

**Public Release Summary
on**

**Evaluation of the new active
METHOXYFENOZIDE**

in the product

PRODIGY 240 SC INSECTICIDE

**National Registration Authority
for Agricultural and Veterinary Chemicals**

May 2002

**Canberra
Australia**

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Pat Robinson
National Registration Authority for Agricultural and Veterinary Chemicals
PO Box E 240
KINGSTON ACT 2604

Ph: (02) 6271 6320
Fax: (02) 6272 3218
e-mail probinso@nra.gov.au

FOREWORD

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) 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 NRA works in close cooperation with advisory agencies, including the Department of Health and Ageing (Chemicals and Non-prescription Medicines Branch), Environment Australia (Risk Assessment and Policy Section), the National Occupational Health and Safety Commission and State departments of agriculture and environment.

The NRA 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 NRA 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 NRA's publications *Ag Manual: The Requirements Manual for Agricultural Chemicals* and *Ag Requirements Series: Guidelines for Registering Agricultural Chemicals*.

This Public Release Summary is intended as a brief overview of the assessment that has been completed by the NRA 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 NRA. Alternatively, the reports can be viewed at the NRA Library, 22 Brisbane Ave, Barton, ACT.

The NRA welcomes comment on the usefulness of this publication and suggestions for further improvement. Comments should be submitted to the Executive Manager—Registration, National Registration Authority for Agricultural and Veterinary Chemicals, PO Box E240, Kingston, ACT 2604.

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LIST OF ABBREVIATIONS AND ACRONYMS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ANZFA	Australian New Zealand Food Authority
bw	body weight
CCPR	Codex Committee on Pesticide Residues
d	day
DAT	days after treatment
DM	Dry Matter
DT₅₀	Time taken for 50% of the concentration to dissipate, half life
EA	Environment Australia
EC₅₀	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
F	female
FAO	Food and Agriculture Organisation of the United Nations
g	gram
GAP	Good Agricultural Practice
GC-MSD	Gas Chromatography with Mass Selective Detector
h	hour
ha	hectare
HPLC	High Pressure Liquid Chromatography <i>or</i> High Performance Liquid Chromatography
HPLC-UV	High Performance Liquid Chromatography with Ultra-Violet Detector
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
IOBC	International Organisation for Biological Control
IPM	Integrated Pest Management
IRM	Insecticide Resistance Management
JMPR	Joint FAO/WHO Meeting on Pesticide residues
kg	kilogram
K_{oc}	adsorption or desorption coefficients based on organic carbon content
kt	kilotonne
L	litre
LC₅₀	concentration that kills 50% of the test population of organisms
LD₅₀	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOEC	lowest observed effect concentration
LOQ	Limit of Quantitation – level at which residues can be quantified
M	male
MFL	maximum feeding level
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimate of Dietary Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	no observable effect concentration/level

NOHSC	National Occupational Health & Safety Commission
%OC	percentage organic carbon
%OM	percentage organic material
PHI	Pre-Harvest Interval
pka	acid dissociation constant
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
s	second
SC	Suspension Concentrate
SPE	solid phase extraction
STMR	Supervised Trials Median Residue
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TRR	Total Radioactive Residues
T-Value	a value used to determine the First Aid Instructions for chemical products that contain two or more poisons
mg	microgram
VMD	Volume Median Diameter
WHO	World Health Organisation
WHP	Withholding Period

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INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Prodigy 240 SC Insecticide (Prodigy) containing the chemical methoxyfenozide to control *Helicoverpa* spp., rough bollworm and cotton looper in cotton and *Helicoverpa* spp. in tomatoes.

Responses to public consultation will be considered prior to registration of the product. They will be taken into account by the NRA 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 methoxyfenozide, covering toxicology, occupational health and safety aspects, environmental impacts and residues in food, are available from the NRA on request. They can also be viewed at the NRA library located at the NRA's offices, 22 Brisbane Ave, Barton, ACT.

Written comments should be received by the NRA by 4 June 2002. They should be addressed to :

Pat Robinson
Senior Product Evaluator
Agricultural Chemicals Evaluation Section
National Registration Authority
PO Box E240
KINGSTON ACT 2604
Fax 02 6272 3218
E-mail: probinso@nra.gov.au

Applicant

Bayer Australia Limited

Product details

Prodigy will be marketed as a suspension concentrate formulation containing 240g/L methoxyfenozide.

Prodigy will be formulated in Australia using imported active constituent.

Bayer Australia Limited intend to market Prodigy in all States and Territories.

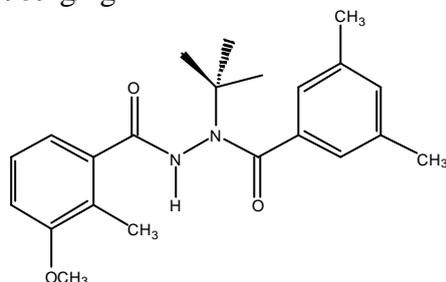
CHEMISTRY AND MANUFACTURE

ACTIVE CONSTITUENT

The active constituent methoxyfenozide is manufactured by Rohm and Haas Company, Strada Stalale 11, Kilometro 109.200, 24050, Mozzanica, Italy.

Chemical Characteristics of the Active Constituent

Common Name:	Methoxyfenozide (ISO/SA approved)
IUPAC Name:	N-tert-butyl-N'-(3-methoxy-o-toluoyl)-3,5-xylolhydrazide
CA Name:	Benzoic acid, 3-methoxy-2-methyl-2-(3,5-dimethylbenzoyl)-2-(1,1-dimethylethyl)hydrazide
CAS Number:	161050-58-4
Manufacturer's Code:	RH-2485, RH-112485
Minimum Purity	959 g/kg
Structure:	



Methoxyfenozide

$C_{22}H_{28}N_2O_3$
Mol. Wt.: 368.47

Molecular formula:	$C_{22}H_{28}N_2O_3$
Molecular weight:	368.5 amu or dalton

Physical and Chemical Properties of Pure Active Constituent

Physical state:	Solid
Colour:	White powder
Odour:	Faint
Melting point:	203.8 – 206.4 °C
Boiling point:	Decomposes at > 240 °C
Solubility in water:	3.3 ppm
Solubility in organic solvents: (g/L at 20 °C)	n-heptane 1.87 xylene 3.38 1,2-dichloroethane 36.72 methanol 192.92 2-propanol 50.22 acetone 126.88 butyl acetate 18.76
Dissociation constant:	none
pH	neutral
Octanol/ Water partition coefficient:	Log $P_{0/w}$ = 3.72

Vapour pressure:

$<1.3 \times 10^{-5} \text{ Pa}$

Volatility:	0.04 % (20 – 97 °C)
	0.04 % (97 – 158 °C)
	0.4 % (158 – 210 °C)
Flammability:	None
Explosive properties:	None
Oxidising/reduction properties:	None
Corrosion characteristics:	Carbon steel 3.3 mL /year
	Aluminium 0.4 mL /year
	Red Brass 0.1 mL /year
Storage stability:	No change in content over 12 months at 25 °C
Chemical family:	Insecticide
Chemical type:	Insect growth regulator
Mode of Action	Upon ingestion, methoxyfenozide mimics the ecdysone receptor of lepidopteran larvae, producing a premature, lethal moult

Summary of the NRA's Evaluation of Methoxyfenozide

The Chemistry and Residues Evaluation Section of the NRA has evaluated the chemistry aspects of methoxyfenozide (manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable. On the basis of the data provided it is proposed that the following minimum compositional standard be established for methoxyfenozide:

Active constituent

Methoxyfenozide	Not less than 959 g/kg
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PRODUCT

Distinguishing name:	<i>Prodigy 240 SC Insecticide</i>
Formulation type:	Suspension Concentrate (SC)
Active constituent concentration:	Methoxyfenozide, 240 g/kg

Physical and Chemical Properties of the Product

Appearance:	Light brown liquid suspension
Odour:	Weak characteristic smell
Density or specific gravity:	1.06 at 20 °C
Acidity, alkalinity or pH value:	pH = 6.6
Viscosity:	? = 67.7×10^{-3}
Flash point:	> 100 °C
Flammability/autoignition:	Exhibits an ignition temperature of 455 °C
Storage stability:	Stability data provided by the applicant supports a shelf life of 2 years when the product is stored below 30 °C.

Conclusion

Based on a review of the chemistry and manufacturing details provided by the applicant, the NRA is satisfied that Prodigy will be manufactured to consistent specifications using a source of active approved by the NRA, and will be stable under normal conditions of storage for two years.

TOXICOLOGICAL ASSESSMENT

The toxicological database for methoxyfenozide, 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 at which no adverse health effects in humans would be expected.

Summary of Toxicology

Methoxyfenozide is closely related to tebufenozide, a compound which has been registered for use as an insecticide in Australia for several years.

Following oral administration, methoxyfenozide is rapidly and moderately well absorbed. It is extensively metabolised and is eliminated from the body in bile, and to a lesser extent in urine. Methoxyfenozide has low acute oral, dermal and inhalation toxicity. It is a slight eye irritant, but not a skin irritant or a skin sensitiser. Acute toxicity studies on a formulation similar to the product Prodigy 240 SC Insecticide gave a comparable profile as for methoxyfenozide, except that it was no longer an eye irritant.

Mild blood thinning (anaemia) and increased weight and microscopic abnormalities in the liver were the dominant features of toxicity in repeat dose studies. The anaemia was characterised by the deposition of a brown pigment, probably resulting from the breakdown of blood components, in the spleen and liver and an increase in red blood cell production in bone marrow. In whole–of–life studies, there was no evidence of an increased frequency of cancer. This result was supported by several other studies, which showed that methoxyfenozide does not damage genetic material.

Methoxyfenozide had no effect on reproduction in rats and no developmental effects were observed in rat or rabbit foetuses at doses that were not toxic to the mother.

Metabolism and Toxicokinetics

After a single oral dose of methoxyfenozide, peak blood or plasma levels were achieved within 15–30 minutes, with the liver having the highest levels of absorbed methoxyfenozide. Methoxyfenozide was recovered in urine (5–10%) and faeces (90–95%). The majority of the dose was excreted within 24 hours, or within 12 hours in bile–cannulated animals. Based on recovery of

the dose in bile, urine, tissues and the residual carcass, 62–70% of the dose was systemically absorbed. The metabolism of methoxyfenozide in rats was rapid with only a small amount of the dose released as CO₂ or volatile compounds. Metabolism of methoxyfenozide involves demethylation, glucuronidation and hydroxylation.

Following dermal exposure of male rats to formulations containing 0.025–2.5% methoxyfenozide, up to 3% of the dose was absorbed and 3–10% was in/on the skin.

Orally administered methoxyfenozide in lactating goats produced only low levels in milk, blood and other tissues. In fat, muscle and milk the major metabolite was the parent compound.

Acute Studies

Methoxyfenozide has low acute oral (LD₅₀ >5000 mg/kg) toxicity in mice and rats and low dermal (LD₅₀ >5000 mg/kg) and inhalational (LC₅₀ >4300 mg/kg) toxicity in rats, was a slight eye irritant but not a skin irritant in rabbits or a skin sensitiser in guinea-pigs. The demethylated metabolite of methoxyfenozide (RH-117,236) also has low acute oral toxicity (LD₅₀ >5000 mg/kg bw) in mice.

A formulation similar to the product Prodigy 240 SC Insecticide has low acute oral toxicity (LD₅₀ >5000 mg/kg bw) in mice and rats, is of low dermal (LD₅₀ >2000 mg/kg bw) toxicity in rats and showed no signs of toxicity at a maximum aerosol concentration of 900 mg/m³ in rats. RH-112,485 2F is not a skin or eye irritant in rabbits or a skin sensitiser in guinea pigs.

