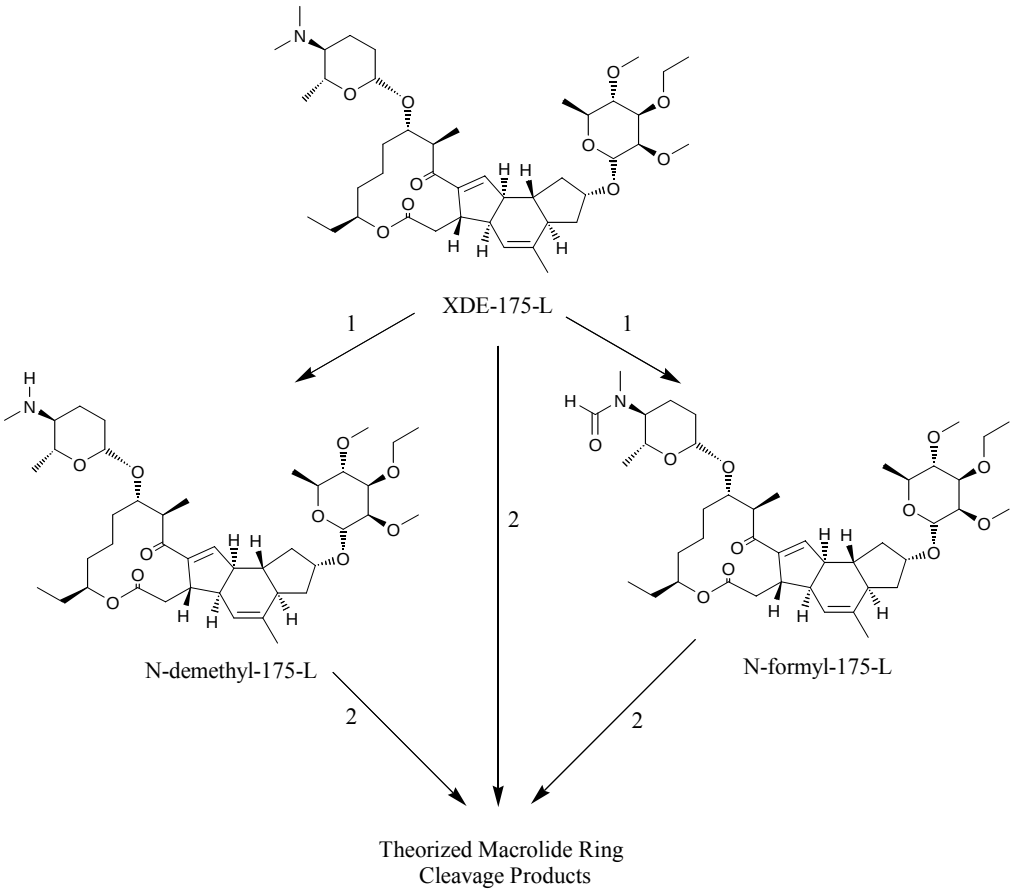
Proposed Metabolic Profile of XDE-175-J in Turnips and Lettuce

In another pathway only observed in the breakdown of XDE-175-J in apples, alterations to the rhamnose portion of the molecule lead to low levels (<5% of the TRR) of the 3-O-deethyl metabolite and C9-pseudoaglycone being formed. All metabolites formed *via* these pathways, as well as the parent compounds, were also subject to alteration by another pathway, which is believed to involve cleavage or opening of the macrolide ring system at one or more positions, which ultimately results in a complex residue mixture that consists of over one hundred components.



Proposed Metabolic Profile of XDE-175-J in Apples

Plant metabolism studies showed that the major residues after foliar applications of XDE-175 are the two active ingredients XDE-175-J (Ethyl-spinosyn-J) and XDE-175-L (Ethyl-spinosyn-L) and their respective *N*-demethyl and *N*-formyl metabolites. However, because XDE-175-L is present in lower amounts in the active material and because XDE-175-L dissipates more readily from crop surfaces, it is thought that levels of XDE-175-L *N*-demethyl and *N*-formyl metabolites will be very low, which was confirmed in field trials.



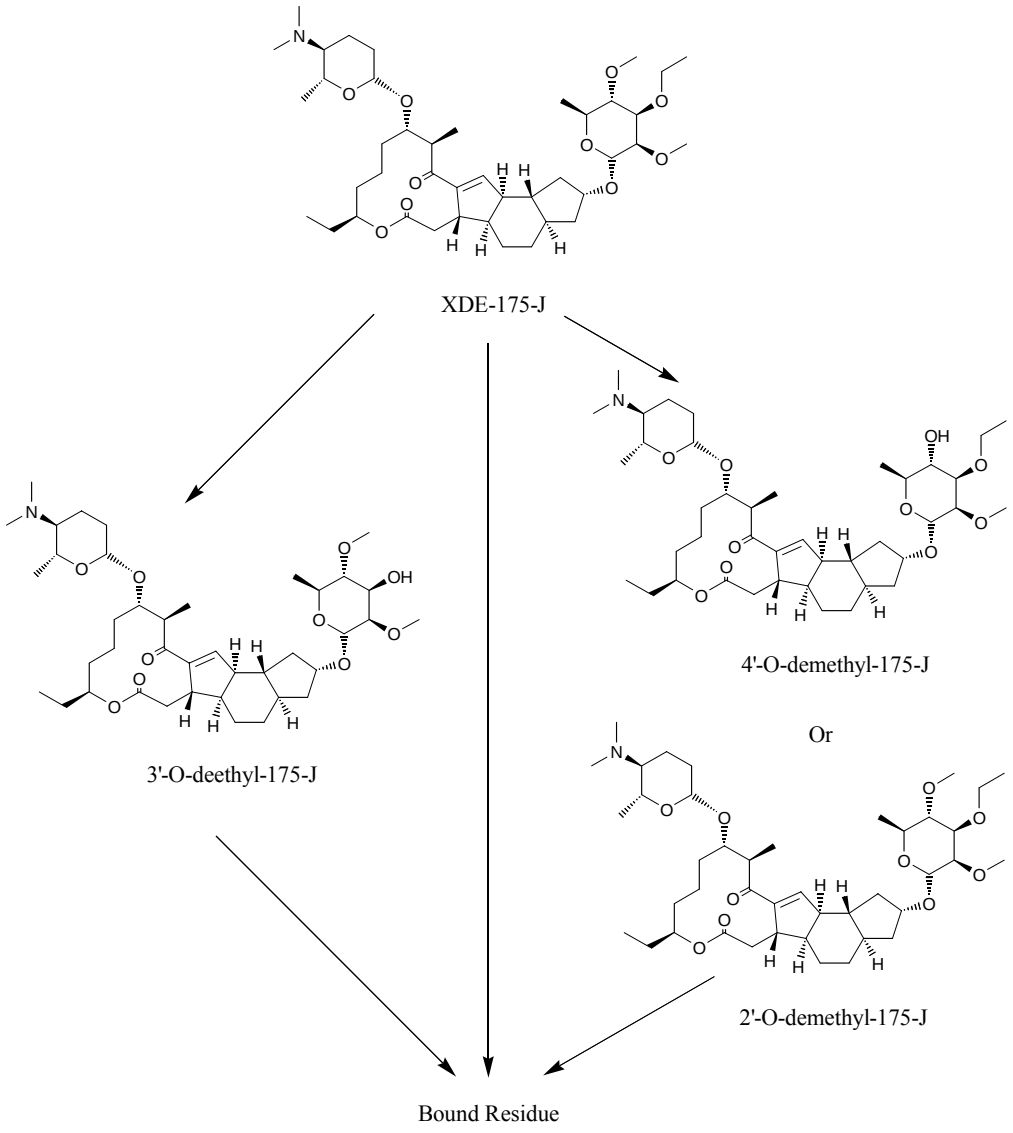
Proposed Metabolic Profile of XDE-175-L in Apples, Turnips and Lettuce

