Public Release Summary
on

Evaluation of the new active

PROTHIOCONAZOLE

in the product

REDIGO FUNGICIDAL SEED TREATMENT

Australian Pesticides and Veterinary Medicines Authority

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FOREWORD

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

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Ageing (Office of Chemical Safety), Department of Environment (Risk Assessment and Policy Section) and State departments of agriculture and environment.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of public release summaries for all products containing new active ingredients and for all proposed extensions of use for existing products.

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

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

More detailed technical assessment reports on all aspects of the evaluation of this chemical can be obtained by completing the order form in the back of this publication and submitting with payment to the APVMA. Alternatively, the reports can be viewed at the APVMA Library, 18 Wormald Street, Symonston, ACT 2609.

The APVMA welcomes comment on the usefulness of this publication and suggestions for further improvement. Comments should be submitted to the Pesticides Program Manager, Australian Pesticides and Veterinary Medicines Authority, PO Box E240, Kingston ACT 2604.

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LIST OF ABBREVIATIONS AND ACRONYMS

AC	active constituent
ACR	Acute to chronic ratio
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute Reference Dose (for humans)
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
CRP	Chemistry and Residues Program
d	day
DAT	Days After Treatment
DM	Dry Matter
DT_{50}	Time taken for 50% of the concentration to dissipate
DT_{90}	Time taken for 90% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EC	Emulsifiable Concentrate
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
ESI	Export Slaughter Interval
EUP	End Use Product
FAO	Food and Agriculture Organisation of the United Nations
Fo	original parent generation
FW	Fresh Weight
g	gram
GAP	Good Agricultural Practice
GC/MS	gas chromatography/mass spectroscopy
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Heamatocrit
HDPE	High-density polyethylene
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HPLC-UV	High Performance Liquid Chromatography with Ultra-Violet Detector
HR	Highest Residue
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LC-MS/MS	liquid chromatography, mass spectroscopy

LOEC	Lowest Observable Effect Concentration
LOEL	Lowest Observable Effect Level
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
MSMS	mass spectroscopy/mass spectroscopy
NOAEC	No Observable Adverse Effect Concentration
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration/Level
OC	Organic Carbon
OM	Organic Matter
PHED	Pesticide Handlers Exposure Database
PHI	Pre-harvest interval
po	oral
POEM	Predictive Operator Exposure Model (UK)
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
s	second
sc	subcutaneous
SC	Suspension Concentrate
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
µg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHO	World Health Organisation
WHP	Withholding Period

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of *REDIGO FUNGICIDAL SEED TREATMENT,* which contains the new active ingredient, prothioconazole. The product is proposed to be used for control of common bunt on wheat seed.

Responses to this Public Release Summary will be considered prior to registration of the product. They will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

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

Written comments should be received by the APVMA by 3 July 2007. They should be addressed to:

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Applicant

Bayer Cropscience Pty Ltd

Product Details

It is proposed to register REDIGO FUNGICIDAL SEED TREATMENT, containing prothioconazole at 100 g/L as a flowable concentrate formulation. REDIGO FUNGICIDAL SEED TREATMENT will be imported fully formulated and packaged in 10 L containers.

Prothioconazole is a new fungicide of the new fungicidal class of triazolinthiones. With respect to fungicide resistance, prothioconazole is classed as a Group C Fungicide.

Application is as a seed treatment to control common bunt *(Tilletia laevis and T.tritici)* of wheat.

Overseas registrations: Prothioconazole formulations are currently registered in the following countries: United Kingdom, France and Austria. It is used as a seed treatment to control various diseases of cereal crops including barley, rye, triticale and wheat.

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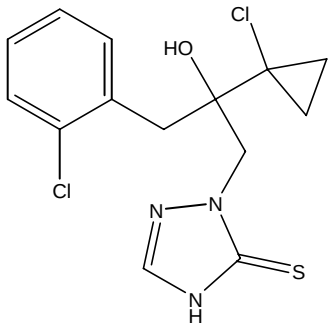
CHEMISTRY AND MANUFACTURE

Active Constituent

The active constituent prothioconazole is manufactured in Germany by Bayer CropScience GmbH at Bayer CropScience AG, BCS IOP A.I. Manufacturing Alte Heerstrasse, D-41538 Dormagen, and the application for approval is pending.