Short-Term Studies

Methoxyfenozide (0, 75, 300 and 1000 mg/kg bw/day) was applied dermally to rats for 6 hours on 20 occasions over a 28 day period. There were no mortalities or treatment-related clinical signs. Food consumption was significantly reduced in males at 1000 mg/kg bw/day during the last week of the study. There were no treatment-related effects on body weight, haematology and clinical chemistry parameters. There were no treatment-related pathological findings.

Male dogs were fed methoxyfenozide (0 and 30000 ppm) for 4 weeks, followed by a 4 week recovery period. There were no treatment-related mortalities or effects on body weight or food consumption. Increases in methaemoglobin, mean red cell volume, mean cell haemoglobin and platelet count, and decreases in erythrocyte count, haemoglobin and haematocrit after 4 weeks of treatment were approaching normal levels after a 4 week recovery period.

Mice were fed methoxyfenozide (0, 70, 700, 2500 and 7000 ppm) for 3 months. There were no treatment-related mortalities, clinical signs or effects on food consumption, haematological or clinical chemistry parameters, organ weights or histopathological changes observed at any dose, and no effects on body weights in animals of either sex up to and including 2500 ppm. A reduction in mean body weight and cumulative weight gain in males and females at 7000 ppm was most likely treatment-related. The NOEL for this study was 2500 ppm (equal to 428 mg/kg bw/day in males and 589 mg/kg bw/day in females).

Rats were fed methoxyfenozide (0, 50, 250, 1000, 5000 and 20,000 ppm) for 3 months. There were no treatment-related mortalities or clinical signs and no effects on mean body weights, body weight changes or food consumption, haematological, clinical chemistry or urinalysis parameters. Ophthalmology, organ weights, gross pathology and histopathology were unaffected by treatment.

Relative liver weights were increased in males at 5000 and 20,000ppm and in females at 20,000 ppm, with periportal hepatocellular hypertrophy observed at 5000 and 20,000 ppm in animals of both sexes. Absolute liver weights were slightly increased in the same dose groups. The NOEL for this study was 1000 ppm (equal to 69 mg/kg bw/day in males and 72 mg/kg bw/day in females).

Dogs fed methoxyfenozide (0, 15, 50, 500 and 5000 ppm) for 13 weeks. There were no treatment–related deaths, clinical signs, changes to body weight or body weight gain or food consumption observed after 13 weeks at doses up to and including 5000 ppm, or after extended treatment for 6 weeks at 15000 ppm in animals initially treated for 13 weeks at 15 ppm. Haematological, clinical chemistry and urinalysis or ophthalmological parameters were not affected by treatment with methoxyfenozide. There were no treatment–related microscopic changes in any organ or tissue after 13 weeks at doses up to and including 5000 ppm, or after extended treatment for 6 weeks at 15000 ppm in animals initially treated for 13 weeks at 15 ppm. The NOEL for this study was 5000 ppm (equal to 198 mg/kg bw/day in males and 209 mg/kg bw/day in females).

Long-term Studies

Mice were fed methoxyfenozide (0, 70, 2800 and 7000 ppm) for 78 weeks. There was no difference in survival between groups and there were no treatment–related clinical signs or changes in body weight, food consumption or differential leucocyte counts. There were no treatment–related changes in organ weight, pathological findings or the incidence of tumours in any tissues. The NOEL is 7000 ppm (equal to 1020 mg/kg bw/day in males and 1354 mg/kg bw/day in females).

Rats were fed methoxyfenozide (0, 200, 8000 and 20000 ppm) for 89–99 weeks. The survival of males at 20000 ppm was reduced, due to increased severity of chronic progressive glomerulonephropathy. There were no treatment–related clinical signs. Mean cumulative body weight gain was reduced in females at 20000 ppm from week 49, but there were no treatment–related changes in food consumption. Erythrocyte count, haemoglobin and haematocrit levels were significantly reduced in rats at 8000 and/or 20000 ppm and methaemoglobin and platelet count were increased at 20000 ppm. Gamma glutamyl transferase was increased and bilirubin decreased for the majority of the study at 8000 and/or 20000 ppm. Liver weights were increased at 8000 ppm and above. An increased incidence in hyperplasia of the renal pelvic epithelium occurred at 20000 ppm. Chronic progressive glomerulonephropathy for all study animals was increased in rats at 20000 ppm and females at 8000 ppm. Incidences of peri–portal hepatocellular hypertrophy, thyroid follicular hypertrophy and altered colloid in the thyroid were increased at 8000 ppm and above. There were no treatment–related effects on the incidence of adenomas or carcinomas. The NOEL is 200 ppm (equal to 10 mg/kg bw/day in males and 12 mg/kg bw/day in females).

Dogs were fed methoxyfenozide (0, 60, 300, 3000 and 30000 ppm) for 52 weeks. There were no mortalities or treatment–related clinical signs. Cumulative body weight gain was reduced in dogs at 30000 ppm, but there were no effects on food consumption. Increases in methaemoglobin, platelet count, and decreases in erythrocyte count, haemoglobin and haematocrit occurred from 3000 ppm. Bilirubin was increased in dogs at 3000 and 30000 ppm and potassium was increased in dogs at 30000 ppm. Mean red cell volume was increased in males at 30000 ppm and leucocyte count was increased in females at 30000 ppm. Thyroid gland and liver weights were increased at 30000 ppm. An increase in pigmentation, which was likely to be haemosiderin, of liver and spleen cells and an increase in cellularity of rib and sternum bone marrow, characterised by a decrease in fat vacuoles

and an increase in erythrocytes and erythrocyte precursors occurred in dogs at 30000 ppm. The NOEL is 300 ppm (equal to 10 mg/kg bw/day in males and 13 mg/kg bw/day in females).

Reproduction and Developmental Studies

Rats were fed methoxyfenozide (0, 200, 2000 and 20000 ppm) over 2 generations. There were no treatment-related mortalities or clinical signs of toxicity in adult rats in either generation. Cumulative body weight gain was slightly reduced in F₀ males at 20000 ppm over the entire study period. There were no treatment-related effects in either generation on oestrous cycles, mating and fertility indices, gestation length, parturition, pup survival, body weight or sex ratio. The mean age of vaginal patency was increased in F₁ and F₂ female pups at 20000 ppm, but there were no treatment-related effects on preputial separation of males or on anogenital distance of either sex. Liver weights were increased in adult rats at 20000 ppm from both generations. Peri-portal to mid-zonal hepatocellular hypertrophy was observed in all adult rats at 20000 ppm, with a lower incidence in females at 2000 ppm. The incidence of pigmentation (F₀ females) and vacuolation of (adult F₁ males) of liver cells was increased at 20000 ppm. There were no treatment-related effects on sperm motility, morphology, epididymal sperm count/concentration and testicular spermatid count. The NOEL for adults is 200 ppm (equal to 15 mg/kg bw/day in males and 18 mg/kg bw/day in females) and for neonatal toxicity is 2000 ppm (equal to 153 mg/kg bw/day in males and 181 mg/kg bw/day in females).

Methoxyfenozide (0, 100, 300 and 1000 mg/kg bw/day) was administered orally to rats and rabbits on days 6–15 and days 7–19 of gestation, respectively. There were no treatment-related mortalities or clinical effects observed, and there were no adverse effects on mothers or foetuses.

In a single-generation study in rats fed buprofezin in the diet at 10, 100 or 1,000 ppm, reduced pup-weight gain and increased relative liver weight were observed in animals of both sexes at 1000 ppm. The NOEL in this study was 100 ppm, equal to 6.4 mg/kg bw/day and 8.9 mg/kg bw/day for males and females respectively.

Genotoxicity Studies

Methoxyfenozide (50–500 µg/mL) was not mutagenic in *Salmonella typhimurium* strains and did not induce an increase in the number of cells with chromosome aberrations or cause gene mutation at the HGPRT locus in cultured Chinese Hamster Ovary (CHO) cells. In an *in vivo* study, methoxyfenozide was not genotoxic in mouse bone marrow cells after single oral doses of 500, 2500 and 5000 mg/kg. The demethylated metabolite of methoxyfenozide was not mutagenic in *Salmonella typhimurium* strains in the absence (50–1600 µg/plate) or presence (50–3000 µg/plate) of metabolic activation.

RH-112,485 2F (50–5000 µg/plate) was not mutagenic in *Salmonella typhimurium* strains or genotoxic after single oral doses of 1250, 2500 and 5000 mg/kg bw in mouse bone marrow cells.

Special studies

There were no mortalities in rats given methoxyfenozide as a single (0, 500, 1000 and 2000 mg/kg bw) or repeated dose for 3 months (0, 200, 2000 and 20000 ppm). There were no

treatment–related effects on Functional Observational Batteries (FOB), motor activity assessments or pathological findings.

PUBLIC HEALTH STANDARDS

Poisons Scheduling

The National Drugs and Poisons Schedule Committee (NDPSC) considered the toxicity of the product and its active ingredients and assessed the necessary controls to be implemented under States' poisons regulations to prevent the occurrence of poisoning. On the basis of its toxicity, the NDPSC has recommended that methoxyfenozide need not be included in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP).

NOEL/ADI

The lowest NOEL obtained for methoxyfenozide was 10 mg/kg bw/day in an 89–99 week dietary rat study and a 52 week dietary dog study. Since the toxicology database was extensive, a safety factor of 100 was used to establish an ADI of 0.1 mg/kg bw/day.

Conclusion

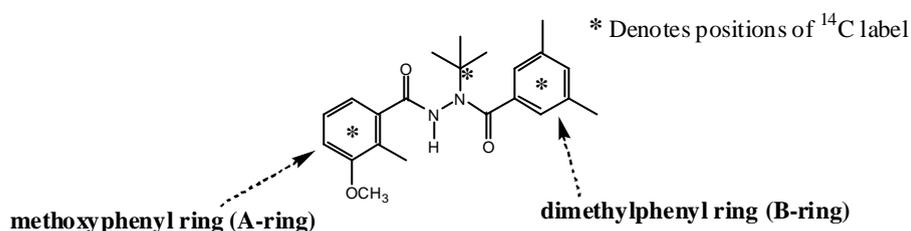
Based on an assessment of the toxicology, it is considered that there should be no adverse effects on human health from the use of this product when used in accordance with the label directions.

RESIDUES ASSESSMENT

Data concerning residues in cotton and tomato, metabolism in plants and animals, analytical methodology, storage stability, processing and chemistry were considered as part of the residue evaluation of the application.

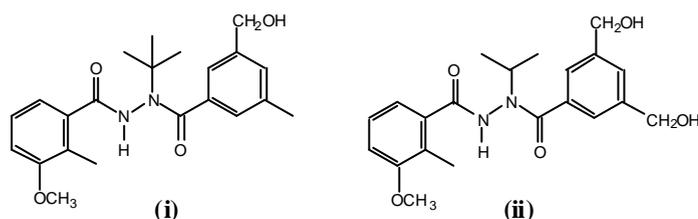
Metabolism

Metabolism studies conducted in apples, cotton, grapes and rice were provided for evaluation. Methoxyfenozide *per se* was the most significant component of the total radioactive residue (TRR) in all crops. Test substances used in metabolism studies included methoxyfenozide labelled with ^{14}C at the tertiary t-butyl carbon atom (t-butyl) or uniformly on the methoxyphenyl ring (A-ring) or dimethylphenyl ring-labelled (B-ring).



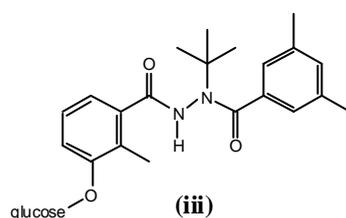
Radiolabelled test substance was applied twice to the foliage of field grown cotton as either t-butyl, A-ring or B-ring methoxyfenozide. Samples of mature bolls were collected 21 days after the second application. Transformation of the parent compound appeared to be negligible with no other metabolites found to be present, irrespective of the position of the radiolabel used in the experiment.