Animals

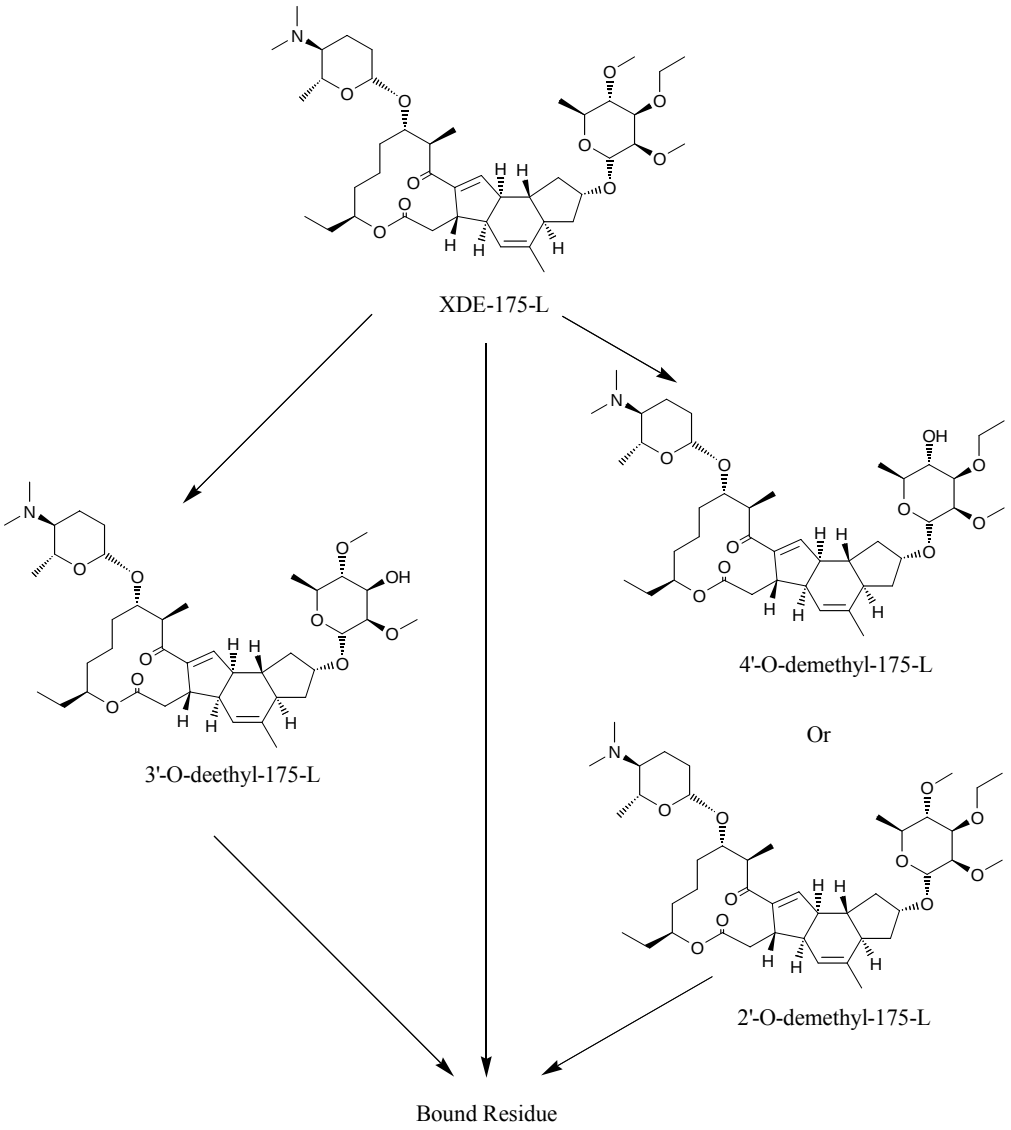
For animals, studies have been provided which investigate the metabolism of spinetoram in laying hens and lactating goats.

Laying hens

Residues in the excreta accounted for over 90% of the administered dose for both XDE-175-J and -L, dosed separately, in a hen metabolism study conducted over 7 days. Unchanged XDE-175-J was a significant proportion of the TRR in muscle (70.0%), fat (74.8%), skin with fat (82.9%) and eggs (69.2%), but to a much lesser extent in liver (13.6%). Similarly, unchanged XDE-175-L was a significant proportion of the TRR in muscle (44.8%), fat (56.6%), skin with fat (55.9%) and eggs (49.0%) and also to a much lesser extent in liver (11.8%). Metabolism was primarily through dealkylation of the rhamnose sugar to give 3'-*O*-deethyl-175-J and –L and 2'- and 4'-*O*-demethyl-175-J and -L. Multiple minor metabolites were also observed, each <10% of the TRR. Some metabolites were >10% of the TRR in some tissues.



Proposed Metabolic Profile of XDE-175-J in Laying Hens



Proposed Metabolic Profile of XDE-175-L in Laying Hens

Lactating goats

A goat metabolism study, conducted over 5 days, showed that faeces contained over 50% of the administered dose for ^{14}C-XDE-175-J and over 78% of the administered dose for ^{14}C-XDE-175-L. Unchanged parent was the primary residue component in all milk and tissue samples. Unchanged XDE-175-J was a significant proportion of the TRR in muscle (42.3%), fat (80.8%), kidney (53.9%) and day 5 milk (84.4%), but to a much lesser extent in liver (29.0%). Similarly, unchanged XDE-175-L was a significant proportion of the TRR in muscle (45.8%), fat (72.3%), kidney (64.3%) and day 5 milk (84.2%) and to a much lesser extent in liver (26.0%). No residue components apart from unchanged parent molecules were observed in milk, kidney or fat. Liver and muscle also contained an unidentified polar component that did not match any of the reference standards, while liver also contained <2% of an unidentified metabolite thought to be *N*-demethyl-175-J or –L.

Analytical methods

Residues of spinetoram and associated metabolites in pome and stone fruit were extracted by homogenising and shaking with acetonitrile/water (80/20). A mixed XDE-175 and metabolites stable isotope internal standard solution was added to each sample. Analysis was by liquid chromatography with positive ion electrospray ionization (ESI) tandem mass spectrometry

(LC/MS/MS). A similar method was used for the determination of residues in milk and tissue samples.

The LOQ for spinetoram in all crops and animal tissues was 0.01 mg/kg for each parent component and metabolite. Average recoveries from fortified samples were within acceptable limits (70-110%).

Storage stability of the two forms of spinetoram, XDE-175-J and XDE-175-L (as well as metabolites of both species), was investigated in a frozen storage stability study. All species were shown to be stable in a variety of crops (wheat grain, soybean grain, orange whole fruit, lettuce leaf and sugar beet root) for at least 12 months at < -20°C. The % remaining (corrected for recoveries) after 372 days over the 5 crops, for the parents and metabolites were: XDE-175-J 88 - 103%; XDE-175-L 74 - 108%; XDE-175-*N*-demethyl-J 85 - 100%; XDE-175-*N*-demethyl-L 73 - 98%; XDE-175-*N*-formyl-J 93 - 107% and XDE-175-*N*-formyl-L 83 - 112%.

In the residue trials submitted, all samples were maintained under freezer conditions, (*i.e.* –20 °C) prior to analysis and tested within 12 months of collection. This is acceptable for the purposes of the current application.

Residue Definition
Based on the metabolism data, residue data and analytical methodology provided, the following residue definition is appropriate:

"Sum of Ethyl-spinosyn-J and Ethyl-spinosyn-L".

Ethyl-spinosyn-J (XDE-175-J) is

(2S, 3aR, 5aS, 5bS, 9S, 13S, 14R, 16aS, 16bS)-13-{[2S, 5S, 6R)-5-(dimethylamino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-9-ethyl-4,14-dimethyl-7,15-dioxo-
2, 3, 3a, 5a, 5b, 6, 7, 9, 10, 11, 12, 13, 14, 15, 16a, 16b-hexadecahydro-1H-as-indaceno[3, 2-d]oxacyclododecin-2-yl 6-deoxy-3-O-ethyl-2, 4-di-O-methyl-beta-L-mannopyranoside

Ethyl-spinosyn-L (XDE-175-L) is

(2R, 3aR, 5aR, 5bS, 9S, 13S, 14R, 16aS, 16bR)-13-{[2S, 5S, 6R)-5-(dimethylamino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-9-ethyl-14-methyl-7,15-dioxo-
2, 3, 3a, 4, 5, 5a, 5b, 6, 7, 9, 10, 11, 12, 13, 14, 15, 16a, 16b-octadecahydro-1H-as-indaceno[3, 2-d]oxacyclododecin-2-yl 6-deoxy-3-O-ethyl-2, 4-di-O-methyl-beta-L-mannopyranoside

Residue Trials
Pome Fruit
The proposed use pattern for Delegate Insecticide on pome fruit is up to 4 applications per season at 14 day intervals, at a spray concentration of 10 - 20g product/100L (≡ 5g a.i./100L). Four studies (16 trials) have been submitted that determine the residues of spinetoram after treatment of apples and pears in Australia, New Zealand, Canada and the U.S.A. In twelve trials carried out in Australia and New Zealand in which 4 or 7 applications of spinetoram (5 - 5.04g a.i./100L) were made at 5 - 21 day intervals to apples and pears, residues were in the range of ND - 0.04 mg/kg, 7 days after last application (DALA). In four trials carried out in Canada and the U.S.A. in which 3 applications of spinetoram were applied at 8.1 - 8.5 g a.i./100L at 7 day intervals to apples, spinetoram residues were in the range of 0.006 - 0.024 mg/kg, 5 - 7 DALA. The Australian and New Zealand data were considered to be a good representation of Australian

GAP. These data were considered sufficient to recommend a group MRL for pome fruit set at 0.1 mg/kg. A 7 day harvest WHP is recommended. Based on the structural similarity between spinetoram and spinosad, processing data for dry apple pomace from the latter, was bridged to the former. An MRL of 1 mg/kg is recommended for spinetoram on dry apple pomace.