Chemical Characteristics of the Active Constituent

Common name:	Prothioconazole
Synonyms and Code Number:	JAU 6476
Chemical name (IUPAC):	(*RS*)-2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-2,4-dihydro-1,2,4-triazole-3-thione
(CA):	2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-trazole-3-thione
Chemical Abstracts Service (CAS) Registry Number:	178928-70-6
Molecular formula:	$C_{14}H_{15}Cl_2N_3OS$
Molecular weight:	344.26
Chemical structure:	

Physical and Chemical Properties of the Pure Active Constituent

Physical state:	Powder	
Colour:	Colourless to faintly beige	
Odour:	Faint uncharacteristic	
Optical rotation:	not optically active	
Melting point (for solids):	139.1 – 144.5 °C	
Boiling point (for liquids):	487 °C ± 50 °C at atmospheric pressure	
Density/specific gravity:	1.36 g/mL at 20 °C	
Solubility in water:	0.005 g/L at 20 °C at pH 4	
	0.3 g/L at 20 °C at pH 8	
	2.0 g/L at 20 °C at pH 9	
Solubility in fat and various organic solvents (20 °C):	ethyl acetate	> 250 g/L
	n-heptane	< 0.1 g/L
	xylene	8 g/L
	dichloromethane	88 g/L
	1-octanol	58 g/L
	2-propanol	87 g/L
	polyethylene glycol	> 250 g/L
	acetonitrile	69 g/L
	acetone	> 250 g/L

	dimethylsulfoxide 126 g/L
Vapour pressure:	<< 4 x 10^{-7} kPa at 20 °C << 4 x 10^{-7} kPa at 25 °C
Dissociation constant (pKa):	6.9
Photostability:	Shown to degrade under simulated sunlight conditions, with a mean photochemical half life of 47.7 hours, corresponding to 7.1 days in Phoenix, Arizona in June and 11 days in Athens in June.
Octanol/Water Partition Coefficient:	log P_{ow} = 4.05 at 20 °C unbuffered log P_{ow} = 4.16 at 20 °C pH 4 log P_{ow} = 3.82 at 20 °C pH 7 log P_{ow} = 2.00 at 20 °C pH 9
pH:	Not applicable
Storage stability:	Prothioconazole is chemically stable at temperatures of 54 °C for 2 weeks and is expected to be stable for at least 2 years when stored away from direct sunlight.
Corrosion characteristics:	not corrosive
Oxidizing properties:	not oxidizing
Flammability	not highly flammable
Explosive properties:	not explosive (although the dust may cause dust explosion and has a lower explosible limit of 50 g/m^3)
Chemical type:	Fungicide
Chemical family:	triazolinthiones

Formulated Product

Distinguishing name:	Redigo Fungicidal Seed Treatment
Formulation type:	Water dispersible granule
Active constituent concentration:	Prothioconazole (100 g/L)
Mode of Action:	Inhibition of the demethylation of lanosterol or 24-methylene-dihydrolanosterol, which are precursors of sterols in fungi (Avcare mode of action class C).

Physical and Chemical Properties of the Product

Physical state:	liquid
Colour:	red
Odour:	weak characteristic
Density/specific gravity (liquids):	1.15
Acidity, alkalinity or pH value:	4.5 – 6.5 (neat)
Viscosity:	28 – 43 seconds flow time at 20 °C
Surface tension:	36.6 mN/m at 20 °C
Flash point:	no flash point up to the boiling point (100 °C)
Flammability:	auto-ignition temperature: 425 °C
Explosive properties:	not explosive
Corrosion Characteristics:	slightly corrosive to tinplate, significantly corrosive to plain steel, not corrosive to aluminium, copper, brass, stainless steel, high density polyethylene

Storage Stability:	Stability data provided by Bayer Cropscience Pty Ltd supports a storage life of 2 years when stored under normal conditions in high density polyethylene containers.