Field grown apples were treated with 2 foliar applications of ^{14}C -methoxyphenyl ring-labelled (A-ring) methoxyfenozide. Samples of apples and foliage were collected for analysis 0-69 days after the last treatment. Parent compound accounted for more than 90% of the TRR in apples sampled 14 and 36 days after treatment. Metabolites formed by oxidation of the B-ring methyl groups to the

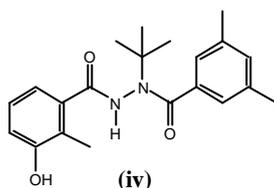


corresponding B-ring alcohol (i) and B-ring diol (ii) were present at less than 2% of the TRR each.

Field grown grapes were treated with 2 foliar applications of methoxyfenozide labelled with ^{14}C at the tertiary t-butyl carbon atom. Samples of grapes were harvested 27 days after the second application for characterisation of the radioactive residues. The parent compound accounted for approximately 80% of the TRR. Glucose conjugates of the A-ring phenol (iii) and B-ring alcohol were identified as minor metabolites.

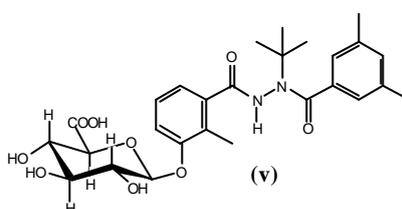


Paddy rice grown in screenhouse enclosures was treated with 2 applications of t-butyl-¹⁴C-labelled, ¹⁴C-methoxyphenyl ring-labelled (A-ring) or ¹⁴C-dimethylphenyl ring-labelled (B-ring) methoxyfenozide. Mature grain and straw was harvested for analysis 62 days after the second application. The parent compound accounted for around 65% of the TRR in grain and straw, irrespective of the position of the radiolabel used in the experiment. Several minor metabolites were identified, although none accounted for more than 5% of the TRR. Identified metabolites included the B-ring alcohol and diol species as well as the A-ring phenol (iv) and its glucose conjugate (iii).



The proposed metabolic pathways for all crops were broadly similar. The routes of metabolism included oxidation at the B-ring methyl group(s) to the corresponding alcohol, diol or carboxylic acid, demethylation on the A-ring to the corresponding phenol and glucose conjugation.

The metabolism of methoxyfenozide in rats was investigated using test substances labelled with ¹⁴C at either the tertiary t-butyl carbon atom or uniformly on the methoxyphenyl or dimethylphenyl rings. Results were similar irrespective of the position of the radiolabel. Methoxyfenozide was rapidly absorbed, metabolised and eliminated following oral administration. A total of 62-70% of the oral dose was systemically absorbed. Greater than 90% of the dose was excreted in feces with around 10% excreted in urine over the 5 days post-dosing. Around 70-80% of the dose was excreted in the feces and urine in the first 24 hours after dosing. Biliary excretion was identified as a major pathway of elimination. Concentrations of glucuronide conjugates in the bile were higher than in the feces suggesting possible deconjugation of metabolites prior to excretion and/or significant enterohepatic circulation. A total of 32 compounds were identified in excreta and bile. Unchanged parent compound was the most significant compound, although 7 metabolites in excreta accounted for 5% or more of the total dose individually. Important routes of metabolism included demethylation of the A-ring methoxy group to give the A-ring phenol (iv), hydroxylation of the A-ring, oxidation of the B-ring methyl group/s to form the alcohol or diol (i, ii) and glucuronide conjugation (v).



Laying hens were dosed orally for 7 consecutive days with methoxyfenozide labelled with ¹⁴C at either the tertiary t-butyl carbon atom or uniformly on the methoxyphenyl or dimethylphenyl rings. The parent compound was the most significant component of the TRR in fat and skin and the only component accounting for >10% of the TRR in those tissues. Methoxyfenozide was extensively metabolised in liver, kidney and eggs where the most significant component of the TRR was the glucuronide of the A-ring phenol (v).

Approximately 27-50% of the liver TRR was not extractable in organic solvents. The amount of radioactivity in the hexane fractions of liver and kidney from the t-butyl label dose group was approximately 10 times higher than the A-ring and B-ring hexane extracts. It was concluded that some of the t-butyl portion of the molecule was associated with fatty endogenous compounds, probably triglycerides.

Lactating goats were dosed orally for 7 consecutive days with methoxyfenozide labelled with ^{14}C at either the tertiary t-butyl carbon atom or uniformly on the methoxyphenyl or dimethylphenyl rings. Parent compound was the major component of the TRR in muscle, fat and milk accounting for up to 25%, 81% and 35% of the TRR respectively. The A-ring phenol glucuronide (v) was the most significant residue identified in liver and kidney (up to 29% and 42% respectively). Other metabolites that accounted for >5% of the TRR in kidney and liver were the A-ring phenol (iv), B-ring alcohol (i) and/or carboxylic acid and hydroxylated A-ring phenol glucuronide. Methoxyfenozide with glucuronide conjugation in the A-ring was a significant metabolite in loin muscle. Over 30% of the radioactivity in milk of animals dosed with t-butyl labelled test substance was found to be incorporated into lactose.

The metabolic pathways for methoxyfenozide in plants and animals were broadly similar although transformation was more extensive in animals. Important transformations in plants and animals included oxidation to alcohols, diols and carboxylic acids on the B-ring, demethylation to the A-ring phenol and conjugate formation. The A-ring phenol glucuronide was a significant metabolite in some animal tissues while the corresponding glucose conjugate was a minor metabolite in grapes and rice. Some cleaved species (cleavage of A and B rings) were observed in rats but they were minor metabolites. It is concluded that the metabolism of methoxyfenozide is adequately understood in representative plants and animals.

Analytical methods

Analytical methodology for the determination of methoxyfenozide in commodities of plant and animal origin were provided.

Residues in cotton seed and processed fractions are extracted with acidic methanol and the extract is cleaned up by a combination of solvent partitioning, column chromatography and solid phase extraction (SPE). Methoxyfenozide is determined by HPLC-UV with external standard calibration. Acceptable recoveries were demonstrated at a limit of quantitation of 0.01 mg/kg cotton seed, meal, hulls and oil. The validated limit of quantitation for gin trash was 0.05 mg/kg. Radiovalidation studies demonstrated adequate extraction of incurred residues.

Methoxyfenozide residues in tomatoes are determined in a similar manner to those in cotton. The method involves blending in acidic methanol followed by solvent partitioning, column chromatography, SPE and HPLC-UV determination. Acceptable recoveries in tomatoes were demonstrated at the LOQ of 0.02 mg/kg. The validated LOQ for tomato juice, puree and past was 0.2 mg/kg. Radiovalidation of the method showed adequate extraction efficiency for incurred residues.

Methodology was provided for separate determination of methoxyfenozide and the glucuronide metabolite in kidney and liver. The sample is extracted with acidic methanol and the extract is

divided into two portions. The first portion is subjected to solvent partition and then cleaned up by column chromatography and SPE. The second portion is subjected to two separate SPE clean-up steps. Methoxyfenozide and the glucuronide metabolite are determined in separate extracts by HPLC-MS using external standards. The LOQ/LOD for parent compound is 0.01/0.003 mg/kg. The LOQ/LOD for the metabolite is 0.02/0.006 mg/kg.

Methoxyfenozide residues in milk and muscle are extracted by Matrix Solid Phase Dispersion using C-18 silica. The extract is cleaned up by a combination of column chromatography and SPE with determination by HPLC-UV. The LOQ/LOD is 0.01/0.003 mg/kg.

Residues in fat are extracted with methanol and partitioned against hexane. The extract is cleaned up by a combination of column chromatography and SPE with determination by HPLC-UV. The LOQ/LOD is 0.01/0.003 mg/kg.

Analysis of samples containing incurred residues of radiolabelled methoxyfenozide from the goat metabolism study showed adequate extraction of the residue.

Storage stability

Samples of cotton seed were stored frozen for 8-21 months prior to analysis. Tomatoes were stored frozen for 2-7 months prior to analysis. Storage stability data for samples of cotton seed, gin trash oil and tomatoes were provided and indicate that residues do not degrade significantly when samples are stored frozen for 12-24 months. The results obtained in the residue trials are considered to be an accurate reflection of the residues present at sampling.

Residue definition

The major residue in all plant species and most animal tissues was the parent compound. The major residue observed in kidney and liver of lactating goats was a glucuronide conjugate of the parent compound. The glucuronide metabolite was not a significant metabolite in other tissues or milk. It was noted that the proposed liver and kidney residue definition in the US includes the metabolite (Federal Register, 5 July 2000, Volume 65, Number 129).

Based on the animal transfer study and an estimated maximum feeding level of 4 ppm in the diet residues of the glucuronide metabolite in liver and kidney are predicted to be 0.005 and 0.0008 mg/kg respectively. These levels are less than the LOQ and LOD of the analytical method respectively. Determination of the glucuronide metabolite increases the complexity of the analysis and the time required for analysis, as the two components cannot be determined in the same extract. Given the very low levels of the metabolite expected to be present in liver and kidney it is concluded that its inclusion in the residue definition is not warranted for the purposes of monitoring compliance with good agricultural practice.

Residue trials

Cotton

Six Australian trials and 3 US trials that were compatible with Australian GAP were provided for evaluation. Considering the Australian trials and the US trials (scaled results) as a single population, residues of methoxyfenozide 28 days after last application were <0.05, <0.05, <0.05, <0.05, 0.47, 0.50, 0.87, 1.13 and 1.79 mg/kg. An MRL of 3 mg/kg is recommended for cotton seed.

Tomatoes

Six Australian trials and 12 US trials that were compatible with Australian GAP were provided for evaluation. Combining the Australian and US trials gives residues of (median underlined) 0.06, 0.09, 0.12, 0.13, 0.14, 0.16, 0.16, 0.18, 0.19, 0.20, 0.21, 0.25, 0.31, 0.33, 0.57, 0.73, 1.0, 1.4, 1.6 and 1.9 mg/kg (280-400 g ai/ha, 4-6 applications, PHI 0-10 days, n=20). An MRL of 3 mg/kg is recommended for tomato.

Processing studies

US studies were provided to show the fate of methoxyfenozide through cotton and tomato processing procedures. Methoxyfenozide was not concentrated in any cotton fractions. Processing factors for meal, hulls and refined oil were <0.14, 0.14 and <0.24 respectively. Methoxyfenozide did not concentrate in any tomato fraction studied. Processing factors for washed tomatoes, juice, puree and paste were 0.14, 0.17, 0.27 and 0.75 respectively.

Methoxyfenozide concentrated in the cream fraction of milk by a factor of 4.3. It was depleted in skim milk by a factor of 0.19. Residues in fat were approximately 40 times higher than residues in muscle.

Animal feed commodity MRLs

Residues of methoxyfenozide did not concentrate in any cotton seed fraction (meal, hulls, oil) that could be used as an animal feed. Separate MRLs for these commodities are not required.

Residues in cotton forage and trash were up to 309 mg/kg and 188 mg/kg on a dry weight basis 28 days after treatment. Since feeding of cotton forage and trash is not consistent with GAP MRLs will not be recommended for these commodities. The following restraint will appear on the product label: "Do not allow livestock to graze cotton crop or stubble. Do not cut for stock feed."

Data were not provided for tomato forage or stubble. Feeding of tomato foliage is not expected to occur frequently, however, the applicant has agreed that a grazing restraint should apply to treated tomato plants. The following restraint will appear on the product label: Do not allow livestock to graze any treated crop.