Stone Fruit
The proposed use pattern for Delegate Insecticide on stone fruit crops is up to 4 applications per season at 14 day intervals, at a concentration of 15g product/100L (≡ 3.75g a.i./100L). Six trials were carried out in Australia, in which 4 applications of spinetoram (5g a.i./100L) were applied at 14 day intervals or 7 applications of spinetoram were applied at 5g a.i./100L (3 applications at 5 day intervals and 4 applications at 14 day intervals) to cherries, peaches, apricots and nectarines. Spinetoram residues were in the range of 0.01 - 0.18 mg/kg, 0 DALA. In addition, data from trials conducted in Spain and Southern France, showed that after spinetoram was applied three times to peaches, at a concentration of 8.11 – 8.33 g a.i./100L, residues 3 DALA were 0.02 - 0.08 mg/kg. The Australian and European data were considered sufficient to recommend a group MRL for stone fruit set at 0.2 mg/kg. A 3 day harvest WHP is recommended.

Processing studies
No data from residues studies on spinetoram in processed fruit has been provided.
Based on the similarity in structures and similar metabolism, processing data for spinosad was extrapolated to spinetoram without the provision of further data. An appropriate factor for processing spinetoram apple fruit to dry apple pomace, is 12.4, based on previous studies on spinosad. It is therefore recommended that an MRL of 1mg/kg be set for spinetoram in dry apple pomace.

Animal commodity MRLs
Dry apple pomace can comprise up to 20% of the diet of livestock and poultry. Based on a feeding study in which Holstein dairy cows were dosed once per day (37.55 ppm) for 29 consecutive days by gelatin capsules containing 86% XDE-175-J and XDE-175-L, residues were determined to be highest in perirenal fat (16.5 mg/kg). Based on a maximum animal feeding level of 0.02 ppm in the diet and a residue definition of spinetoram of "Sum of Ethyl-spinosyn-J and Ethyl-spinosyn-L", the predicted residues in milk, muscle, liver, kidney and fats were all below LOQ (0.01 mg/kg). The establishment of MRLs at the analytical limits of quantification based on the provided method is therefore considered appropriate. Although residues were seen to concentrate in cream in comparison with milk reflecting the fat solubility of spinetoram, predicted residues in milk fats are also below LOQ.

Although a consumption figure of 20% for dry apple pomace has also been used for the determination of the dietary burden for poultry, advice from the NSW Department of Primary Industries suggests that apple pomace is only fed to poultry at a maximum of 5% of the diet. In current OECD guidelines it is not fed at all to poultry[1]. In the absence of a poultry transfer study, a poultry metabolism study, in which poultry were dosed with either XDE-175-J or XDE-175-L at 10 ppm, was used to estimate residues from feeding XDE-175 at 0.02 ppm, the maximum feeding level from poultry being fed dry apple pomace at 20% of the diet. The predicted residues in muscle, fat, skin with fat, liver and eggs were all below LOQ (0.01 mg/kg). The establishment

[1] OECD. Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Series on Testing and Assessment: Number 64. Series on Pesticides: Number 32. Guidance Document on Overview Of residue Chemistry Studies. ENV/JM/MONO(2006)32.
http://www.olis.oecd.org/olis/2006doc.nsf/LinkTo/NT00003EC2/$FILE/JT03215494

of MRLs at the analytical limits of quantification based on the provided method is therefore considered appropriate.

On the basis of the results of these studies, it is appropriate to establish the following animal commodity MRLs for spinetoram:

Compound	Food		MRL (mg/kg)
Spinetoram	MO 0105	Edible offal (mammalian)	*0.01
	PE 0112	Eggs	*0.01
	MM 0095	Meat (mammalian) [in the fat]	*0.01
	ML 0106	Milks	*0.01
	FM 0183	Milk fats	*0.01
	PO 0111	Poultry, edible offal of	*0.01
	PM 0110	Poultry meat (in the fat)	*0.01

Estimated dietary intake

The chronic dietary exposure to spinetoram 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 spinetoram is equivalent to 0.5% of the ADI.

It is concluded that the chronic dietary exposure of spinetoram is acceptable and residues in food will not pose an undue hazard to the safety of people.

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 acute exposure (24 hour period) to chemical residues in food.

An acute reference dose has not been established for spinetoram. Therefore, a NESTI calculation cannot be undertaken at this time.

Bioaccumulation potential

XDE-175-J has a K_{ow} logP = 4.09 (pH 7, 19^{o}C) and XDE-175-L has a K_{ow} logP = 4.49 (pH 7, 19^{o}C) suggesting some fat solubility. Spinetoram is sparingly soluble in water with much greater solubilities in polar organic solvents such as acetone. The K_{ow} log P values at pH 7 are greater than the cut-off designating a chemical as fat soluble (log P = 3)[3]. In the lactating cow transfer study, spinetoram residues in composite fat were up to 29x higher than in muscle indicating the potential for bioaccumulation in the fat. The MRL for spinetoram in meat was therefore established on an "in-the-fat" basis. In addition residues were concentrated in cream in comparison with milk, reflecting the fat solubility of spinetoram. A separate MRL was therefore set for milk fats.

[2] Guidelines for predicting dietary intake of pesticide residues, WHO, 1997.
[3] Pesticide Residues In Food – 2005, Report pp. 27-31 (JMPR).

Spray drift

Chemical residues can be deposited onto nearby animal feed sources (*e.g.* cereal hays or pasture) through spray drift. Depending on the magnitude of the residue in the feed, animals could develop tissue or milk residues that violate domestic MRLs and/or residue tolerances of trading partners. Since some export markets for Australian meat (e.g. Japan) do not have MRLs in place, it must be assumed that residues of spinetoram in animal commodities exported to those markets must be non-detectable. The limit of quantitation (LOQ) is normally used as the threshold in these circumstances.

In the case of spinetoram the target tissue for compliance is cattle fat. In the animal transfer study, a feeding level of 37.55 ppm gave a highest residue of 16.524 mg/kg in perirenal fat. A feeding level of 0.0227 ppm would therefore be required for residues in perirenal fat to be at the LOQ (0.01 mg/kg).

Spray drift modelling was conducted using AgDRIFT for airblast application. A maximum feeding level of 0.0227 ppm was used in the calculation. Using 1500 kg dry matter per hectare as a minimum yield for pasture, means that a drift of 0.0341g a.i./ha can be tolerated.

If application of spinetoram is carried out at 100g a.i/ha (the maximum use rate for pome fruit with an assumed spray volume of 2000L), a down-wind no spray zone of 134 -136m is necessary for residues to be below the maximum feeding level of 0.0227 ppm in a 1500 kg /ha dry matter pasture.

If application of spinetoram is carried out at 75g a.i/ha (the maximum use rate for stone fruit with an assumed spray volume of 2000L), a down-wind no spray zone of 106 -108m is necessary for residues to be below the maximum feeding level in a 1500 kg /ha dry matter pasture.

The following restraints are to be included on the label:

"DO NOT APPLY WHEN THERE ARE LIVESTOCK, PASTURE OR ANY LAND THAT IS PRODUCING FEED FOR LIVESTOCK WITHIN 150m DOWNWIND OF THE APPLICATION AREA."

"DO NOT APPLY FROM AIRCRAFT."

Recommendations

The following MRLs are recommended:

Table 1

Compound	Food		MRL (mg/kg)
ADD: Spinetoram	MO 0105	Edible offal (mammalian)	*0.01
	PE 0112	Eggs	*0.01
	MM 0095	Meat (mammalian) [in the fat]	*0.01
	ML 0106	Milks	*0.01
	FM 0183	Milk fats	*0.01
	PO 0111	Poultry, edible offal of	*0.01
	PM 0110	Poultry meat (in the fat)	*0.01
	FP 0009	Pome Fruit	0.1

	FS 0012	Stone Fruit	0.2

Table 3

Compound	Residue
ADD: Spinetoram	"Sum of Ethyl-spinosyn-J and Ethyl-spinosyn-L".

Table 4

Compound	Animal feed commodity		MRL (mg/kg)
ADD: Spinetoram	AB 0226	Apple pomace, dry	1

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

Harvest: POME FRUIT: DO NOT HARVEST FOR 7 DAYS AFTER THE LAST APPLICATION.
STONE FRUIT: DO NOT HARVEST FOR 3 DAYS AFTER THE LAST APPLICATION.

Grazing: DO NOT GRAZE ANY TREATED AREA OR CUT FOR STOCKFOOD.

The following label restraints are also applicable:

"DO NOT APPLY WHEN LIVESTOCK, PASTURE OR ANY LAND THAT IS PRODUCING FEED FOR LIVESTOCK ARE WITHIN 150m DOWNWIND OF THE APPLICATION AREA."

"DO NOT APPLY FROM AIRCRAFT."

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Commodities exported

Pome fruit and stone fruit are major export commodities, considered as part of this application.

Destination and Value of Exports

Pome Fruit

The total exports of Australian apples in 2002/03 amounted to 32.48 kt, with a value of $41.37 m.[4] The main export markets include the United Kingdom, India, Malaysia, Taiwan, Sri Lanka and Singapore. The total exports of Australian pears in 2002/03 amounted to 17.65 kt, with a value of $22.41 m.[4] The main export markets include Singapore, Malaysia, Indonesia, Canada and New Zealand.