Recommendation

The Chemistry and Residues Program have evaluated the chemistry aspects of Redigo Fungicidal Seed Treatment (manufacturing process, quality control procedures, batch analysis results, analytical methods, storage stability, and specifications for container for the product) and support registration of Redigo Fungicidal Seed Treatment.

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TOXICOLOGICAL ASSESSMENT

Evaluation of Toxicology

The toxicological database for prothioconazole consisting primarily of toxicological studies conducted in laboratory 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 may occur 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. Similarly, 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 adverse effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are used to develop acceptable limits for dietary or other intakes (ADI and ARfD) at which no adverse health effects in humans are expected.

Toxicokinetics and Metabolism Studies

Following oral dosing in rats, prothioconazole was rapidly and extensively (>90%) absorbed. The highest concentration levels were observed in the gastrointestinal tract and liver, followed by kidney, fat, thyroid and adrenal gland. The concentration in liver was markedly higher in males relative to females. Excretion was extensive and relatively rapid, mainly via faeces. Extensive biliary excretion was shown by bile duct cannulated rats, and there was evidence of enterohepatic recirculation. Absorption was slower in females, with an apparently greater extent of enterohepatic recirculation and greater urinary excretion. A slightly lower extent of absorption was indicated by multiple dosing. Otherwise, there were no significant differences related to sex, high or low dosing or multiple dosing. The principle metabolic reactions were desulphuration, oxidative hydroxylation of the phenyl moiety and conjugation with glucuronic acid (a number of glucuronide-conjugated metabolites were identified). Many metabolites were derived from the desthio metabolite (prothiconazole-desthio). The desthio metabolite and prothioconazole were the principal components in excreta.

Acute Studies

Prothioconazole was of low oral (LD_{50} >6200 mg/kg bw), dermal (LD_{50} >2000 mg/kg bw), and inhalation toxicity (LC_{50} >4990 mg/m^3) in rats. The compound was neither an irritant for skin and eyes in rabbits, nor a skin sensitiser in guinea pigs.

The product, Redigo Fungicidal Seed Treatment containing 100 g/L prothioconazole, was of low oral toxicity in rats (LD_{50} >2500 mg/kg bw), and had low dermal toxicity (LD_{50} >4000 mg/kg bw) and inhalational toxicity (LC_{50} >2735 mg/m^3) in the rat. The product was non-irritating to eyes and skin, but exhibited slight skin sensitisation in guinea pigs.

Short-term Studies

Prothioconazole in the diet was administered to rats at 0, 196, 1480 and 9250 ppm for 4 weeks. An increased ALAT and alkaline phosphatase were seen at 1480 ppm. However the clinical chemistry changes recorded at 1480 ppm are not considered to be toxicologically

significant in the absence of any other findings. Similar but more marked clinical chemistry findings were recorded in both sexes at 9250 ppm, along with reduced bodyweight gains, increased food and water consumption and raised liver weights. Gross necropsy and histopathological findings in the kidneys at 9250 ppm indicated a toxic effect on the kidneys which may have accounted for the reduced urinary output at this dosage (despite increased water consumption). Thyroid hormone levels were affected in females at 9250 ppm but there were no histopathological findings in the thyroids. The NOAEL for the study is therefore considered to be 1480 ppm (equal to approximately 146 and 151 mg/kg bw/day in males and females respectively). The study also indicated that prothioconazole was relatively unstable when formulated with diet.

In order to compare the effect of different routes of dose administration on the toxicity of prothioconazole, rats were given the test compound in the diet (10000 ppm) or by gavage (1000 mg/kg bw/day) for 4 weeks. There were no deaths. The only clinical sign was piloerection in males and females treated with prothioconazole. Food consumption was slightly higher in treated animals - on a per bodyweight basis only in gavage animals, and on a grams per animal basis only in animals receiving prothioconazole in the diet. Water consumption was markedly higher in animals receiving prothioconazole in diet. Reduced bodyweight gains were recorded in treated animals. ALAT (both sexes), alkaline phosphatase (females) and urea (males) were slightly increased in treated animals. Treatment-related hepatic enzyme activities (increases in ECOD, EH and GS-T and GLU-T, but a decrease in ALD activity) were observed. Treatment-related histopathological effects (increased frequency and/or severity of predominantly bilaterally occurring basophilic tubules of kidney, minimal to slight cytoplasmic change in centrilobular hepatocytes) were evident in the animals of both sexes administered prothioconazole by diet and by gavage. Consistently gavage dosing led to more marked effects than dietary administration. The study was not designed for establishing an NOAEL value.