Animal commodity MRLs

Based on the proposed uses of Prodigy 240 SC Insecticide the maximum animal dietary burden from consumption of treated cotton seed, meal, hulls and tomato pomace is estimated to be 4 ppm in the diet. The estimated dietary burden excludes any contribution from treated forage or fodder as grazing/feeding restraints should apply. The maximum residues of methoxyfenozide in animal commodities derived from animals dosed at 15-150 ppm for 28 consecutive days are shown below:

Dose, ppm	Maximum methoxyfenozide residue, mg/kg, in tissue ¹				
	Milk	Muscle	Liver ²	Kidney ²	Fat
15	0.0063 (<LOQ)	ND (<LOD)	0.0094 (<LOQ) [0.027 (<LOQ)]	ND (<LOD) [ND (<LOD)]	0.0109
45	0.0076 (<LOQ)	ND (<LOD)	0.0305 [0.080]	0.038 [0.012]	0.082
150	0.0996	0.0103	0.150 [0.305]	0.0336 [0.092]	0.440

1. LOQ 0.01 mg/kg, LOD 0.003 mg/kg.
2. Liver and kidney were also analysed for the glucuronide conjugate metabolite. Maximum total residue shown in []. LOQ for combined residue is 0.03 mg/kg.

At the 15 ppm feed level the only tissue containing a measurable residue (>0.01 mg/kg) of methoxyfenozide was fat. Based on the estimated dietary burden of 4 ppm it is unlikely that residues >0.01 mg/kg of parent compound would occur in any tissue or milk, provided that residues scale proportionately with dose. Estimated residues are 0.002 mg/kg, not detectable, 0.0025 mg/kg, not detectable and 0.0029 mg/kg for milk, muscle, liver, kidney and fat respectively. All the predicted residues based on feeding at 4 ppm in the diet are less than the LOD of the analytical method.

At the 15 ppm feed level the maximum residue of methoxyfenozide + glucuronide metabolite in liver was 0.027 mg/kg which is just below the LOQ for the combined residue (LOQ is 0.01 + 0.02 = 0.03 mg/kg). Scaling for a feed level of 4 ppm gives a total residue in liver of 0.0072 mg/kg. This is less than 1/3 LOQ. Total residues in kidney were not detectable in the 15 ppm feed group.

It is recommended that animal commodity MRLs be established based on a maximum animal feeding level of 4 ppm in the diet and a residue definition of parent compound only. The following MRLs are appropriate: meat [in the fat] *0.01 mg/kg; milk *0.01 mg/kg and edible offal (mammalian) *0.01 mg/kg. Although animal commodity MRLs have been established based on a maximum feeding level (MFL) of 4 ppm in the diet, feeding at up to 10 ppm in the diet would be unlikely to result in residues above the LOQ.

Rotational crops

A confined rotational crop study using radiolabelled test substances was provided. Methoxyfenozide was sprayed directly onto bare soil and mustard, radish and wheat were planted into the treated soil at plantback intervals equivalent to 30, 90 and 365 days after treatment. Plots received 3 applications of 0.75 kg ai/ha at 3-4 day intervals for a total application rate of 2.25 kg ai/ha. Residues of parent compound in the plantback crops were up to 0.027 ppm (mustard leaf), 0.013 ppm (radish leaf), 0.033 ppm (radish root), 0.009 ppm (wheat forage) and 0.021 ppm (wheat straw) at the 30 DAT plantback intervals. It should be noted that the study methodology probably leads to an exaggerated estimate of residues in plantback crops. Methoxyfenozide was applied to bare soil ensuring that 100% of the application rate reached the soil. In reality the covering crop would intercept a significant proportion of the spray and it would not be deposited on the soil for

accumulation in the following crop. Despite the exaggerated nature of the study, the actual residue levels were still less than or close to the likely LOQ of a tolerance enforcement method (0.02 mg/kg, see Table 27). Under actual conditions of use finite residues in plantback crops are considered unlikely.

Spray drift potential

Depending on application technique residues on adjacent pasture could exceed the maximum animal feeding level as a result of off-target deposition when methoxyfenozide is applied up to the crop/pasture boundary. Livestock grazing contaminated pasture could develop detectable residues of methoxyfenozide in tissues or residues in excess of the domestic MRL. In export markets where no residue tolerance has been established residues in animal must be less than the LOQ/LOD to ensure compliance.

Prodigy 240 SC may be applied by aerial spraying and this method is likely to pose the highest risk of off-target deposition. The product is to be applied with VMD of 120-150 microns with swath width not exceeding 20-22 m. It is not to be applied by ultra low volume methods. The recommended VMD for ground application is 150-180 microns.

The LOQ for methoxyfenozide in the animal transfer study was 0.01 mg/kg with an LOD of 0.003 mg/kg. The LOQ for the combined methoxyfenozide/glucuronide residue in kidney and liver was 0.03 mg/kg.

Differences in residue definitions may also be important. Trading partners (such as the US) may include the glucuronide metabolite in the residue definition for liver and kidney. In all but the 15 ppm dose group the highest residue of parent compound was observed in fat. The methoxyfenozide residue in fat of 45 and 150 ppm animals was higher than the parent+glucuronide residue in liver and kidney. For compliance purposes fat is likely to be the target tissue. The glucuronide would not be included in any residue definition for fat as it is not a significant part of the residue in that tissue. It is appropriate to consider the parent compound in fat when evaluating spray drift potential.

The Australian Cotton Industry Best Management Practices Manual, Application (1st Edition, 1997, page AP-10) recommends the use of a 300 m buffer zone on the downwind boundary of fields adjacent to sensitive areas where chemicals are applied by air. Based on spray drift modelling the pasture residue at the downwind edge of a 300 m buffer zone would be 5.5 ppm dry weight. The model predicts that the use of the BMP buffer zone would be adequate to give compliance with the domestic MRL. The domestic MRL is set at the limit of quantitation, therefore the same buffer zone should provide adequate protection against residue detections in export markets.

The Australian Cotton Industry Best Management Practices Manual, Application (1st Edition, 1997, page AP-10) recommends the use of a 100 m buffer zone on the downwind boundary of fields adjacent to sensitive areas where chemicals are applied by ground rig. The domestic MRL is set at the limit of quantitation, therefore the same buffer zone should provide adequate protection against residue detections in export markets.

Formal advice is required from Meat and Livestock Australia as to the perceived magnitude of the risk and the adequacy of the proposed management strategy.

The product label contains several generic statements related to spray drift minimisation. These include: “Keep animals out of operational areas during treatment”, “Avoid spray drift onto adjoining properties or stock areas” and “A spray drift minimisation strategy should be employed at all times when applying sprays. The strategy envisaged is exemplified by the cotton industry’s Best Management Practices Manual”. The value of such statements may be limited, as they do not give specific advice to the applicator. Depending on consultation with stakeholders, specific references to buffer zones may be appropriate on the product label.

Bioaccumulation potential

Methoxyfenozide has a log P value of 3.72 which is less than the cut-off described in the FAO Manual for designating a chemical as fat soluble (log P= 4). The fat solubility of compounds with log P between 3 and 4 should be considered on a case-by-case basis. In a lactating cow transfer study methoxyfenozide residues in perinephric fat were up to 40× higher than in hindquarter muscle. The available animal residue depletion data are limited (single animal) but it would appear that methoxyfenozide residues decline quickly following withdrawal from dosing.

Dietary risk assessment

The chronic dietary risk is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and dietary intake data from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with the Guidelines for predicting dietary intake of pesticide residues (revised) (World Health Organisation, 1997).

The NEDI for methoxyfenozide is equivalent to less than 1% of the ADI. Chronic dietary exposure to methoxyfenozide at this level is unlikely to present an undue risk to human health.

The acute toxicology of methoxyfenozide was considered by the Therapeutic Goods Administration and an acute reference dose was not considered necessary. Acute dietary exposure to methoxyfenozide is unlikely to pose a significant risk to human health.

Recommended amendments to the MRL Standard:

Table 1

Compound	Food	MRL
Methoxyfenozide		
Delete:		
	SO 0691 Cotton seed	T*0.05
	VO 0448 Tomato	T2
Add:		
	SO 0691 Cotton seed	3
	VO 0448 Tomato	3
	MM Meat [mammalian] (in the fat)	*0.01
	ML 0106 Milks	*0.01
	MO Edible offal (Mammalian)	*0.01

The MRL recommendations indicated above will be conveyed to the Australia and New Zealand Food Authority (ANZFA) for consideration for incorporation into Standard A14 of the Food Standards Code and consequent adoption into the State/Territory food legislation.

Withholding periods:

The following withholding period statements are recommended in conjunction with the above MRLs:

Cotton- Do not harvest for 4 weeks after application.

Tomato- Not required when used as directed.

Restraints

The following protection statements are recommended for inclusion on the product label:

Cotton- Do not allow livestock to graze cotton crop or stubble. Do not cut for stock feed.

Tomato- Do not allow livestock to graze any treated crop.

In accordance with the Cotton Industry's Best Management Practice, cotton trash **MUST NOT BE FED TO ANIMALS**.

Conclusion

The NRA is satisfied that the proposed use of Prodigy will not be an undue hazard to the safety of people using anything containing its residues.

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Commodities exported and main destinations

Cotton

Australian exports of cotton seed and related products are summarised below:

Commodity	Amount exported (1998/99) ¹	Major destinations ²
Cotton seed	359.94 kt	USA, Japan, Korea
Cotton seed oil	1.35 kt	Japan, Korea, India
Meal	29.97 kt ³	Korea
Hulls	No figure available	Korea, Japan

1. Figures from ABARE, Australian Commodity Statistics 1999
2. Information provided by Cargills Australia (major oilseed merchant)
3. Combined total of sunflower seed meal and cotton seed meal.

Total Australian tomato production in 1997 was 393,118 tonnes with exports of 6,790 tonnes. Major export markets are shown below:

Tomato

Major export markets for tomatoes (1997/98) are shown below:

Country	Volume, tonnes	Value, \$'000
New Zealand	3,395	4,598
Singapore	2,618	2,743
Hong Kong	554	892
Indonesia	95	254
Malaysia	43	62
Japan	16	92
Thailand	9	10
Brunei	27	71
Fiji	6	12
New Caledonia	2	7
Other	25	92
Total	6,790	8,833

Animal commodities

Australian exports of beef/veal and live cattle in 1998/99 were 855.3 kt and 511.2 kt respectively. Major export markets for beef/veal were US (285.2 kt) and Japan (320.9 kt). The value of beef/veal exports to these two markets alone was worth over \$2 billion in 1998.

Overseas registration status

The applicant advised that methoxyfenozide MRLs have been established for some crops in the following countries: Argentina, Bolivia, Brazil, Chile, Columbia, Mexico, Indonesia, Israel, Korea and USA.

Overseas MRLs for relevant commodities are shown below:

Commodity	Country	MRL, mg/kg
Tomato	Argentina (greenhouse tomato)	0.2
	Brazil	0.1
Milk	USA	0.02
Meat		0.02
Liver		0.1
Meat by-products (except liver)		0.02
Fat		0.1

CODEX Alimentarius Commission MRL

Methoxyfenozide has not been considered by Codex and there are no Codex MRLs established.

Potential risk to Australian export trade

Cotton

Residues in cotton seed 28 days after last treatment were less than the analytical LOQ in 4 of the 6 Australian trials. In the other 2 trials residues were up to 1.79 mg/kg. In the trials that yielded finite residues the last application was made at 50-80% bolls open. Application at 50-80% bolls open is probably later than would be required in practice for control of *Heliothis*. Finite residues were also observed in 3 USA decline trials where sampling was conducted at 28 days post-treatment.

Finite residues are not expected to occur in cotton meal or refined oil. The processing factor for hulls was 0.14 indicating that measurable residues could theoretically occur in this fraction. The predicted maximum residue for cotton hulls is 0.42 mg/kg [3×0.14].

A residue tolerance of 2 mg/kg for methoxyfenozide in cotton seed has been proposed in the US. Other markets do not appear to have suitable tolerances in place. The Australian MRL has been recommended at 3 mg/kg, however, it is unlikely that residues would exceed 2 mg/kg, particularly with normal bulking and blending processes.

It is concluded that finite residues may occur in cotton seed and cotton hulls and these commodities may be exported to countries where suitable residue tolerances have not been established.