Stone Fruit

The total exports of Australian peaches in 2002/03 amounted to 1.587 kt, with a value of $5.54 m.[4] The main export markets include Taiwan, Singapore, U.A.E. and Hong Kong. The total exports of Australian nectarines in 2002/03 amounted to 7.959 kt, with a value of $22.66 m.[2] The main export markets include Taiwan and Hong Kong.

The total exports of Australian apricots in 2002/03 amounted to 228 tonnes, with a value of $0.80 m.[4] The main export markets include Hong Kong and U.A.E. The total exports of Australian plums in 2002/03 amounted to 10,773 tonnes, with a value of $26.22 m.[2] The main export markets include Hong Kong, Taiwan, Singapore and Malaysia. The total exports of Australian cherries in 2002/03 amounted to 1,720 tonnes, with a value of $13.74 m.[2] The main export markets include Hong Kong, Taiwan and Singapore.

Overseas Registration Status

Spinetoram formulations are relatively new to the world insecticide market. Registrations for Delegate Insecticide have been granted in Canada and USA, and in New Zealand for use on pome fruit.

Codex Alimentarius Commission and overseas MRLs/tolerances

Spinetoram has not been considered by Codex. It is on the schedule of the 2008 Joint FAO/WHO Meeting on Pesticide Residues. However, the following overseas residue MRLs/ tolerances have been established for spinetoram in pome and stone fruit:

Commodity	Country	Tolerance, mg/kg
Pome Fruits	Canada	0.1
	U.S.A.	0.2
	New Zealand	0.05
Stone Fruits	Canada	0.2
	U.S.A.	0.2
	New Zealand	0.05

[4] The Australian Horticulture Statistics Handbook 2004

Potential Risk to Australian Export Trade

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

The relevant commodities in the current application are exported and detectable residues are expected to occur above the standards of key export markets. The applicant is proposing to mitigate this risk to trade by inclusion of the following trade advice statement on the label:

"CAUTION: Delegate Insecticide may leave detectable chemical residues in harvested produce. Overseas markets may not have appropriate residue tolerances in place or may have established tolerances which are lower than Australian maximum residue limits. Some crops for export to these destinations may require a longer harvesting withholding period. If you are using this product on crops destined for export, please contact your exporter for advice."

A determination of undue prejudice to trade or commerce will be made following the completion of the trade consultation process.

Conclusions

Quantifiable residues of spinetoram are likely to occur in pome and stone fruit when Delegate Insecticide is used as directed. Residues in animal commodities from livestock and poultry fed on apple pomace are expected to be below the limits of quantification.

The APVMA welcomes comment with regard to whether the proposed use of Delegate Insecticide on pome and stone fruit to control codling moth, lightbrown apple moth and oriental fruit moth poses an undue prejudice to Australia's export trade in these commodities.

Formulation, Packaging, Transport, Storage and Retailing
Spinetoram is expected to be manufactured overseas and the product Delegate Insecticide is expected to be formulated overseas and imported into Australia. It is expected to be supplied in 1-5 kg HDPE jerry cans, or foil-lined sachets (0.5 to 2.5 kg).

Use pattern
The product is intended for the control of codling moth, light brown apple moth and oriental fruit moth in pome and stone fruit as shown in Table 1.
In the case of crops, they are to be carefully monitored for eggs and larvae of pest species by regular field scouting. Target sprays are applied against mature eggs and newly-hatched larvae. Repeat applications are to be applied at 14 day intervals as new infestations occur unless otherwise directed.

Table 1: Application to tree crops

Crop	Pest	Rate	Critical comments
Pome fruit, including apples, pears and nashi pears	Codling moth (*Cydia pomonella*)	10 –20 g/100 L + Wetting agent	Use the higher rate when adverse weather conditions may cause the spray interval to become greater than 14 days, or in high pressure conditions, in orchards with a history of damage or when mating disruption does not provide adequate protection.
	Lightbrown apple moth (*Epiphyas postvittana*) Oriental fruit moth (*Grapholita molesta*)	10 or 15 g/100 L + Wetting agent	Use the higher rate under high pest pressure or when adverse weather conditions may cause the spray interval to become greater than 14 days.
Stone fruit	Lightbrown apple moth Oriental fruit moth		

No more than four applications to any fruit crop are to be made in any one season.
The withholding periods specified on the label are as follows:
Pome fruit: Do not harvest for 7 days after the last application. Do not cut for stock feed.
Stone fruit: Do not harvest for 3 days after the last application
A crop re-entry period was not specified on the proposed label.
When mixing, the spray tank is to be half-filled with water and the appropriate amount of GF-1640 added. Tank filling is to be completed. Thorough agitation is to be applied.
The directions for use include directions for dilute spraying and concentrate spraying.
Operational matters: Using high-volume spray equipment (mistblowers), usually with 2000-3500 L spray tanks, growers may spray at around 1000 -2000 L of spray solution/ha. Maximum contact with the product (active ingredient) as suggested by the applicant, would involve the case of a 2000 L tank being used per ha, which requires a maximum of 300 g of product per

operation. With high-volume spraying, it is unlikely that more than 5 ha per working day will be covered, particularly with the time taken to fill the tank with water.
No. of mixing/loading operations = 5/day at maximum
Application = 5 ha using 1.5kg of product/day
Concentrate sprayers (mistblowers) with 200-600 L tanks are more commonly used, with about 200 L/ha water volume/ha. At 3 ha per tank, the number of ha per day can be up to around 10-12, which requires *a maximum of 4 mixing/loading operations*. As most orchards are < 20 ha, use of this product on average would be for about 10 days/year.
No. of mixing/loading operations = 4/day at maximum
Application = 12 ha using 3.6 kg of product/day at a maximum

Exposure profile
Because it is most likely that the product will be manufactured and formulated overseas and imported into Australia and because the product is not intended for the home garden and public exposure, pome and stone fruit growers and their employees will be the main users of the product.

Workers may be exposed to the product when opening containers, mixing/loading, and during application and cleaning up spills and equipment. The main route of exposure to the product dust or spray will be ocular or inhalation in the case of dust and dermal, inhalation or ocular in the case of the spray.

Quantitative worker exposure estimates were considered unnecessary because of the absence of toxicity in a 28 day dermal repeat dose study using 1000 mg/kg bw/day of spinetoram and because of low acute oral (LD_{50} > 5000 mg/kg bw), dermal (LD_{50} > 5000 mg/kg bw) and inhalation toxicity (LD_{50} > 5280 mg/m^3) of the product and the absence of evidence that spinetoram is genotoxic, teratogenic or carcinogenic.

The crops intended for treatment are tree crops and post-application exposure is unlikely if the sprayed product is allowed to dry *in situ* before contact is made with trees.

Risks to workers during use and recommended PPE
The only apparent acute exposure risk to workers is slight eye irritation and the use of personal protective equipment (PPE) is not considered necessary.

Exposure During Re-entry
Based on the low toxicological profile of spinetoram and the estimated low post-application exposure for workers undertaking crop management activities, a specific re-entry statement was not recommended.

Hazardous classification
With the available toxicology information, the OCS classified spinetoram and the product containing it according to the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004) and determined that the following risk phrases are to apply:

Spinetoram: R43 May cause sensitisation by skin contact

Recommendations for Safe Use
Users should follow the instructions and Safety Directions on the product label.

Conclusion

The registration of spinetoram at 250 g/kg in Delegate Insecticide, as a water dispersible granule formulation, for use on pome and stone fruits, for the control of codling moth, lightbrown apple moth and oriental fruit moth, is supported.

Delegate Insecticide can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product MSDS.

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ENVIRONMENTAL ASSESSMENT

Environmental Fate

Physicochemical Degradation

Hydrolysis

Radiolabelled spinetoram components XDE-175 J and L studied separately are stable to hydrolysis at pH values of 5-7, but hydrolyse slightly at pH 9. A degradation rate constant could not be calculated for XDE-175-J due to the very slow rate of hydrolysis, however, a minor transformation product, N-demethyl-175-J was observed at a maximum concentration of 6.7% of the applied radiocarbon. XDE-175-L demonstrated a higher rate of hydrolysis with DT_{50} and DT_{90} values of 154 and 512 days, respectively. In addition, a major transformation product, N-demethyl-175-L, was observed at a maximum concentration of 11.9% of the applied radiocarbon. Hydrolysis is not considered to be a major route of degradation of spinetoram in the environment.

Aqueous photolysis

Radiolabelled spinetoram components XDE-175 J and L, applied separately to neutrally buffered HPLC grade water, degraded rapidly under continuous exposure to artificial sunlight, with half-lives of 0.5 and 0.3 days at 40°N latitude in summer sunlight calculated for the 2 factors, respectively. Major transformation products were an unidentified degradate from XDE-175-J (known as MW813) and N-demethyl-175-L, which reached levels >10% of the applied radiocarbon, but declined to ≤1% by the end of the 21 day study, with half-lives of 6.8 and 0.5 days, respectively. In addition to the major degradates, numerous minor transformation products were detected. Aqueous photolysis is considered to be a major route of degradation of spinetoram in the environment.