Prothioconazole was administered dermally to rats at concentration of 0, 100, 300 and 1000 mg/kg bw/day. There were no mortalities, no clinical signs, no ophthalmoscopy effects, and no effect on skin thickness. Bodyweights and food consumption were not affected by treatment. There were isolated incidences of erythema in 1/10 females at 100 mg/kg bw/day and 2/10 females at 1000 mg/kg bw/day, but not at 300 mg/kg bw/day. In the absence of a consistent effect these findings were attributed to mechanical irritation at the application site due to the dosing procedure. Haematology and clinical chemistry values were similar between controls and treated animals. There were no effects on organ weights and no treatment-related macroscopic or microscopic findings. Plasma levels of prothioconazole were below the limit of quantification in all animals except for one male and one female at 1000 mg/kg bw/day. The NOAEL was 1000 mg/kg bw/day, the highest dose tested.

Subchronic Studies

In a 14-week gavage study, rats were administered prothioconazole at dose levels of 0, 20, 100 and 500 mg/kg bw/day. Three deaths were attributed to blood collection and two were attributed to misdosing. The remaining death, (a high dose female) was killed in a moribund condition after 96 days; necropsy findings were dilations in the urinary bladder, histopathology findings were inflammation of the tongue and basophilic tubules in the kidney. There were no clinical signs and no significant ophthalmoscopy findings in high dose animals at the end of the study. Water consumption was increased in both sexes at the high dose level. Decreased urinary volume in high dose males (weeks 4 and 13) and females (week 4 only), with corresponding increases in urine density and protein concentration. At 500 mg/kg bw/day, the absolute and relative liver weights of female animals were significantly increased, and those of the spleen of males were significantly decreased. Slight hepatocytic hypertrophy

with cytoplasmic change was recorded in both sexes at 500 mg/kg bw/day. Increased severity of basophilic tubules in the renal cortex was also recorded in males at 500 mg/kg bw/day. A NOAEL in this study was established as 100 mg/kg bw/day.

In the other rat gavage study, animals were given prothioconazole at dose levels of 0, 25, 100, and 400 mg/kg bw/day for 14 weeks. One animal died following misdosing and five animals died during blood collection. A significant increase in absolute and relative liver weights in all treated male groups and in females at 100 and 400 mg/kg bw/day were seen. Consistently the microsomal enzyme activities in liver homogenates determined were increased in a dosage-related pattern in all treated females groups. Increases were also recorded in most enzymes in treated males at 400 and 100 mg/kg bw/day, but the increases were less marked. Hepatocellular hypertrophy with cytoplasmic change was recorded in both sexes at 100 and 400 mg/kg bw/day with severity increasing with dose. The NOAEL in this study was 25 mg/kg bw/day, based on histopathological findings in the liver at 100 mg/kg bw/day.

In a 13-week gavage study, dogs were administered prothioconazole at dose levels of 0, 25, 100 and 300 mg/kg bw/day. One female animal in the high dose group died due to misdosing. The kidneys and possibly the liver were identified as target organs for prothioconazole in dogs. There was also evidence of effects on the liver at the high dose level (300 mg/kg bw/day), including increased ALT levels and increased relative liver weights, but no treatment-related histopathological findings in the liver. Changes in thyroid hormone levels (without histopathological changes in the thyroids) may have been secondary to changes in liver enzyme activity, but only minor changes in microsomal liver enzyme activities were recorded. Increased liver weights did not persist following an 8 week recovery period, but increased ALT levels demonstrated only partial recovery. The NOAEL in this study was 25 mg/kg bw/day based on histopathological changes in the kidneys at 100 mg/kg bw/day.