Theoretically the export of these commodities could unduly prejudice trade between Australia and places outside of Australia. The Australian residue trials demonstrate that finite residues are unlikely to occur in *all* crops treated with methoxyfenozide. Normal bulking and blending of seed and hulls would dilute residues and may effectively mitigate the risk of finite residues occurring in bulk lots. It should also be noted that seed from the Australian residue trials was ginned by hand and the portions analysed probably contained more lint than would occur in commercial situations. Fully delinted seed is likely to contain lower residues than seed with excessive amounts of adhering lint.

A specific cautionary statement should be included on the product label. The following wording is suggested as an example:

Caution: Prodigy 240 SC Insecticide may leave detectable chemical residues in harvested produce. Overseas markets may not have appropriate residue tolerances in place or may have established residue tolerances that are lower than Australian Maximum Residue Limits. If you are using this product on crops destined for export, please contact Bayer Australia Limited.

Peak industry bodies should be given the opportunity to comment on the potential trade risk during the public consultation phase of the registration process.

Tomato

Measurable residues of methoxyfenozide are expected to occur in tomatoes as a result of the use of Prodigy 240 SC Insecticide. The proposed Australian MRL is 3 mg/kg.

According to 1997/98 figures, less than 2% of total domestic production of tomatoes is exported. Residues in tomatoes exported to New Zealand (approximately 50% of total exports) would be covered by an entry in Standard A14 of the Australian Food Standards Code under the Trans Tasman Mutual Recognition Arrangement.

None of the other importers of Australian tomatoes have suitable MRLs or bilateral agreements in place, however, exports to countries other than New Zealand account for less than 1% of total domestic production. There is a theoretical risk to Australian trade relations if tomatoes treated with Prodigy 240 SC Insecticide are exported to markets that do not have residue tolerances in place, however, in this case the risk is considered to be small.

It is recommended that the applicant include a cautionary statement on the product label concerning export of treated crops. See recommended statement recommended above.

Peak industry bodies should be given the opportunity to comment on the potential trade risk during the public consultation phase of the registration process.

Animal commodities

Based on the predicted livestock dietary burden (excluding off-target contamination), residues of methoxyfenozide are not expected to be above the LOQ in tissues or milk. It should be noted that the proposed US residue definition for liver and meat by-products (except liver) includes methoxyfenozide and the glucuronide metabolite RH-1518. Based on the predicted livestock dietary burden, combined residues of methoxyfenozide and metabolite RH-1518 in liver and kidney are not expected to exceed the LOQ of the analytical method (LOQ for combined residue is 0.03 mg/kg).

Fodder and forage from treated cotton and tomato crops have not been included in the estimation of livestock dietary burden as grazing restraints are recommended for these items. Feeding of cotton trash to livestock is not considered to be consistent with GAP. Feeding contaminated trash is likely to result in detectable residues of methoxyfenozide in animal commodities which could unduly prejudice trade. In accordance with the Cotton Industry's Best Management Practice, cotton trash **MUST NOT BE FED TO ANIMALS.**

Livestock grazing pasture contaminated by off-target deposition of methoxyfenozide could develop detectable residues of methoxyfenozide in edible tissues and milk. It is expected that the potential risk to trade can be effectively managed by the use of downwind no spray zones (buffer zones). Modelling conducted by the NRA (see previous discussion under Spray Drift Potential) indicates that adherence to the minimum buffer zones recommended in the Cotton Industry Best Management Practice should be adequate to reduce the risk to an acceptable level.

Formal advice from Meat and Livestock Australia will be sought as part of the consultation phase of registration. It is recommended that any required mitigation strategies should be incorporated onto the product label.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Methoxyfenozide is not on the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999). Based on the available information, NOHSC did not determine methoxyfenozide and Prodigy as hazardous.

Methoxyfenozide will be manufactured overseas as a white powder. It has low acute oral toxicity in mice and rats and low dermal toxicity in rats and has no inhalation toxicity at the maximum attainable aerosol concentration in rats. Methoxyfenozide is a slight eye irritant in rabbits, but not a skin irritant in rabbits or a skin sensitiser in guinea pigs.

Formulation, transport, storage and retailing

The active constituent, methoxyfenozide, is manufactured overseas and will be imported into Australia in 236 L (90.7 kg) fibre drums with polyethylene bag insert. The product, Prodigy, will be formulated in Australia from the imported active ingredient and will be packed in 1L and 2.5L plastic bottles, 5L, 10L, 20L, 50L and 200L plastic drums and in 1000L plastic drums supported with frames. The approximate standard size of each batch will be 4000 kg suspension concentrate.

Storemen, transport workers, laboratory staff, formulators and packers will handle the active constituent and the product. The submission contains sufficient information on the categories of workers, nature of work done and prevention of worker exposure required for workplace assessment.

Use and Exposure

Prodigy 240 SC Insecticide is indicated for the control of insects in cotton and tomato crops. It will be applied to cotton by ground or aerial spraying. The application rate varies between 1.7 and 2.5 L/ha depending on the pests being treated. For aerial spraying, the recommended minimum volume is 25 L/ha (10% product (v/v) and 2.4% methoxyfenozide (w/v)). For ground application, 100 – 200 L/ha spray volume would be used (2.5% product (v/v) and 0.6% methoxyfenozide (v/v)). Maximum of 3 applications per season are recommended at least 10 days apart.

For tomato crops, Prodigy 240 SC Insecticide will be applied by aerial and ground spraying. The recommended application rate for tomatoes is 1.25 or 1.7 L/ha. The spray volume for ground application is 1000 L/ha (0.17 % product (v/v) and 0.04% methoxyfenozide (w/v)). For aerial spray, the minimum recommended spray volume is 25 L/ha (6.8% product (v/v) and 1.63% methoxyfenozide (w/v)). For both crops, hydraulic nozzle and rotary disc atomiser will be used for ground application.

The main routes of exposure are dermal and ocular. Categories of workers that can be potentially exposed to the product are formulators, mixer/loaders, ground applicators, clean-up personnel and re-entry workers. Human flaggers can be exposed to the product during aerial applications.

There are no worker exposure data on Prodigy 240 SC Insecticide. NOHSC used the UK Predictive Operator Exposure Model (POEM) to estimate applicator exposure to Prodigy 240 SC.

The estimates demonstrated that the use of gloves during mixing, loading and application is necessary to protect workers from repeated exposure. The worker exposure information on a similar product provided by the applicant also suggests the requirement of gloves during mixing/loading and application.

Large areas of crops will be treated by aerial application. The spray pilots will be protected from direct contact with the spray. The use of human flagging is possible in aerial operations. As exposure levels to these workers cannot be quantified, human flaggers should be protected by engineering controls such as vehicles with cabs. A statement to this effect should appear on the product label.

In order to protect workers from repeated exposure to Prodigy 240 SC Insecticide during mixing/loading and application, the use of the following personal protection equipment is recommended: cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves.

Entry into treated areas

Workers entering treated areas can be exposed to product residues and degradation products during bug checking, harvesting or other crop management activities.

Studies on dislodgeable foliar residues demonstrated it was safe to re-enter treated fields after the spray has dried. NOHSC recommends entry to treated areas only after the spray has dried.

Re-entry statement

“Do not allow entry into treated areas until the spray has dried. If prior entry is necessary, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day’s use.”

Recommendations for safe use

Users should follow the instructions and Safety Directions on the product label. Safety Directions include the use of cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves when preparing and applying the spray.

The PPE recommended should meet the relevant *Standards-Australia*.

Precautionary Statement

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

Conclusion

The NRA is satisfied that Prodigy not be an undue hazard to the safety of people exposed to it during its handling and use if handled in accordance with the instructions on the product label.

Environmental Assessment

Introduction

Bayer Australia Ltd has applied for registration for the product Prodigy 240 SC Insecticide and approval of the new active constituent, methoxyfenozide which it contains. Registration is sought for the control of caterpillar pests in cotton and tomatoes. Methoxyfenozide acts by mimicking the natural insect moulting hormone, 20-hydroxyecdysone, ie it is an ecdysone agonist. It arrests larval feeding and induces premature moulting, killing the insect within a few days.

Environmental Fate

Hydrolysis

A study to US EPA and OECD Guidelines of hydrolysis at 25°C in the dark indicated that methoxyfenozide was stable in sterile buffers at pH 5, 7 and 9 (estimated half-lives 587-1572 days extrapolated from the 30 day incubation period).

Photolysis

Aqueous photolysis studies based on US EPA Guidelines were provided with sterile, deionised water buffered at pH 7 and in natural water obtained from a pond (in both cases at 25°C, with 12 h light:12 h dark cycles from a lamp simulating natural sunlight wavelengths). Methoxyfenozide in sterile pH 7 buffer was stable to photolysis (extrapolated half-life 2166 days both with and without simulated sunlight irradiation), but some degradation occurred in natural water when it was irradiated (extrapolated half-life 866 days in darkness, 77 days with irradiation). A total of seven minor degradates were detected. The different results for sterile deionised water and pondwater indicate that photodegradation in the pond water was facilitated by the presence of photosensitisers.

A soil photolysis study based on US EPA Guidelines indicated that some degradation occurred over the 30 day incubation period, more so with exposure to simulated sunlight than in the dark (extrapolated half-lives 173 days and 332 days, respectively). Three minor degradates were detected. The results suggest that some microbial degradation occurred, in addition to slight photodegradation.

Degradation in soil and water

Three studies based on US EPA Guidelines were reported with ¹⁴C-labelled methoxyfenozide (incubated in the dark at 25°C for 365 days), providing results for four soils. All indicated that methoxyfenozide degraded only slowly (extrapolated half-lives 431-1100 days, generally somewhat faster initially), though some mineralisation was evident (cumulative ¹⁴CO₂ production at day 365 was 2-5.5% of applied radioactivity). Three minor metabolites were detected, two of them inferred to be RH-131154 and RH-117236 (both retaining the same overall molecular structure, respectively a carboxylic acid metabolite and a hydroxy metabolite). In each case a significant proportion (16-35% of applied radioactivity) became bound to soil, some of which was released by acid hydrolysis and found to be largely unchanged methoxyfenozide.

The aerobic aquatic metabolism of ^{14}C -labelled methoxyfenozide in two soil/water systems based on US EPA Guidelines was reported (incubation in the dark at 25°C for 365 days). Degradation from the soil/water system was more rapid in a clay/paddy water system than a loam/irrigation water system (half-life over 0-365 days = 387 days and 963 days, respectively; initially more rapid, before slowing greatly: half-life over 0-60 days = 86 days and 145 days, respectively). The difference in degradation rates was attributed to a greater amount of applied radioactivity binding to the clay soil (approximately 44% and 10% of applied radioactivity, respectively, at day 365 after solvent extraction of the soil, whereas a significant amount of residues in the loam remained extractable in solvent). Significant partitioning of methoxyfenozide to the soil was evident from the start of incubation, more so in the clay/paddy water system. Despite slow degradation, some mineralisation was evident over the incubation period (cumulative $^{14}\text{CO}_2$ production at day 365 was 5-6% of applied radioactivity). The metabolites RH-117236 and RH-131154 and some other minor metabolites were detected in both water and soil in both systems (RH-131154 reached ~16% of applied radioactivity in the clay system).

An anaerobic aquatic metabolism study of ^{14}C -labelled methoxyfenozide in a sediment/water system (clay sediment and water from a pond) based on US EPA Guidelines was reported (incubation in the dark at 25°C for 365 days under anaerobic conditions). Degradation from this system was slow (extrapolated half-life over 0-365 days = 654 days). Four minor metabolites were detected, including RH-131154. Significant partitioning of methoxyfenozide to the soil was evident from the start of incubation, and binding to soil was one of the main routes of disappearance of methoxyfenozide from the system. Despite slow degradation, some mineralisation was evident over the incubation period (cumulative $^{14}\text{CO}_2$ production at day 365 was ~3% of applied radioactivity).

Mobility

Due to its low vapour pressure, methoxyfenozide has negligible potential to volatilise from soils and also has negligible volatility from water or moist surfaces.