Soil photolysis

Photolytic breakdown of radiolabelled spinetoram components XDE-175 J and L separately applied on a loam soil surface under continuous exposure to artificial sunlight for 15-18 days resulted in the production of multiple low level metabolites, each less than 7% of the applied radiocarbon. The study was performed under non-sterile conditions, but metabolism in the dark controls was factored into the half-life calculations. The calculated half-lives of 116 and 18 days for XDE-175-J and XDE-175-L, respectively, reported in the study did not appear to reflect the data. Recalculations performed by DEWHA gave half-lives of 24 and 10.5 days for the 2 spinetoram factors, respectively, at 40°N latitude in summer sunlight. Based on these results, soil photolysis is considered to contribute to the degradation of spinetoram in the environment.

Photodegradation in Air

Based on the low vapour pressure and low Henry's constant for XDE-175, and the estimated atmospheric half-lives of 0.03 and 0.02 days for XDE-175-J and XDE-175-L, respectively, no significant residues will be present in the air.

Biodegradation

Aerobic soil metabolism

The degradation of radiolabelled spinetoram components XDE-175 J and L were separately studied for up to 1 year under dark laboratory conditions on 4 US soils with low organic carbon and pH values ranging from 5.8-8.1. The components were applied at rates significantly higher than the proposed maximum application rate. Both parent components rapidly degraded during the first 50 days of the study, but this rate declined significantly, with low levels (0-3% of applied radiocarbon) of XDE-175-J and XDE-175-L detected at study termination. The major

metabolites N-demethyl-175-J and N-demethyl-175-L rapidly increased at rates mirroring parent degradation, to maximum levels and then degraded themselves to moderate (5.1-46% of applied radiocarbon for N-demethyl-175-J) and low levels (0-9.7% of applied radiocarbon for N-demethyl-175-L). The results indicate that the metabolites degrade further to numerous unidentified low level metabolites as non-extractable residues and to CO_2. The parent half-lives of ranged from 8-29 d and 3-17 d for for the J and L factors, respectively, while the metabolite half-lives ranged from 32-273 d and 5-88 d for N-demethyl-175-J and N-demethyl-175-L, respectively.

Anaerobic soil metabolism

The applicant requested a data waiver from provision of an anaerobic soil metabolism study based on 2 criteria. Firstly, that the degradation of spinetoram in soil and water is well understood and that a laboratory anaerobic soil study would be unlikely to generate novel information. Secondly, that the objective of this study, according to Canadian guidelines, is to determine biotransformations under anaerobic soil conditions where the insecticide is for use on flooded or poorly drained areas, or when assessment indicates potential migration to subsoil. In addition, the Canadian guidelines state that anaerobic biotransformation studies are not required when anaerobic sediment/water studies are done. DEWHA/APVMA accepted the arguments presented by the applicant and agreed to waive this study as part of the data requirements for this application.

Aerobic aquatic metabolism

Separate aerobic metabolism studies of pond water/sediment systems in darkness showed that radiolabelled spinetoram components XDE-175 J and L moved mainly from the water column to the sediment. Both parents degraded slowly over the 30 day study period, with 75.6 and 76.7% of the applied radiocarbon remaining in the sediment as XDE-175-J and XDE-175-L, respectively. While the J component remaining in the water column declined from 6.2-1.7% of the applied radiocarbon during the study period, the L component did not appear to degrade in water. The minor transformation products, N-demethyl-175-J, O-demethyl-175-L and N-demethyl-175-L at maximum levels of ~10% of the applied radiocarbon were detected in sediment only, with non-extractable residues identified as another significant dissipation pathway. Unidentified radiocarbon partitioned mainly to sediment but was also detected in the water column at low levels. The calculated DT50 values for the system were 117 and 124 for XDE-175-J and XDE-175-L, respectively. Degradation was not observed for the metabolites. The results should be treated with caution as they are much longer than the 30 day test period. In addition, analysis of the system indicated that the pond water was slightly aerobic, but the sediment was anaerobic.

Anaerobic aquatic metabolism

Separate anaerobic metabolism studies of pond water/sediment systems in darkness showed that radiolabelled spinetoram components XDE-175 J and L moved mainly from the water column to the sediment. Both parents degraded slowly over the 365 day study period, with 50.5 and 75.1% of the applied radiocarbon remaining in the sediment as XDE-175-J and XDE-175-L, respectively. Both the J and L parent componentsremaining in their respective water columns degraded from 8.4 and 3.5% to 0.4 and 0.9%, respectively, of applied radiocarbon. Two major transformation products, O-demethyl-175-J and O-demethyl-175-L were detected at Day 0 and maintained increasing levels to 26.7 and 10.4% of the applied radiocarbon by study termination, with non-extractable residues also increased in the sediment to 12.1 and 7.6%. Unidentified radiocarbon levels were unstable and generally low (<6% for J and <3% for L factors). The calculated system DT_{50} values were 385 and 1386 for XDE-175-J and XDE-175-L, respectively. Degradation was not observed for the metabolites.

Mobility

Soil adsorption/desorption

The adsorption/desorption of radiolabelled spinetoram components XDE-175 J and L and their respective N-demethyl metabolites was studied on 4 US soils, including a loamy sand, silt loam, sandy loam and a loam, all with low organic carbon, and a pH range of 5.8-8.1. The adsorption constants (k_{oc}) ranged from 1800-24648 and 3936-43873 for the parent J and L factors, respectively, while ranges of 1631-12127 and 3718-30918 were estimated for the J and L metabolites, respectively. Some degree of non-proportional concentration dependence was observed in XDE-175-J but not for XDE-175-L. The desorption k_d values were higher than the respective adsorption constants, indicating some degree of irreversible sorption. Based on McCall's Mobility classification, the mobility of XDE-175-J and its major metabolite N-demethyl-XDE-175-J is considered low to immobile, depending on the soil type. The mobility of XDE-175-L and N-demethyl-XDE-175-L was lower, ranging from slight to immobile.

Field dissipation

Aquatic field dissipation

A liquid suspension concentrate formulation was applied at 7.1 and 7.4 g ac/ha, in a spray drift simulation, to the respective water surface of shallow ponds at each of 2 US sites. Pond water was analysed over 42 hours after application and residues of spinetoram and its metabolites determined from water column average concentrations. No spinetoram parent or metabolite residues were detected in the sediment at any time. Analysis of the water column at both sites indicated rapid degradation of spinetoram during the first hour post-application, after which the lack of UVB radiation during night-time most likely results in a significant reduction in the degradation rate, resulting in a biphasic degradation pattern over the course of the study. A very similar degradation pattern is observed at both sites, even with significantly different extinction depths. The respective N-demethylated metabolites were formed and dissipated rapidly following application. The calculated half-lives for the parent J and L componentswere 0.04 and 0.03 days, respectively, at both sites, while the DT_{90} values were significantly longer at 2.1-2.6 and 1.3-1.7 days, respectively. The metabolite half-lives were calculated at 1.2-2.1 days and 1.0-1.4 days for N-demethyl-175-J and N-demethyl-175-L, respectively.

Terrestrial field dissipation

A liquid suspension concentrate formulation was applied 512 and 654 g ac/ha to bare ground plots at 2 US sites, respectively. Soils were sampled for periods up to 358 days after application and residues of spinetoram and its metabolites determined. Both parents dissipated steadily and rapidly at both sites to undetectable levels by ~Day 300 for the parent J factor, and by 30-36 days for the parent L factor. Most residues were confined to the upper 15 cm of soil with only a few detections at 15-30 cm at one of the sites. Very low levels (<10 g/ha) of the metabolite N-demethyl-175-L were observed, which degraded rapidly. N-demethyl-175-J, however, was present at maximum levels of 93 and 161 g/ha but degraded slowly to 6.7 and 36.7 g/ha by study termination, at the respective sites. The calculated half-lives for the parent J and L componentswere 3-5 and 1-2 days, respectively, while the DT_{90} values were 9-16 and 2-8 days, respectively. The calculated half-life and DT_{90} values for N-demethyl-175-L were 1-36 and 4-121 days, respectively, and 10-165 and 230-548 days, respectively for N-demethyl-175-J.