Chronic/Carcinogenicity Studies

In a 52-week study, dogs were administered prothioconazole at dose level of 0, 5, 40, and 125 mg/kg bw/day by gavage. There were no deaths and no treatment related ophthalmological effects. The only significant clinical signs noted were sporadic post-dose vomiting and increased salivation. These signs occurred in both treated and control animals with no relationship to dosage and were attributed to being a behavioural response to gavage dosing. Food consumption was lower than controls in high dose females throughout most of the study. Overall bodyweight gain was lower than controls in high dose animals, and was also marginally lower in males only at 40 mg/kg bw/day. Bodyweights at termination in high dose females were markedly lower than other female groups. There were no effects of treatment on electrocardiogram, rectal temperatures, thoracic auscultation or neurological assessments, haematology parameters, and on urinalysis parameters. Clinical chemistry analysis revealed increased serum alkaline phosphatase in females at 40 and 125 mg/kg bw/day. From liver sections an increased cytochrome P450 activity in males at 125 mg/kg bw/day and in all treated females was seen. The pattern of gross necropsy findings did not indicate any effects of treatment. Absolute and relative liver weights were increased in males and females at 125 mg/kg bw/day. Absolute and relative liver weights were also higher than controls in females at 40 and 5 mg/kg bw/day but the increases were < 20% and there was no dose-response relationship. Absolute and relative kidney weights were also increased in females at 125 mg/kg bw/day. The increase in relative kidney weight was marked due to the lower terminal bodyweights in this group. There were no other notable organ weight findings. Treatment-related histopathological changes were apparent in the liver and kidneys of both sexes at 125 mg/kg bw/day. The morphological changes in the kidney were characterised by minimal to mild focal to multifocal chronic inflammation of the renal cortex, often with

extensions into the medulla. Minimal inflammatory cells, particularly lymphocytes, were also present. Adjacent tubules frequently showed compensatory hyperplastic changes and in some foci, crystalline material was present. Inflammation occurred in isolated males at 40 and 125 mg/kg bw/day and in all females at 125 mg/kg bw/day. Crystalline material occurred in females at 40 and 125 mg/kg bw/day, and in one male at 125 mg/kg bw/day. In the liver, pigmentation was recorded in all top dose females and one top dose male, most prominently in the Kupffer cells. No hepatocellular hypertrophy was recorded in any group. The degree of pigmentation in the spleen was minimally increased in females at 40 and 125 mg/kg bw/day however the toxicological significance of this is uncertain. There were no notable histopathological findings in any other organs or tissues. The NOAEL in this study was 5 mg/kg bw/day based on histopathological findings in the kidneys at 40 mg/kg bw/day (and marginal effects on bodyweight gains and increases in ALP levels which were more markedly effected at the top dose level).

In the other 1-year gavage study, rats were given prothioconazole at dose levels of 0, 5, 50, and 750 mg/kg bw/day. There were 3 deaths at the high dose which were not apparently related to mis-dosing or blood sampling, but no obvious cause of death related to treatment was identified. There were treatment-related clinical signs in animals at 750 mg/kg bw/day only, namely increased salivation, increased urine excretion and bloody muzzle. Ophthalmoscopy revealed an increased incidence of water clefts in the anterior cortex of the lens in females at 750 mg/kg bw/day. Bodyweight gains of males and females at 750 mg/kg bw/day were significantly lower such that bodyweights at termination were up to 14% lower than controls. Water consumption was markedly increased in both sexes at 750 mg/kg bw/day. Mean haemoglobin concentration (but no other RBC parameters) was slightly reduced in males at 750 mg/kg bw/day at termination only. Platelet count was increased in males at 750 mg/kg bw/day at all time points tested. Alkaline phosphatase activity was statistically significantly increased in males (week 14) and females (weeks 27 and 52) at 750 mg/kg bw/day. Plasma concentrations of urea, creatinine, bilirubin, cholesterol and triglycerides were all increased in males and females at 750 mg/kg bw/day at most time points. Plasma protein concentration was reduced in males at 750 mg/kg bw/day at the end of the study. At 750 mg/kg bw/day an increased urinary volume and correspondingly reduced urinary density and lower urine pH were observed. At 750 mg/kg bw/day an increased relative liver and kidney weights, and treatment-related histopathological findings in males and females were recorded in both sexes. The NOAEL was 50 mg/kg bw/day, based on liver and kidney effects and reduced bodyweights and related effects at 750 mg/kg bw/day.