The adsorptive and desorptive properties of methoxyfenozide in five soils was determined using ^{14}C -labelled methoxyfenozide in a batch equilibrium study based on US EPA Guidelines. The soils ranged in texture from a loamy sand to a silt loam and also varied in OM%, pH and cation exchange capacity. Freundlich adsorption and desorption coefficient values obtained ranged from ~1.1 to 6.2 for adsorption and 1.9-13.6 for desorption (two cycles). Adsorption coefficients based on organic carbon content (K_{OCs}) ranged from 219 to 922 (average 490) for adsorption, placing methoxyfenozide in the low or medium mobility classes. K_{OC} values ranged from 288 to 1598 for the initial desorption cycle and 361 to 5714 for a second desorption cycle.

Methoxyfenozide is persistent and has medium to low mobility in soil. Calculation of the Gustafson Ubiquity Score (GUS) for methoxyfenozide from the available $K_{\text{OC(adsorption)}}$ and half-life data estimates gives GUS values of 2.2 to 4.3. This rates methoxyfenozide as a probable to transitional leacher, though the higher $K_{\text{OC(desorption)}}$ values suggest that after initial binding, the tendency to leach may be slightly reduced (GUS values 1.7 to 3.2).

Pesticide Root Zone Modelling (PRZM) for repeated use of methoxyfenozide in cotton in the USA indicated that in reasonable worst case scenarios for US cotton soils, there was a negligible risk to groundwater supplies (predicted porewater concentration $0.2 \mu\text{g/L}$ at 1 m after 20 years, taking 17 years to reach that depth). Greater leaching potential was evident in the lighter textured soils used for apple production (predicted porewater concentration $\sim 10 \mu\text{g/L}$ at 1 m after 20 years, taking only

5 years to reach that depth). However, because of the typical depth to watertables pertaining, the investigators again concluded that there was minimal potential for groundwater contamination.

Environment Australia concludes that with prolonged, repeated use of methoxyfenozide at high rates there is potential for the substance to leach to shallow watertables where the soil profile drains freely, or for it to reach shallow drains, such as tile or mole drains (not currently common for Australian cotton or tomato crops). Water from shallow drains would probably be returned to surface drains.

Field dissipation studies

Field dissipation studies based on US EPA Guidelines were conducted at four sites in the USA, with methoxyfenozide applied to bare soil. Estimated half-lives for methoxyfenozide residues in the soil profiles ranged from 92 to 327 days (average 177 days). Leaching of methoxyfenozide was evident with all four sites, the rate, extent and depth to which this occurred varying with the soil texture profile (most rapid in a deep sand, where the first detection at 76-91 cm occurred 30 days after the final spray application). The results suggest that methoxyfenozide may dissipate more rapidly from soil under field conditions than under laboratory conditions, but still indicate it is moderately to highly persistent in soil. No information was obtained from these studies on the nature of metabolites or extent of bound residues.

A study was also provided of air blast application of methoxyfenozide in an apple orchard. A large proportion of the applied spray deposited on the apple leaves (79%), with a smaller proportion on interrow turf. Methoxyfenozide accumulated during successive applications on apple leaves and to a lesser extent on turf, but dissipated from both matrices with half-lives of ~55 days in apple leaves and ~13 days in turf following the final spray application (it is uncertain to what extent loss may have been due to wash-off and/or growth dilution, rather than degradation). The estimated half-life in soil was 25-38 days. There was evidence of residues washing off foliage, but leaching below 15 cm in soil was not indicated. The study suggests that the soil half-life in a practical orchard situation may be much shorter than found in the above field dissipation trials where methoxyfenozide was applied to bare soil.

A Confined Accumulation in Rotational Crops study with methoxyfenozide based on US EPA Guidelines was conducted outdoors on a sandy loam soil in the USA. Evaluation of the limited data available indicated half-lives for dissipation of methoxyfenozide from the top 15 cm of soil were 179-433 days, but no measurements were made for leaching below 15 cm. Uptake of radioactive residues was evident in all three crops tested, the amount decreasing with increasing duration before planting. Extensive metabolism of methoxyfenozide was evident, but the metabolites identified all still contained the dibenzoylhydrazide structure. The investigators concluded that methoxyfenozide was translocated from the soil and metabolised by the plants.

Accumulation in soil and sediment

Because of its moderate to high persistence in soil, with repeated application year after year methoxyfenozide has the potential to accumulate in soil or sediment. Assuming a half-life of 92-327 days based on field dissipation study data, and 3 applications per annum to cotton at the maximum application rate, Environment Australia estimates that soil concentrations in the surface 15 cm could accumulate to 0.9-1.4 mg ai/kg soil. Because of typical crop rotation practices, soil accumulation is more likely to occur in cotton, where the maximum application rate is also higher than with tomatoes.

However, medium to low mobility of methoxyfenozide in soil may limit the peak concentration reached in surface soil, as residues leach to deeper soil layers or into surface run-off. In water/sediment situations, in a worst case scenario with strong adsorption to sediment and 10% of applied spray reaching water in spray drift and/or run-off, Environment Australia estimated sediment concentrations could reach 0.12-0.23 mg ai/kg in the surface 10 cm of sediment, or 5-10X these concentrations if confined to the surface 1-2 cm. However, the extent to which this occurred would depend on sediment characteristics, and there is also evidence from benthic toxicity and microcosm studies that movement to sediment may not occur to the extent found in laboratory aquatic metabolism studies, hence accumulation of methoxyfenozide in sediment may be limited by loss via the overlying water.

Bioaccumulation

A study based on US EPA Guidelines was conducted to assess the bioaccumulation potential of methoxyfenozide (¹⁴C-labelled) in bluegill sunfish (*Lepomis macrochirus*). Modelling of results for two different water concentrations indicated a bioconcentration factor (BCF) for ¹⁴C-residues in whole fish of 8.8-8.9, estimated time taken to reach 90% steady state of ~1 day, and 50% depuration estimate of ~0.3 days. While depuration was rapid, some residues persisted. A large number of metabolites were identified, in addition to methoxyfenozide (which comprised ~9–13% of residues in viscera and 38–46% of residues in fillet). Most of the metabolites found in fish retained the dibenzoylhydrazide structure. Thus methoxyfenozide is unlikely to bioaccumulate.

Environmental Toxicity

Avian toxicity

Toxicity tests conducted to USEPA Guidelines showed that with acute oral or subacute dietary exposure, methoxyfenozide (active constituent, and for acute exposure, also the SC formulation) is practically non-toxic to bobwhite quail, but may have subtle reproductive toxicity effects on this species (reproductive No Observed Effect Level [NOEL] = 520 ppm ai). Similarly, methoxyfenozide is practically non-toxic to mallard ducks with subacute dietary exposure, but again, may have subtle reproductive toxicity effects on this species (NOEL = 780 ppm ai). Such effects are conceivable through action as an endocrine disruptor in birds, though in both cases there are arguments to suggest that though statistically significant, the apparent effects were not in fact treatment related (the NOELs for both species would then be 1000 ppm). For both species, the effects occurred at relatively high long-term dietary concentrations unlikely to occur in field situations.

Aquatic toxicity

Concentrations which could be reliably tested in aquatic toxicity tests were limited by the solubility of methoxyfenozide. Acute toxicity tests based on US EPA Guidelines found that methoxyfenozide is at most moderately toxic to the freshwater species rainbow trout (96 h LC50 > 4.2 mg ai/L), bluegill sunfish (96 h LC50 > 4.3 mg ai/L) and fathead minnow (96 h LC50 > 3.8 mg ai/L), and to the estuarine/marine species sheepshead minnow (96 h LC50 > 2.8 mg ai/L). Similar studies with the SC formulation indicated 96 h LC50 values for both rainbow trout and bluegill sunfish of >130 mg total product/L (corresponding to >31 mg ai/L), but the concentrations tested greatly exceeded the solubility limit (in terms of dissolved methoxyfenozide, the 96 h LC50 values were respectively, >2.7

mg ai/L and >3.7 mg ai/L). A 32 day exposure early life stage study based on US EPA Guidelines indicated that methoxyfenozide is very slightly toxic to sheepshead minnow (No Observed Effect Concentration [NOEC] = 2.6 mg ai/L, the highest concentration tested).

Acute toxicity tests based on US EPA Guidelines found that methoxyfenozide is moderately toxic to the water flea *Daphnia magna* (48 h EC50 = 3.7 mg ai/L) and the estuarine/marine species mysid shrimp (96 h LC50 = 1.3 mg ai/L) and eastern oyster (96 h EC50 = 1.3 mg ai/L). A similar study with the SC formulation indicated a 48 h EC50 value for *Daphnia magna* of >420 mg total product/L (corresponding to >95 mg ai/L), but the concentrations tested greatly exceeded the solubility limit. In a 21 day exposure/reproductive study based on US EPA Guidelines, methoxyfenozide was found to be slightly toxic to *Daphnia magna* (NOEC = 390 µg ai/L for neonate production). A 37 day exposure/reproductive study with mysid shrimp based on US EPA Guidelines indicated that methoxyfenozide is moderately toxic to mysids (NOEC = 51 µg ai/L for growth effects).

The greatest toxicity reported to any aquatic species was to the midge *Chironomus riparius*: 28 day benthic studies based on draft BBA (German) or OECD Guidelines indicated NOECs of 10 µg ai/L and 6.5 µg ai/L (initial overlying water concentration) for emergence rate of adult midges, with corresponding EC50 values of 24 µg ai/L and 14 µg ai/L, respectively. In a limit test, the metabolite RH-117236 was found much less toxic to this species than methoxyfenozide (NOEC < 100 µg ai/L, but EC50 > 100 µg ai/L). A 28 day benthic study with methoxyfenozide and the mosquito *Culex quinquefasciatus* indicated a 28 day NOEC of 10 µg ai/L and EC50 of 211 µg ai/L. High toxicity of methoxyfenozide to *Chironomus riparius* was also evident in a microcosm study, where tests with water obtained at various times after application of methoxyfenozide indicated IC50s of 16.0-27.4 µg ai/L and a NOEC of 12.5 µg ai/L. However, this study suggested that midge populations could recover once concentrations in water fell sufficiently. Caddisfly populations were significantly reduced by a concentration of 211 µg ai/L in the microcosm study itself.

Studies based on US EPA Guidelines with the green alga *Selenastrum capricornutum* indicated that methoxyfenozide as the active (120 h exposure) or in the 2F formulation (96 h exposure) are not toxic to this algal species up to the solubility limit of the active (EC50 values > 3.4 mg ai/L for active and > 107 mg product/L for the formulation). Toxicity to algae and aquatic plants is not expected from the mode of action of the substance as an insect ecdysone mimic, and the microcosm study also indicated no adverse effects on bluegreen or green algae or macrophytes at test concentrations peaking at 206 µg ai/L.

Terrestrial invertebrates

The majority of the bee toxicity studies provided involved adult bees only, whereas due its mode of action, methoxyfenozide would be more likely to effect juvenile stages. Laboratory tests where honey bees received acute exposure to methoxyfenozide active or SC formulation indicated that both the active and product were virtually non-toxic to adult bees. The LD50s for acute contact and acute oral dosing with the active were >100 µg ai/bee (48 h observation) and >100 µg ai/bee (72 h observation), respectively. The LD50s for acute contact and acute oral dosing with the SC formulation were >200 µg product/bee (48 h observation) and >289 µg product/bee (48 h observation), respectively. Free flying honey bee colonies were fed syrup containing 400 µL of SC formulation and brood combs examined over a period of three weeks subsequently. In contrast to colonies exposed to diflubenzuron as a toxic control, no adverse effects on honey bee brood

development were found, and there were no harmful effects evident on adult worker bees. Environment Australia concludes that methoxyfenozide applied at field rates is unlikely to affect adult bees or to lead to harmful effects on brood development in nearby hives.