Bioaccumulation

Two studies were presented on the bioaccumulation of spinetoram in rainbow trout, one each for the parent J and L factors. For each study, the bioconcentration and biotransformation of the appropriate radiolabelled spinetoram component was investigated under flow-through conditions in low and high level studies, with a 27 and 28 day exposure periods, followed by 2 and 28 day elimination periods, respectively. Spinetoram was taken up by the fish constantly during the study period, and steady state conditions could not be identified with any confidence. Spinetoram depurated over time from fish after exposure such that after 21 days in uncontaminated water, 88-90% of the Day 28 radioactivity was depurated from whole fish. The parent L component appears to have a significantly higher concentrating effect with whole fish, with Bioconcentration factors (BCF) values of 344 and 348 for the low and high level studies, respectively, compared to BCF values of 46 and 86 for the J component. This result also indicates that test substance concentration results in a greater uptake rate for the L component only, although the elimination rate constants were similar. Both components were rapidly metabolised with km values of 0.71 and 0.45 for XDE-175-J and XDE-175-L, respectively, yielding 2-4 metabolites that are more polar than the parents. However, elimination of metabolites was 2-3× slower than metabolism for both parents. Based on the ratings of Mensinck et al. (1995), the spinetoram J and L components are slightly and moderately concentrating, respectively, to fish.

Plant residues

The separate applications of the parent J and L components as emulsifiable concentrates to mature apple trees demonstrated over 30 days that the majority of residues remained on the surface of apples and leaves (most) and could be removed by rinsing with acetonitrile. A higher proportion of XDE-175-L compared to XDE-175-J was partitioned to the peel, indicating it is more photolabile. Over time, it was apparent that the test substance, particularly the L factor, was more difficult to retrieve from rinsing, with greater proportions of total radiation either bound to the surface or translocated into the peel. Comparison of covered and uncovered samples demonstrated abiotic photolysis to be a major route of degradation, although the results indicated metabolism also contributed to degradation. A decrease in parent components and increase in respective metabolites in the rinses and peel was observed during the study, with metabolites reaching maximum levels by at least Day 7 before degrading themselves. Decline in XDE-175-L metabolites was particularly rapid. However, up to 20% of the total applied radioactivity was present as XDE-175-J in the Day 30 rinses and peel extractions, indicating relatively persistent residues. The greater persistence of the J component is thought to be due to the absence of a double bond in the macrolide ring, making it more resistant to cleavage and therefore photolytically stable.

Environmental Effects

Avian

There were 6 avian studies presented for assessment – an acute oral toxicity, acute dietary toxicity, and effects on reproduction study each for the Mallard duck and Northern bobwhite quail, using technical grade spinetoram.

The survival of mallard ducks and bobwhite quails was not affected by single oral or dietary applications of spinetoram, resulting in LC_{50} values exceeding 5600 mg ac/kg diet and DT_{50} values greater than 2250 mg/kg bw. However, sublethal effects were observed in both species from oral and dietary exposure to spinetoram. Significant effects on bodyweight were observed for bobwhite quails in the oral and dietary studies, resulting in NOEC values of 292 and 1780 mg ac/kg diet, respectively. In addition, clinical signs of toxicity were observed at the highest test concentration in the dietary test, but all birds recovered by test termination. Mallards were

sensitive to dietary exposure of spinetoram, with effects on body weight and feed consumption, resulting in a NOEC of 1780 mg ac/kg diet. Although no significant effects were reported in mallard ducks orally exposed to spinetoram, female body weight changes appear substantially lower than the controls at test substance applications ≥1125 mg ac/kg bw. Statistical analyses were not performed on the data.

Mallard ducks and bobwhite quail are not sensitive to chronic exposure of spinetoram, as demonstrated by the lack of effects on body weight, feed consumption, and reproductive performance. The resultant NOEC value for both species was 1000 ppm in diet, the highest concentration tested.

Fish

There were 4 fish studies presented for assessment – one acute static study with rainbow trout, one acute flow-through study with the bluegill sunfish, and two flow-through chronic studies with the fathead and sheepshead minnow. Technical grade spinetoram was used in all tests.

Rainbow trout were not acutely sensitive to applications of spinetoram, with <10% mortality after exposure to a water accommodated fraction of the test substance, and no sublethal effects, resulting in an LC50 >3.46 mg ac/L and a NOEC of 3.46 mg ac/L. Complete mortality was observed in bluegill sunfish exposed to the highest tested concentration of 4.12 mg ac/L, resulting in a 96 h LC50 of 2.69 mg ac/L. Sublethal effects were reported in fish exposed to 2.03 mg ac/L, however, the number of fish affected is not stated. Based on acceptable mortality, NOEC value of 2.03 mg ac/L was determined.

No test substance related effects of chronic toxicity in adults and their offspring were observed in sheepshead minnows exposed over 37 days to concentrations up to 1.53 mg ac/L. However, significant chronic effects on reproduction and body length were observed in fathead minnows, but the most sensitive endpoint was wet body weight, where a dose-responsive reduction was observed, resulting in a NOEC of 0.182 mg ac/L.

Aquatic invertebrates

There were 6 aquatic invertebrate studies presented for assessment – one acute static and 2 chronic studies (one static and one flow-through) studies with daphnids, one acute and one chronic flow-through study with mysid shrimps, and one acute flow-through study with eastern oysters. Technical grade spinetoram was used in all tests.

Daphnid mobility was not affected from acute exposure under static conditions, resulting in a 48 h EC_{50} of >3.17 mg ac/L and a 48 h NOEC of 3.17 mg ac/L. Likewise, chronic exposure to spinetoram under static renewal of light exposed solutions had no effect on mobility, reproduction or growth, resulting in a 21 day NOEC of 0.951 µg ac/L. However, under flow-through conditions, a dose-responsive reduction in survival was observed at test substance concentrations ≥0.121 µg ac/L, resulting in a NOEC of 0.0624 µg ac/L. The other biological parameters were not statistically analysed at concentrations significantly affecting survival, but it is clear that significant effects on reproduction and possibly dry weight are also occurring at these concentrations.

Acute sensitivity of spinetoram was observed in mysid shrimps, with complete mortality at concentrations ≥0.628 mg ac/L, resulting in an 96 h LC_{50} of 0.355 mg ac/L and a NOEC of 0.0764 mg ac/L. Sublethal effects including floating, lethargy and erratic swimming were also observed. The complete lack of shell growth in eastern oysters exposed to the highest test concentration of 1.2 mg ac/L also demonstrated an acute sensitivity to the test substance, with a resultant 96 h EC50 of 0.393 mg ac/L. In addition, the reduction in shell growth compared to the controls was dose-responsive, with significant reductions occurring at concentrations ≥0.170 mg ac/L. Mysids were sensitive to chronic exposure of spinetoram, with survival and reproduction

being the most sensitive and dose-responsive endpoints. The resultant NOEC value for both endpoints was 0.0352 mg ac/L.

Benthic invertebrates

There was one chronic chironomid study presented for assessment using technical grade spinetoram. Chironomids were sensitive to chronic exposure of the test substance as demonstrated by significant effects of emergence at spinetoram concentrations ≥171 µg ac/kg, resulting in a NOEC value of 97.2 µg ac/kg dry sediment. The EC50 for emergence (calculated by Probit analysis) was 263 µg ac/kg dry sediment. No significant effects on male or female development were observed.

Algae

There were 5 acute studies presented for assessment – one each for green algae, blue-green algae, freshwater diatoms, marine diatoms, and duckweed. Technical grade spinetoram was used in all tests.

Blue-green algae and duckweed were not acutely sensitive to spinetoram up to the highest concentrations tested, resulting in EC_{50} and NOEC values for biomass and growth rate of >12.3 mg ac/L and 12.3 mg ac/L, respectively, for the former, and >14.2 mg ac/L and 14.2 mg ac/L, respectively, for the latter.

Generally dose-responsive and significant reductions in mean cell densities, biomass and growth rate compared to the control were observed in all other species. The freshwater diatom was the most sensitive species, with biomass and growth EC_{50} values of 66 and 117 µg ac/L, respectively, and a NOEC value (growth and biomass) of 7.41 µg ac/L.

Terrestrial invertebrates

There were 11 terrestrial invertebrate studies presented for assessment – 5 with the technical grade of spinetoram, and 6 with the proposed formulation Delegate Insecticide.

Honeybees were acutely sensitive to contact and oral exposure of spinetoram, with mortality increasing in a dose-responsive manner to complete mortality below the highest concentrations tested, resulting in LD_{50} values of 0.024 and 0.11 µg ac/bee for the 2 tests, respectively. However, acute exposure of honey bees to the test substance as foliage residues (aged for 3-24 h) resulted in no adverse effects at the test concentration of 110 g ac/ha.

The absence of mortality and the lack of significant effects on weight and reproduction demonstrate the insensitivity of earthworms to acute and chronic exposure of the test substance. The 14 day EC_{50} and NOEC values were >1000 and 1000 mg ac/kg dry soil, respectively, while the 56 day NOEC was 18.65 mg ac/kg dry soil, the maximum rate tested.

Application of the test substance to parasitic wasps in a Tier 1 dose-response study resulted in dose-responsive mortality effects, with a calculated EC_{50} of 0.0885 g ac/ha, and an Abbott corrected mortality exceeding the 50% trigger value at 0.2 g ac/ha. Effects on fecundity on surviving wasps were not reported as significant. Based on the results of the Tier 1 test, parasitic wasps were exposed to higher rates of spinetoram as residues on barley plants (instead of glass slides) in a Tier 2 extended study. Dose-responsive mortality was again observed, with a calculated EC_{50} of 0.671 g ac/ha. Effects on fecundity were tested at ≤0.5 g ac/ha for which no differences were observed..