In a 2-year gavage study in rats, animals were given prothioconazole at dose levels of 0, 5, 50, 750 mg/kg bw/day. There were no deaths and no treatment related ophthalmological effects. The only significant clinical signs were sporadic post-dose vomiting and increased salivation. Food consumption was lower than controls in high dose female animals throughout most of the study. Overall bodyweight gain was lower than controls in high dose animals, and was also marginally lower in males only at 40 mg/kg bw/day. Bodyweights at termination in high dose females were markedly lower than other female groups. No effects of treatment were recorded on electrocardiogram, rectal temperatures, thoracic auscultation or neurological assessments, haematology and urinalysis parameters. The only consistent clinical chemistry findings were increased serum alkaline phosphatase in females at 40 and 125 mg/kg bw/day. The pattern of gross necropsy findings did not indicate any effects of treatment. Absolute and relative liver weights were increased in males and females at 125 mg/kg bw/day. Absolute and relative liver weights were also higher than controls in females at 40 and 5 mg/kg bw/day but the increases were less than 20% and there was no dose-response relationship. Absolute and relative kidney weights were also increased in females at 125 mg/kg bw/day. Treatment-related histopathological changes were apparent in the liver and kidneys of both sexes treated

at 125 mg/kg bw/day. The NOAEL in this study was 5 mg/kg bw/day based on histopathological findings in the kidneys at 40 mg/kg bw/day.

In a 2-year carcinogenicity study in rats, 0, 5, 50 and 750 mg/kg bw/day prothioconazole were administered by gavage. Mortality was higher in high dose females until the dose level was lowered to 625 mg/kg bw/day, following which the mortality rate was similar to controls. Mortality was also increased in males at the high dose, and remained higher than controls even following the reduction in the high dose level. There were treatment-related clinical signs recorded in animals of both sexes at the high dose level, consisting of increased incidences of emaciation, increased urine excretion and poor general condition. Pallor and bloody muzzle were also recorded in males only. The only notable clinical sign in animals at 50 mg/kg bw/day was increased urine excretion in males. Ophthalmoscopy revealed an increased incidence of water clefts in the anterior cortex of the lens in high dose animals. In both sexes bodyweight gains were significantly lower, and food and water consumption were increased at the high dose level than the controls. Erythrocyte counts, haemoglobin concentration and hematocrit values were depressed in both sexes at 750 mg/kg bw/day. Increased platelet, neutrophil and white blood cell counts were recorded in males at 750 mg/kg bw/day and increased platelet counts were also recorded in males at 50 mg/kg bw/day. At 750 mg/kg bw/day in both sexes ALAT was reduced and ALP was increased. In males only, glucose, protein and albumin were slightly reduced, urea and creatinine were markedly increased and cholesterol was slightly increased. The thyroid hormone T4 was reduced in plasma at the high dose in both sexes and at 5 mg/kg bw/day in males. T3 was slightly reduced at the high dose and TSH was increased at the high dose in females and effects on T3 and TSH were not as consistent as the T4 effects. Treatment-related urinalysis findings at the high dose were increased urinary volume, lower urinary pH and (in males) increased protein excretion. Significant increases in relative liver and kidney weights were recorded in both sexes at the high dose. Increased incidence and/or severity of histopathological findings in the liver, kidneys and urinary bladder were recorded in both sexes at the high dose, and also in males at 50 mg/kg bw/day. There was no increase in the number of tumour-bearing animals or total number of tumours in treated animals. No notable increases in tumours were recorded in any of tested organs (liver, kidneys, urinary bladder, and reproductive organs) and tissues. NOAEL was 5 mg/kg bw/day in this study. It is concluded that prothioconazole was not carcinogenic in rats.