Results of laboratory and semi-field tests with methoxyfenozide indicate that at rates highly toxic to target Lepidoptera species, methoxyfenozide had at most minor effects on the survival and reproductive ability of a range of invertebrate predator and parasite species (green lacewing, a predatory bug, parasitic wasps, predatory mites, lycosid spider and a parasitic nematode). These studies included juvenile stages, monitored toxicity for at least one week and evaluated parameters such as ecdysis, successful production of adults, egg production and egg fertility, which are important if delayed toxic effects due to methoxyfenozide acting as an ecdysone agonist are to be evaluated adequately. There was also some supporting evidence of safety to predators and parasites from Australian efficacy studies. Thus it appears that methoxyfenozide is relatively selective as a 20-hydroxyecdysone agonist to Lepidoptera species, though there may be toxicity of this nature to other insect Orders, such as Diptera (eg this could account for the sensitivity of chironomids and mosquitos to methoxyfenozide).

Studies based on OECD Guidelines found the toxicity of methoxyfenozide active and SC formulation to the earthworm *Eisenia foetida* found 14-day NOEC values of 1213 mg ai/kg dry soil and 1250 mg whole product/kg dry soil, respectively, rating methoxyfenozide as practically non-toxic to earthworms. A further study with *Eisenia foetida* examined reproduction as well as growth and mortality with 28 days exposure to the SC formulation. It found no adult mortality and no reduction in the number of offspring produced, but a small increase in the growth of adult earthworms at the highest rate, calculated to be ~2.1 mg ai/kg dry soil.

Toxicity to other species

Studies indicate that methoxyfenozide is practically non-toxic to mammals. Field experience has shown no phytotoxicity to a wide range of crops and such toxicity is not expected from the mode of action of this insecticide. In soil microorganism studies to European Plant Protection Organisation (EPPO) Guidelines with methoxyfenozide active and SC formulation, soil respiration and soil nitrification indices were affected to at most a minor degree at rates greater than those proposed. Hence both can be categorised as having low risk to soil microflora.

Environmental hazard

It is proposed that Prodigy 240 SC Insecticide will be applied to cotton in at most three applications per crop, at a maximum total rate of 1800 g ai/ha, or to tomatoes at a total rate of 1632 g ai/ha if four sprays occurred on a crop (no maximum number is currently specified on the label). Methoxyfenozide is likely to be persistent in the environment and potentially mobile in soil. Residues would be expected in the crop area on plant and soil surfaces and spray drift, run-off and leaching are potential means of contamination of adjacent areas, surface water and shallow drains or watertables.

Hazard to birds and mammals

Estimated residues on feed at the maximum proposed rate are likely to be well below the acute oral LD50s and 5 day dietary exposure no observed effect concentrations (NOECs) for bobwhite and mallard duck, and also below the corresponding one-generation no observed effect levels (NOELs) for these species. Hence methoxyfenozide used in accordance with label recommendations is not likely to present a hazard to birds ingesting these residues. Acute or chronic toxicity in mammals is also highly unlikely.

Hazard to terrestrial invertebrates and soil microorganisms

Low toxicity to adult honey bees was found in laboratory studies with methoxyfenozide technical or SC formulation, hence methoxyfenozide is unlikely to harm adult bees foraging in treated fields. Similarly, test results indicate that brood development in hives fed by bees foraging in treated fields is unlikely to be affected. Laboratory and semi-field studies evaluated various insect predators and parasites, including insects from several Orders and also spiders, mites and a nematode species. At most minor harmful effects were reported, though the studies were conducted suitably to detect ecdysone agonist activity in the species tested. Hence, at field rates methoxyfenozide is unlikely to directly cause harmful effects to insect predators and parasites such as those tested. This conclusion is supported by the results of some efficacy trials in Australia, where non-target arthropod populations were monitored. However, Environment Australia notes that the evident selectivity in ecdysone agonist activity of methoxyfenozide may not be limited to Lepidoptera species – e.g. it may extend to Diptera species, accounting for the high toxicity to midge larvae (chironomids).

The worst case expected environmental concentration (EEC) in the surface 15 cm of soil calculated with repeated applications of maximum rates to cotton and tomatoes was estimated to be well below the minimum 14-day LC50 estimate for toxicity of methoxyfenozide TGAC to *Eisenia foetida*, and similar to maximum levels tested in a 28-day exposure study which found no harmful effects on adult survival or production of young. Thus methoxyfenozide is unlikely to cause harm to earthworms in soil reached by spraying, run-off or leaching. Laboratory studies indicate that methoxyfenozide can be categorised as having low risk to soil microflora - it is unlikely to cause harmful effects to microorganisms at field rates.

Hazard to plants

Field experience has shown no phytotoxicity to a wide range of crops and such toxicity is not expected from the mode of action of this insecticide.

Aquatic hazard

There is potential for methoxyfenozide to persist in the water column, exacerbated where spraying is repeated. Hence chronic exposure endpoints are more appropriate for aquatic hazard assessment. Comparisons between expected environmental concentrations from the maximum application rates for cotton and tomatoes and toxicity endpoints indicated no significant hazard to fish or algae, even with direct overspray of a 15 cm deep pond and the (there was a marginal hazard to fathead minnow indicated with two direct oversprays). For mysid shrimp (*Mysidopsis bahia* - 37 d NOEC for growth = 51 µg ai/L), a hazard was indicated with a single direct overspray to 30 cm deep water, or with repeated 10% spray drift events to 15 cm deep water. However, no hazard was indicated to

mysids in a 30 cm deep pond, even with three drift events at the cotton rate or four drift events at the tomato rate. Thus, in practice direct overspray of water could present a hazard to aquatic invertebrates such as mysid shrimp, but spray drift is not expected to be hazardous to mysid shrimp, nor less sensitive aquatic invertebrates, such as daphnids and eastern oyster.

However, test data indicated that methoxyfenozide was very highly toxic to the chironomid (midge), *Chironomus riparius* (lower NOEC from benthic studies = 6.5 µg ai/L in overlying water, NOEC from microcosm studies = 12.5 µg ai/L), possibly because this Diptera species is sensitive to activity by methoxyfenozide as an ecdysone agonist. A hazard was indicated to this species with a single direct spray or 10% spray drift event to a 30 cm pond at the maximum application rate for both cotton and tomatoes. Hence further assessment was conducted using modelling to more realistically predict spray drift. Using the more realistic NOEC value from the microcosm studies, with aerial application a hazard to chironomids was indicated in a 30 cm deep pond 100 m downwind of a treated field with cotton, but not tomatoes. With two spray drift events reaching a 30 cm deep pond, or a single event to a 15 cm deep pond, a hazard was indicated to approximately 300 m downwind with cotton and 200-300 m downwind with tomatoes. With boom spray or airblaster application, no hazard was indicated with a single spray drift event to a pond ≥ 5 m downwind, or $>$ approximately 10 m downwind with repeated spraying.

Potential for accumulation and movement to ground water

Due to the potential mobility of methoxyfenozide in soil, Environment Australia identified run-off of methoxyfenozide in water from treated areas as a hazard to sensitive aquatic species. As in addition methoxyfenozide may be persistent in soil, leaching to shallow drains and watertables may also occur. Accumulation in soil and sediment may also occur, but is likely to be limited by leaching and loss to overlying water.

Recommendations

To address these hazards, Environment Australia concluded that suitable label advice should be provided to protect aquatic areas from contamination directly by the product, prepared spray or direct overspray and that a spray drift warning should also be provided. Environment Australia believes that the cotton industry's *Best Management Practice (BMP) Manual* provides appropriate buffer recommendations for aerial and ground application, and the product label refers cotton users to this manual. In addition, Environment Australia has recommended that a 300 m buffer upstream of sensitive aquatic areas should be specified for aerial application. To reduce the risk of run-off to aquatic areas, the applicant has agreed to add a restraint to the label stipulating that initial run-off after rain or irrigation should be retained in the tailwater dam, and there is also a restraint against application if rain is expected within 6 hours. For resistance management reasons, the label already limits the maximum number of sprays per crop to three for cotton, and Environment Australia has recommended a similar label limit for tomatoes. Environment Australia also recommends that methoxyfenozide be included in water monitoring programs. With these precautions, Environment Australia concludes that a low hazard to the environment may be predicted, provided the product is used according to the proposed label recommendations and good agricultural practice.

Conclusion

The NRA is satisfied that the proposed use of Prodigy on cotton and tomatoes is not likely to have an unintended effect that is harmful to animals, plants or the environment.

EFFICACY AND SAFETY ASSESSMENT

Justification for use

Methoxyfenozide is a member of a new insecticide group, the diacylhydrazines. It is effective against *Helicoverpa armigera* at low use rates and less disruptive to beneficial insect species than broad-spectrum groups. Use of such compounds should be more compatible with Integrated Pest Management (IPM) and new technologies such as transgenic cotton.

Methoxyfenozide has a novel mode of action unlike existing nerve poisons, metabolic inhibitors, insect growth regulators and biological insecticide groups, with no known cross-resistance to existing chemical and biological groups in *Helicoverpa* species. This feature will significantly contribute to the effective rotation of chemical groups, essential for the successful implementation of Insecticide Resistance Management (IRM).

It is anticipated that Prodigy 240 SC Insecticide will be a useful management tool in cotton, both in terms of IPM and IRM.

Registration is supported by Australian agricultural authorities.

Mode of action

Methoxyfenozide belongs to a novel chemical class of insecticides – the diacylhydrazines. This class of compound expresses an insecticidal mode of action totally unlike classical neurotoxins, metabolic inhibitors, insect growth regulators and biological toxins. It is an ecdysone agonist insecticide that controls a broad range of lepidopteran larvae at low use rates, primarily by ingestion. It also exhibits selective contact, ovicidal and root systemic activity. The compound binds to the ecdysone receptor of lepidopteran larvae within a few minutes of ingestion, arrests larval feeding, induces a premature larval moult within a few hours and kills the insect within a few days. Because of its selectivity for the lepidopteran ecdysteroid receptor, methoxyfenozide does not affect pollinators, arthropod predators or insect parasitoids and therefore is suitable for Integrated Pest management (IPM).

Proposed use pattern

Prodigy 240 SC Insecticide will be applied to cotton and tomatoes by ground or aerial spraying. The maximum application rate for cotton is 2.5 L/ha and for tomatoes 1.7 L/ha. For aerial spraying, the recommended minimum volume is 25 L/ha. For ground application to cotton, a minimum spray volume of 100 L/ha would be used. A maximum of 3 applications per season are recommended for tomatoes and cotton with a minimum re-application interval of at least 7 days for tomatoes and 10 days for cotton. Use is proposed for all State and Territories.

It is proposed the product will be available in 1L and 2.5L plastic bottles, 5L, 10L, 20L, 50L and 200L plastic drums and in 1000L plastic drums.

The following Withholding Period statements are recommended for the product:

Cotton- Do not harvest for 4 weeks after application.

Tomato- Not required when used as directed.

The following protection statements are recommended in conjunction with the uses on cotton and tomatoes:

Cotton- Do not allow livestock to graze cotton crop or stubble. Do not cut for stock feed.

Tomato- Do not allow livestock to graze any treated crop.

In accordance with the Cotton Industry's Best Management Practice, cotton trash **MUST NOT BE FED TO ANIMALS**.

Evaluation of efficacy

The data presented supported the claim for control of *Helicoverpa* spp., rough bollworm and cotton looper in cotton and *Helicoverpa* spp. in tomatoes. Detailed efficacy data from 25 field trials and one laboratory trial were presented, typified by good experimental design and analysis.

Cotton

Prodigy was trialled in a range of crops, under a range of pest pressures, different populations of *Helicoverpa* species, weather conditions and soil types typical of those experienced during the Australian cotton season. The statistical analysis of the field trial data was appropriate, thorough and clearly laid out in the submission. The trial data gave a thorough indication of the efficacy of the product against *Helicoverpa* spp. and whilst data for rough bollworm were less compelling, a high level of efficacy was demonstrated against cotton looper, as expected for methoxyfenozide against a foliage feeding pest. These data support coincidental management of rough bollworm and cotton looper when targeting *Helicoverpa* spp.