Ladybird beetles were exposed to spinetoram in an extended Tier 2 study to determine whether ageing of the test substance had an effect on toxicity. Four applications of the test substance were

made over 42 days and the beetles immediately exposed after the final application. However, as no effect ≥50% trigger value was observed (although a dose-response effect was seen) up to the highest application rate of 4×150 g ac/ha, the results further aging bioassays (leaves aged for 7 and 14 days after the final application), have not been reported. In addition, no significant effects on fecundity were reported.

Rove beetles were also exposed to spinetoram in an extended aged residue study at maximum application rates of 4×150 g ac/ha applications over 42 days, with the results of the additional ageing bioassays reported. Dose-responsive mortality effects were apparent in beetles exposed immediately after the final application, with significant effects observed at the highest application rate and on fecundity at all rates (LOEC = 2×43.8 + 2×23.6 g ac/ha). However, mortality effects from exposure to aged residues were neither dose-responsive, nor significant (NOEC = 4×150 g ac/ha). Significant effects to fecundity from exposure to aged residues were observed (LOEC = 4×75 g ac/ha), but these became less apparent with increasing age of the residues.

Application of the test substance to predatory mites in a Tier 1 dose-response study resulted in dose-responsive mortality effects, with a calculated EC_{50} of 0.138 g ac/ha, and an Abbott corrected mortality exceeding the 50% trigger value at 0.4 g ac/ha. Effects on fecundity on surviving mites were not reported as significant. Based on the results of the Tier 1 test, the mites were exposed to higher rates of spinetoram as residues on bean leaves (instead of glass slides) in a Tier 2 extended study. Dose-responsive mortality was again observed, with a calculated EC_{50} of 0.476 g ac/ha, and mortality NOEC of 0.063 g ac/ha. Effects on fecundity were not dose responsive and the only significant result was not considered to be biologically significant.

Soil microorganisms

There was one soil microflora study presented for assessment. Technical grade spinetoram was used in the test.

Exposure of the test substance to microorganisms resulted in no significant toxic effects in glucose simulated respiration or nitrogen transformation up to the highest concentration tested (5× maximum annual field rate or 4 mg ac/kg dry soil). It can be concluded that spinetoram is not inhibitory to microbial activity in the soil at likely field rates.

Terrestrial plants

There was one terrestrial study presented for assessment. The formulation Delegate Insecticide was used in the test.

The spinetoram formulation, when applied at the highest proposed seasonal application rate of 150 g ac/ha, caused no significant (based on 25% effect criteria) effects to the emergence, growth and vegetative vigour for any of the 10 species tested. A range of positive and negative effects were observed, with no negative effect exceeding 10% compared to the control. Symptoms of phytotoxicity were absent, except for very small levels in 2 species.

Risk Assessment

Spinetoram will most likely be applied using airblast ground equipment to stone and pome fruit. Environmental exposure is expected to primarily involve the crop and underlying soil, with aquatic exposure also possible through spray drift and runoff.

Spinetoram is not expected to be persistent or mobile in soil nor persist as residues on leaves. In aquatic environments, spinetoram has been shown to preferentially partition to sediment, however, under daylight conditions rapid dissipation in the water column is expected prior to the occurrence of any partitioning.

The toxicity to terrestrial vertebrates, aquatic plants, terrestrial plants and soil microorganisms is low. Spinetoram is acutely toxic to some aquatic species, but the risk from single applications at the maximum proposed rate is acceptable. In addition, cumulative effects are not expected due to rapid degradation in aqueous environments. Honeybees and some beneficial insects, such as the parasitic wasp and the predatory mite, are particularly sensitive from exposure, at well below the maximum application rate of spinetoram. The risk is high, indicating that use of the product is not complementary with use in all integrated pest management (IPM) situations. The label contains suitable warning statements for protection of livestock (honeybees) and warnings advising of appropriate risk management for use in IPM situations.

EFFICACY AND CROP SAFETY ASSESSMENT

Justification for use and Mode of Action

Spinetoram is a new active constituent from the spinosyn group of insecticides. Spinosyns are nicotinic acetylcholine receptor agonists (allosteric) in Group 5A for Insecticides Resistance Management, which act through contact or ingestion and are particularly effective against lepidopteran pests.

DELEGATE INSECTICIDE (*DELEGATE*), a water dispersible granule product containing 250g/kg spinetoram, offers control of codling moth (*Cydia pomonella* (CM)), lightbrown apple moth (*Epiphyas postvittana* (LBAM)) and oriental fruit moth (*Grapholita molesta* (OFM)) in pome fruit, and lightbrown apple moth and oriental fruit moth in stone fruit. *DELEGATE* offers an alternative mode of action to assist with resistance management of codling moth and oriental fruit moth.

Registration is supported by Australian agricultural authorities.

Proposed use pattern

DELEGATE will be applied to pome fruit, including apples, pears and nashi pears, at an application rate of 10 to 20g/100L water, or to stone fruit, at an application rate of 10 or 15 g/100L, with optional addition of a non-ionic wetting agent, applied at label rate, to improve control under less than ideal application conditions.

Use is proposed for all State and Territories.

It is proposed that the product will be available in 1-5 kg HDPE jerry cans, or foil-lined sachets (0.5 to 2.5 kg).

The following Withholding Period statements are recommended for the product:

Harvest:
Pome fruit: DO NOT harvest for 7 days after the last application.
Stone fruit: DO NOT harvest for 3 days after the last application.
Grazing:
DO NOT graze any treated area or cut for stockfood.

The following Protection of livestock statement is included on the label:
Bee safety: Delegate is dangerous to bees and will kill bees foraging in the crop being treated or in hives which are over-sprayed or reached by spray drift. Once the spray deposit has dried, foraging bees should not be affected when using spray volumes of 2000L/ha or less. However, if using spray volumes greater than 2000L/ha, it is possible that foraging bees may be affected for some days after spraying.

Evaluation of efficacy

The data presented supported the claims for control of codling moth (CM), lightbrown apple moth (LBAM) and oriental fruit moth (OFM) in pome fruit, and lightbrown apple moth and oriental fruit moth in stone fruit. Detailed efficacy data was presented including results from a range of Australian field trials.

This submission included 15 trials in total. 10 were conducted on pome fruit (4 against CM on apples; 2 against LBAM on apples; 2 against CM & LBAM on apples; 2 against CM & OFM on

pears) and 5 were conducted on stone fruit (3 against OFM on peaches, 1 against LBAM on apricots, 1 against LBAM on plums). The trial designs were generally sound, and appropriate statistical analyses were conducted.

The efficacy claim of commercially acceptable control of CM, LBAM and OFM in pome and stone fruit using the proposed rates of *DELEGATE* is generally supported by the body of results presented in the 15 trial submissions.

Crop safety

The fact that no phytotoxic effects have been noted on a wide range of crops, even when above-label rates were applied, leads to the conclusion that when used in accordance with label conditions, *DELEGATE* will not cause crop damage.

Resistance management

Spinetoram is a new active constituent from the spinosyn group of insecticides. Spinosyns are nicotinic acetylcholine receptor agonists (allosteric) in Group 5A for Insecticides Resistance Management (RM) purposes. For resistance management no more than 4 applications of spinetoram are allowed to any fruit crop in any one season.

Conclusion

Sufficient statistically analysed data from suitably designed and scientifically conducted trials has been presented to substantiate the claims for use shown on the proposed label. The data demonstrate that the product *DELEGATE* should be suitable for control of codling moth (*Cydia pomonella* (CM)), lightbrown apple moth (*Epiphyas postvittana* (LBAM)) and oriental fruit moth (*Grapholita molesta* (OFM)) in pome fruit, and lightbrown apple moth and oriental fruit moth in stone fruit, when used in accordance with the proposed label instructions and Good Agricultural Practice (GAP).

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

Delegate*

Insecticide

ACTIVE CONSTITUENT: **250 g/kg SPINETORAM**

GROUP	5A	INSECTICIDE

For the control of codling moth, lightbrown apple moth and oriental fruit moth in pome and stone fruit as specified in the Directions for Use.

Net Contents: 500g, 800 g, 1 Kg, 2.5 Kg, 5 Kg

Dow AgroSciences Australia Limited
A.B.N. 24 003 771 659
Level 5, 20 Rodborough Road
Frenchs Forest NSW 2086
www.dowagrosciences.com.au

APVMA Approval No 61717/800g/0808

CUSTOMER SERVICE TOLL FREE 1- 800 700 096

* Trademark of Dow AgroSciences

DIRECTIONS FOR USE

RESTRAINTS

DO NOT make more than 4 applications to any FRUIT crop in any one season (see the RESISTANCE statement).

DO NOT apply when livestock, pasture or any land that is producing feed for livestock are within 150m downwind of the application area.

DO NOT apply from aircraft.