In a18-month carcinogenicity study in mice, prothioconazole was given to the animals by gavage at dose levels of 0, 10, 70 and 500 mg/kg bw/day. There was no significant effect of treatment on survival and survival was acceptable for the assessment of carcinogenicity. There were no clinical signs considered to represent a specific effect of treatment. Bodyweight gains were significantly reduced in both sexes at 70 and 500 mg/kg bw/day. Food consumption was similar between treated animals and controls. Liver weights (absolute and relative) were significantly increased in both sexes at 70 and 500 mg/kg bw/day. Absolute and relative kidney weights were lower in high dose males. Significant gross necropsy findings were increased incidence of distinct lobulation of the liver (males) and changes to the surface (males) and the colour of the kidneys (both sexes) at 70 and/or 500 mg/kg bw/day. Treatment-related non-neoplastic histopathological findings were recorded in the liver and kidneys. There was no increase in the number of tumour-bearing animals or total number of tumours in treated animals. Treatment was also not associated with earlier occurrence of tumours. The NOAEL in this study was 10 mg/kg bw/day. It is concluded that prothioconazole was not carcinogenic in mice.

Reproduction Studies

In a multigeneration gavage study, Groups of 30/sex Wistar rats were treated with prothioconazole (0, 9.7, 95.6 and 726 mg/kg bw/day) from pre-mating through to weaning of F1 generation pups. Toxicity was recorded in parental animals (lower bodyweight gains and increased liver weights) at the intermediate dose level. Slightly more marked toxicity consistent with effects seen in previous repeat dose rat studies (hepatocytomegaly, multifocal chronic nephrosis) was recorded at the high dose level, but overall the level of parental toxicity was no more than moderate in this study. Reproductive effects were recorded in parental females at the high dosage which could have the potential to affect reproductive outcome (disruption to the oestrous cycle), but these effects were accompanied by other evidence of systemic toxicity and did not result in effects on mating, fertility or gestation indices. Effects on developing pups were restricted to the high dose level and consisted of reduced pup weight gain, reduced spleen weights and delayed preputial separation (which was considered secondary to retarded pup growth.). Since these effects occurred at a dose level also giving rise to effects in parental animals, a selective effect on offspring was not indicated. There was a clear margin between the NOAELs for parental toxicity (9.7 mg/kg bw/day) and the NOAELs for reproductive effects (95.6 mg/kg bw/day) and effects on offspring (95.6 mg/kg bw/day); therefore prothioconazole was not considered to be selectively toxic to the reproductive system or developing offspring.

Developmental Studies

In a developmental study, groups of 26 inseminated female Wistar rats received daily gavage doses of 0, 80, 500 and 1000 mg/kg bw/day prothioconazole from days 6 to 19 *post coitum*. An increased incidence of microphthalmia was observed at the high dose level. The increased incidence of rudimentary supernumerary ribs at the high dose level was also considered to be treatment related. However, marked maternal toxicity was also recorded at this dose level (transient bodyweight loss and reduced bodyweight gains, significantly increased water consumption). An increased incidence of microphthalmia was also recorded at the low dose level, but not at the intermediate dose level, and this absence of a dosage-related trend and the fact that the incidence at the intermediate dose was within the historical control range suggests that this finding at the low dose level was spontaneous rather than treatment-related. The NOAEL for dams was 80 mg/kg bw/day based on reduced bodyweight gains and increased water consumption. The NOAEL for direct fetotoxicity was 500 mg/kg bw/day based on retarded development of foetuses, and reduced foetal weights. An increased incidence of engorged placentas (but not an increase in placental weight) was also recorded at the LOEL. The increased incidence of supernumerary ribs is equivocal when compared with historic control data and is possibly related to maternal toxicity. Findings of increased incidence of renal pelvis dilatation and incomplete ossification in this group were considered to be secondary to the retarded foetal growth. The NOAEL for developmental effects was 500 mg/kg bw/day, based on the incidence of microphthalmia and supernumerary ribs above the historical control range.

In a rat dermal developmental toxicity study, groups of mated female Wistar rats received daily topical applications of test material [dose levels: 1000 mg/kg bw/day prothioconazole technical and 1000 mg/kg bw/day of an EC formulation and an aqueous dilution of an EC formulation (containing 250 mg/kg bw/day prothioconazole plus non-active constituents)] from days 6 to 19 *post coitum*. Dermal application of the undiluted EC250 formulation was associated with skin irritation. There were no systemic toxic effects identified in any group, and no effects on developing offspring. The NOAEL for maternal and developmental toxicity via dermal application was 1000 mg/kg bw/day for prothioconazole technical material, 1000 mg/kg bw/day for the EC250 formulation (equivalent to 250 mg/kg bw/day

prothioconazole) and 1000 mg/kg bw/day for the diluted EC250 formulation (equivalent to 62.5 mg/kg bw/day prothioconazole). Hence, the use of the formulation was not associated with an obvious increase in toxicity when administered by the dermal route.