Tomatoes

Data from 11 trials were presented in support of the application. The majority of trials were well designed, conducted, analysed and reported. The data provided good evidence of efficacy against *Helicoverpa* with confirmatory evidence through significant reduction of damage to fruit and improved yields of marketable tomatoes. Equivalent performance to biological pesticides such as DiPel Forte and Xentari (*Bacillus thuringiensis*) was demonstrated and equivalent or better performance to such industry standards as beta-cyfluthrin and sulprofos.

Safety to Beneficial Organisms

Prodigy demonstrated greater selectivity when compared with broad-spectrum alternatives, to a range of beneficial arthropod species common in cotton growing systems. These data are consistent with a good potential fit for Prodigy in IPM programs.

Crop Safety

Applications of Prodigy did not cause phytotoxicity to cotton or tomatoes in any of the submitted trials at rates up to twice the proposed label rate.

Resistance management

Methoxyfenozide has been included in Insecticide Resistance Group 16A. The compound has a novel mode of action unlike existing nerve poisons, metabolic inhibitors, insect growth regulators and biological insecticide groups, with no known cross-resistance to existing chemical and biological groups in *Helicoverpa* species. This feature will significantly contribute to the effective rotation of chemical groups, essential for the successful implementation of Insecticide Resistance Management (IRM).

Conclusion

Sufficient statistically analysed data from suitably designed and scientifically conducted trials has been presented to substantiate the claims for use shown on the draft labels. As long as the product is used according to label instruction and Good Agricultural Practice it should be suitable for the proposed purposes.

LABELLING REQUIREMENTS

READ SAFETY DIRECTIONS

Prodigy® 240 SC Insecticide

Active Constituent: 240 g/L METHOXYFENOZIDE

GROUP	16A	INSECTICIDE
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For the integrated management of *Helicoverpa* spp., rough bollworm and cotton looper in cotton and *Helicoverpa* spp. in tomatoes

1 L
2.5 L
5 L
10 L
20 L
50 L
200 L
1000 L

BN:
DOM:

DIRECTIONS FOR USE

RESTRAINTS: DO NOT apply if rain is expected within 6 hours. Retain the first flush of tailwater/stormwater in the tailwater dam after application.

DO NOT apply within 300 m (aerial application) or 100 m (ground application), upwind of neighbouring land which livestock could potentially graze. If the wind direction is at an angle with regard to the field then the buffer should be observed on both downwind sides of the field.

Crop	Pest	Rate	Critical Comments
Cotton	<i>Helicoverpa</i> spp.	1.7 or 2.5 L/ha + 2 mL/L Agral Use the higher rate on rapidly growing crops	Prodigy is a moult accelerating insecticide that requires ingestion for control. Feeding ceases almost immediately after ingestion. Larvae in protected feeding sites (eg squares, flowers and bolls) will not be controlled. Mortality of <i>Helicoverpa</i> larvae will not be evident until 4-6 days after application. Apply Prodigy to brown eggs or at egg hatch. Apply when pest numbers reach treatment threshold levels as determined by field checks. Ensure thorough coverage of plants. See application details in General Instructions. DO NOT make more than three applications per season. Can be applied by ground rig or aircraft. DO NOT re-apply Prodigy within 10 days of the previous Prodigy spray.
	Rough bollworm	2.5 L/ha + 2 mL/L Agral	
	Cotton looper	1.7 L/ha + 2 mL/L Agral	
Tomatoes	Native budworm (<i>Helicoverpa punctigera</i>) Tomato grub (<i>Helicoverpa armigera</i>)	Ground Application <i>Dilute:</i> 125 or 170 mL/100 L <i>Concentrate:</i> see general instructions <i>Per hectare:</i> 1.25 or 1.7 L/ha (bush tomatoes only) Aerial application 1.25 or 1.7 L/ha (not desirable for trellis tomatoes)	Prodigy is a moult accelerating insecticide that requires ingestion for control. Feeding ceases almost immediately after ingestion. Larvae in protected feeding sites (eg flowers) will not be controlled. Mortality of larvae will not be evident until 4-6 days after application. Apply Prodigy to brown eggs or at egg hatch. Apply when pest numbers reach treatment threshold levels as determined by field checks. Maintain field checks and reapply after 7 days if necessary. DO NOT make more than three applications to any crop. Ensure thorough coverage of plants. Use the higher rate under heavy egg pressure. Apply in a minimum of 25 L/ha. Higher water volumes may improve control.

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

COTTON: DO NOT HARVEST FOR 4 WEEKS AFTER APPLICATION

TOMATOES: NOT REQUIRED WHEN USED AS DIRECTED

Cotton: Do not allow livestock to graze cotton crop or stubble. Do not cut for stock feed.

Tomato: Do not allow livestock to graze any treated crop.

In accordance with the Cotton Industry's Best Management Practice, cotton trash MUST NOT BE FED TO ANIMALS.

CAUTION: Prodigy 240 SC 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 Bayer Australia Limited.

General Instructions

Insecticide Resistance Warning

GROUP	16A	INSECTICIDE
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For insecticide resistance management, Prodigy is a Group 16A insecticide. Some naturally occurring insect biotypes resistant to Prodigy and other Group 16A insecticides may exist through normal genetic variability in any insect population. The resistant individuals can eventually dominate the insect population if Prodigy and other Group 16A insecticides are used repeatedly. The effectiveness of Prodigy on resistant individuals could be significantly reduced. Since occurrence of resistant individuals is difficult to detect prior to use, Bayer Australia Limited accepts no liability for any losses that may result from the failure of Prodigy to control resistant insects. Prodigy may be subject to specific resistance management strategies. For further information contact your local supplier, Bayer representative or local agricultural department agronomist.

Mixing

Prior to pouring, shake container vigorously, then add the required quantity of Prodigy to water in the spray vat while stirring or with agitators in motion.

Compatibility

Prodigy is compatible with Dithane® DF, Antracol®, Confidor® 200 SC, Bayer Chlorothalonil 500 SC and Agral®. Prodigy is incompatible with mineral spray oils. Do not mix concentrates together but add each to the spray tank separately. As formulations of other manufacturers' products are beyond the control of Bayer Australia Limited, all mixtures should be tested prior to mixing commercial quantities. As changes in climatic conditions can alter the sensitivity of plants to mixtures of sprays, Bayer cannot be responsible for the behaviour of such mixtures.

Application (Cotton)

Thorough coverage of cotton plants is essential to achieve maximum performance from Prodigy. Equipment should be calibrated to achieve a minimum of 60 droplets/cm² on the target foliage. A droplet Volume Median Diameter (VMD) for optimum performance from Prodigy is dependent on equipment and is defined below. Do not apply when unfavourable environmental conditions may reduce the quality of spray coverage.

A spraydrift minimisation strategy should be employed at all times when applying sprays. The strategy envisaged is exemplified by the cotton industry's Best Management Practices Manual.

Ground Application (Cotton)

Application using ground equipment should be made using hollow cone nozzles with a minimum spray volume of 100 L/ha. Flat fan nozzles are not recommended but if used, higher water volumes will be required. A droplet VMD of 150 - 180 microns must be used. Where multiple nozzles per row are used, they should be of the same specification to ensure that each nozzle contributes an equal proportion of the required dose. Where multiple nozzles per row are used (particularly for banded applications) ensure the correct nozzle overlap pattern is achieved on the target foliage. Banded applications less than 100% are not recommended beyond the 15 node crop stage.

Aerial Application (Cotton)

Apply in a minimum spray volume of 25 L/ha. A droplet VMD of 120 - 150 microns must be used. Do not exaggerate swath width or exceed a swath width of 20 to 22 m. Do not apply Prodigy using Ultra Low Volume (ULV) methods. The use of large droplet placement equipment is not recommended.

Concentrate Spraying Equipment (Tomatoes)

Where concentrate equipment is used, increase the rate of Prodigy per 100 L in proportion to the reduction in spray volume applied per hectare. For example, if it requires 1000 L/ha of dilute spray mix to spray to runoff and the equipment applies 500 L/ha, use two times the rate of Prodigy/100 L. Do not use Prodigy in equipment requiring concentration greater than 5X (eg 625 mL/100 L is the maximum concentrate rate for the 125 mL/100 L dilute rate, and 850 mL/100 L is the maximum concentrate rate for the 170 mL/100 L dilute rate).

Precaution

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

Re-entry

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

Protection of Livestock

DO NOT graze any treated area or cut for stock food.
Low hazard to bees. May be applied on any plants at any time.
Keep animals out of operational areas during treatment.
Avoid spray drift onto adjoining properties or stock areas.

Protection of Wildlife, Fish, Crustaceans and Environment

Do NOT contaminate ponds, waterways and drains with this product or used container.
A spraydrift minimisation strategy should be employed at all times when aurally applying sprays. The strategy envisaged is exemplified by the cotton industry's Best Management Practices Manual.

DO NOT apply under meteorological conditions or from spraying equipment which could be expected to cause spray to drift onto adjacent areas, particularly wetlands, waterbodies or watercourses. DO NOT spray across open bodies of water.

Storage and Disposal (1 litre pack size)

Keep out of reach of children. Store in the closed, original container in a cool, well ventilated area. Do not store for prolonged periods in direct sunlight. Rinse container before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. Dispose of at a local authority landfill. If no landfill is available, bury the container 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.

Storage and Disposal (other sizes except 1000 L)

Keep out of reach of children. Store in the closed, original container in a cool, well ventilated area. Do not store for prolonged periods in direct sunlight. Triple or preferably pressure rinse container before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush or puncture and bury empty containers in a local authority landfill. If no landfill is available, bury the containers below 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.

Storage and Disposal (1000 L)

Keep out of reach of children. Store in the closed, original container in a cool, well ventilated area. Do not store for prolonged periods in direct sunlight. Empty contents fully into application equipment. Close all valves and return to point of supply for refill or storage.

Safety Directions

When opening the container, preparing the spray and using the prepared spray, wear cotton overalls buttoned to neck and wrist (or equivalent clothing) and elbow-length PVC gloves. After each day's use, wash gloves and contaminated clothing.

First Aid

If poisoning occurs contact a doctor or Poisons Information Centre (131126). For further information refer to the Material Safety Data Sheet for the product.

Liability

This product must be used strictly as directed. Bayer Australia Limited accepts no responsibility for loss or damage arising from failure to follow directions for use.

®Trademark

NRA Approval Number 52516/

Bayer Australia Limited emergency contact

1800 033 111

Australia wide, 24 hours



Bayer Australia Limited
875 Pacific Highway
Pymble NSW 2073
Telephone (02) 9391 6000

Bayer

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 partitioning 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.

Suggested Further Reading

National Registration Authority for Agricultural and Veterinary Chemicals 1996, *Ag Manual: The Requirements Manual for Agricultural Chemicals*, NRA, Canberra.

National Registration Authority for Agricultural and Veterinary Chemicals 1997, *Ag Requirements Series: Guidelines for Registering Agricultural Chemicals*, NRA, Canberra.

National Registration Authority for Agricultural and Veterinary Chemicals 1996, *MRL Standard: Maximum Residue Limits in Food and Animal Feedstuffs*, NRA, Canberra.

National Registration Authority for Agricultural and Veterinary Chemicals 1997, *Ag Labelling Code—Code of Practice for Labelling Agricultural Chemical Products*, NRA, Canberra.

NRA PUBLICATIONS ORDER FORM

To receive a copy of the full technical report for the evaluation of methoxyfenozide in the product Prodigy 240 SC Insecticide, please fill in this form and send it, along with payment of \$30 to:

Mr David Hutchison
Agricultural Evaluation
National Registration Authority for Agricultural and Veterinary Chemicals
PO Box E240
Kingston ACT 2604

Alternatively, fax this form, along with your credit card details, to the contact officer above at (02) 62723218.

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