SPRAYING TREE CROPS: *In the following table, all rates are given for dilute spraying where spray volumes may vary in order to obtain good coverage to the point of run-off. For concentrate spraying refer to the "CONCENTRATE SPRAYING" section on this label.*

CROP	PEST	RATE	CRITICAL COMMENTS
FOR ALL TREE CROPS: Carefully monitor crops for eggs and larvae of pest species by regular field scouting. Target sprays against mature eggs and newly-hatched larvae. Apply repeat applications at 14 day intervals as egg hatch continues or as new infestations occur unless otherwise directed in the CRITICAL COMMENTS.			
Pome fruit, *including*: apples, pears and nashi pears	Codling moth	10 – 20 g/ 100 L + wetting agent*	Use higher rates when adverse weather conditions may cause the spray interval to become greater than 14 days, or in high pressure conditions, in orchards with a history of damage or when mating disruption does not provide adequate protection.
	Lightbrown apple moth and Oriental fruit moth	10 or 15g/ 100 L + wetting agent*	Use the higher rate under high pest pressure or when adverse weather conditions may cause the spray interval to become greater than 14 days.
Stone fruit	Lightbrown apple moth and Oriental fruit moth		
*Aa Addition of a non-ionic wetting agent at its label rate, such as Agral® at 10 mL/100 L, may improve control under less than ideal application conditions.			
PE PEST NAMES: Codling moth: *Cydia pomonella*; Lightbrown apple moth: *Epiphyas postvittana*; Oriental fruit moth: *Grapholita molesta.*			

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

WITHHOLDING PERIODS:

POME FRUIT: **DO NOT HARVEST FOR 7 DAYS AFTER THE LAST APPLICATION**

STONE FRUIT: **DO NOT HARVEST FOR 3 DAYS AFTER THE LAST APPLICATION**

DO NOT GRAZE ANY TREATED AREA OR CUT FOR STOCKFOOD

PRECAUTION: Delegate Insecticide may leave detectable chemical residues in harvested produce. Overseas markets may not have appropriate residue tolerances in place or may have established tolerances which are lower than Australian maximum residue limits. Some crops for export to these destinations may require a longer harvesting withholding period. If you are using this product on crops destined for export, please contact your exporter for advice.

General Instructions

GROUP 5A INSECTICIDE

For insecticide resistance management, Delegate is a Group 5A insecticide. Some naturally occurring insect biotypes resistant to Delegate and other Group 5A insecticides may exist through normal genetic variability in any insect population. The resistant individuals can eventually dominate the insect population if Delegate and other Group 5A insecticides are used repeatedly. The effectiveness of Delegate on resistant individuals could be significantly reduced. Since occurrence of resistant individuals is difficult to detect prior to use, Dow AgroSciences Australia Limited accepts no liability for any losses that may result from the failure of Delegate to control resistant insects. Delegate may be subject to specific resistance management strategies. For further information contact your local supplier, Dow AgroSciences representative or local agricultural department agronomist.

MIXING
Half-fill the spray tank with water, add the appropriate amount of accurately measured Delegate Insecticide, then complete filling the tank.
Ensure thorough agitation by mechanical or hydraulic action at all times during mixing and application.
Use only clean water within the range pH 5-9 to dilute Delegate Insecticide.

APPLICATION
Thorough coverage of the crop is essential. Do not apply when conditions are unsuitable for water-based spray applications. Avoid high temperature, strong winds, inversion conditions, imminent rain or any conditions that may reduce the quality of spray coverage or result in drift from the target area. Techniques to minimise drift should be employed at all times when applying sprays to, or near, sensitive areas.

DILUTE SPRAYING
Use a sprayer designed to apply high volumes of water up to the point of run-off and matched to the crop being sprayed. Set up and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient water to cover the crop to the point of first run-off. Avoid excessive run-off. The required water volume may be determined by applying different test volumes, using different settings on the sprayer, from industry guidelines or expert advice. Add the amount of product specified in the Directions for Use table for each 100 L of water. Spray to the point of runoff. If volume to be applied is <1000 L/ha then use the low volume (concentrate) application method for calculation of chemical rate. For volumes > 1000 L/ha use dilute spray rate.

CONCENTRATE SPRAYING
Use a sprayer designed and set up for concentrate spraying (that is, a sprayer which applies water volumes less than those required to reach the point of run-off) and matched to the crop being sprayed. Set up and operate the sprayer to achieve even coverage throughout the crop canopy using your chosen water volume. Determine an appropriate dilute spray volume (see DILUTE SPRAYING above) for the crop canopy. Consult your local adviser, agronomist or Department of Agriculture to determine this volume. This is needed to calculate the concentrate mixing rate. The mixing rate for concentrate spraying can then be calculated in the following way:

CONCENTRATE SPRAYING EXAMPLE
1. Dilute spray volume as determined above: e.g. 1500 L/ha
2. Your chosen concentrate spray volume: e.g. 500 L/ha
3. The concentration factor is 3X (1500 / 500)
4. If the dilute label rate is 10g/100 L, then the concentrate rate becomes 3 X 10, *i.e*. 30g/100 L of concentrate spray

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

RAINFASTNESS
Rain can wash Delegate Insecticide from treated plant surfaces and result in reduced insect control. Avoid making spray applications if rain is expected before the spray can dry completely.

CLEANING SPRAY EQUIPMENT
After using Delegate Insecticide empty the tank and completely drain the system. Rinse the tank, pumps, lines, hoses, filters and nozzles by circulating clean water through the system. Drain and repeat the rinsing procedure twice.

PROTECTION OF LIVESTOCK
Bee safety: Delegate is dangerous to bees and will kill bees foraging in the crop being treated or in hives which are over-sprayed or reached by spray drift. Once the spray deposit has dried, foraging bees should not be affected when using spray volumes of 2000L/ha or less. However, if using spray volumes greater than 2000L/ha, it is possible that foraging bees may be affected for some days after spraying.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Risk to non-target insects. Spinetoram may have adverse effects on some non-target beneficials, such as foliage dwelling predators, particularly where IPM is practiced.
Toxic to aquatic invertebrates and algae. Do not allow the product or used containers to enter dams, ponds, waterways or drains. Do not allow irrigation water from treated paddocks to enter adjacent pastures, crops or water supplies. Do not apply in strong winds, inversion conditions or any other conditions that may result in drift onto adjacent pastures, crops or water supplies.

STORAGE AND DISPOSAL
Store in the closed, original container in a cool well-ventilated area. DO NOT store for prolonged periods in direct sunlight. DO NOT store near food, feedstuffs, fertilisers or seed.

This container can be recycled if it is clean, dry, free or visible residues and has the ***drum****MUSTER* logo visible. Triple or pressure rinse containers for disposal. Dispose of rinsate by adding it to the spray tank. Do not dispose of undiluted chemicals on site. Wash outside of the container and the cap. Store cleaned container in a sheltered place with the cap removed. It will then be acceptable for recycling at any ***drum****MUSTER* collection or similar container management program site. The cap should not be replaced but may be taken separately. If not recycling break, crush or puncture and bury empty packaging in a local authority landfill. If no landfill is available, bury the packaging below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should not be burnt.

SMALL SPILL MANAGEMENT
Sweep up material and contain in a refuse vessel for disposal in the same manner as for the container (see STORAGE AND DISPOSAL section).

SAFETY DIRECTIONS
Will irritate the eyes. Avoid contact with eyes. Wash hands after use.

FIRST AID
If poisoning occurs, contact a doctor or Poisons Information Centre (Phone: Australia 13 11 26).

MATERIAL SAFETY DATA SHEET
Additional information is listed in the Material Safety Data Sheet for **DELEGATE INSECTICIDE**, which is available from Dow AgroSciences on request. Call Customer Service Toll Free on 1-800 700 096 or visit www.dowagrosciences.com.au

NOTICE:
Seller warrants that the product conforms to its chemical description and is reasonably fit for the purposes stated on the label when used in accordance with the directions for use. No warranty of merchantability or fitness for a particular purpose express or implied, extends to the use of the product contrary to label instructions, or under off-label permits not endorsed by Dow AgroSciences, or under abnormal conditions.

EMERGENCY RESPONSE
(All Hours)
RING FROM ANYWHERE IN AUSTRALIA
1-800 033 882
(LOCAL CALL FEE ONLY)

IN A TRANSPORT EMERGENCY ONLY
DIAL 000
FOR POLICE OR FIRE BRIGADE

Barcode
for stock
identification

APVMA Approval No. 61717/B/0808

APVMA Approval No. 61717/500 g/0808 not commercially available
APVMA Approval No. 61717/1.5 kg/0808 not commercially available
APVMA Approval No. 61717/2.5 kg/0808 not commercially available
APVMA Approval No. 61717/5 kg/0808 not commercially available

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product.
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer.
Chronic	Of long duration.
Codex MRL	Internationally published standard maximum residue limit.
Desorption	Removal of an absorbed material from 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	Water repelling
Leaching	Removal of a compound by use of a solvent.
Log P_{ow}	Log to base 10 of octonol water partioning co-efficient.
Metabolism	The conversion of food into energy
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

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