In a developmental gavage study, groups of mated female Chinchilla rabbits received daily gavage doses of 0, 10, 30 and 80 mg/kg bw/day prothioconazole from days 6 to 27 *post coitum*. There was clear maternal toxicity at the high dose level. The only adverse effects on offspring (abortions/total litter loss, reduced fetal weights) were also recorded at the high dose level and were likely to have been secondary to the maternal toxicity. Retarded ossification may have been secondary to the retarded fetal growth. The NOAEL for maternal toxicity was 80 mg/kg bw/day. The NOAEL for developmental effects was 80 mg/kg bw/day. There was no evidence of a teratogenic effect up to 350 mg/kg bw/day.

Prothioconazole was not associated with selective effects on the reproductive system or developing offspring in the absence of toxicity in parental animals. Microphthalmia was indicated in rats (but not rabbits) at a maternally toxic dose, with a NOAEL of 500 mg/kg bw/day, although this may have been an enhancement of a common spontaneous malformation in this species rather than a direct developmental effect.

Genotoxicity Studies

The genotoxicity of prothioconazole has been examined in a battery of *in vitro* genotoxicity studies including the Ames test, HGPRT mutation test and unscheduled DNA synthesis (UDS) assay in rat hepatocytes, and *in vivo* micronucleus and UDS assays. An equivocal results in an in *vitro* UDS assay and positive results in an *in vitro* chromosome aberration assay were recorded. However prothioconazole exhibited negative results in an *in vivo* rat liver UDS test and an *in vivo* micronucleus assay in mouse bone marrow. Prothioconazole is unlikely to be genotoxic *in vivo.*

Public Health Standards

Poisons Scheduling

The National Drugs and Poisons Schedule Committee (NDPSC) considered the toxicity of the product and its active ingredients.

On the basis of its toxicity, the NDPSC has granted prothioconazole an exemption from scheduling in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). There are provisions for appropriate First-Aid Instructions and Safety Directions on the product label.

NOEL/ADI/Acute Reference Dose (ARfD)

The Acceptable Daily Intake (ADI) is that quantity of an agricultural compound, which can safely be consumed on a daily basis for a lifetime and is based on the lowest NOEL obtained in the most sensitive species. This NOEL is then divided by a safety factor, which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.
The existing ADI for prothioconazole remains appropriate at 0.001 mg/kg bw/day, based on a NOAEL of 1.1 mg/kg bw/day in a rat chronic/carcinogenicity study on prothioconazole-desthio (major metabolite), using a 100-fold safety factor.

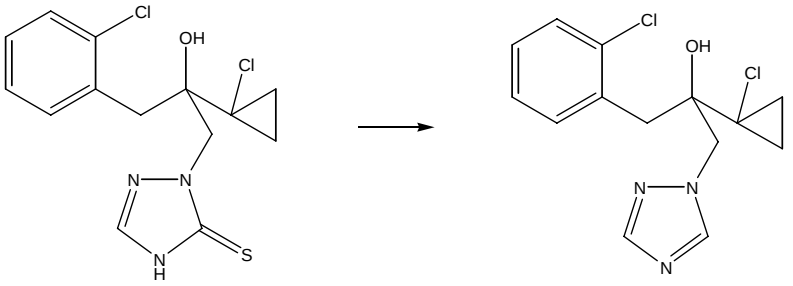
The acute reference dose (ARfD) is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated, event. The ARfD is derived from the lowest single or short term dose which causes no effect in the most sensitive species of experimental animal tested,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

The existing ARfD for prothioconazole remains appropriate at 0.03 mg/kg bw/day, based on a NOAEL of 3 mg/kg bw/day in a rat developmental toxicity study on prothioconazole-desthio (major metabolite), using a 100-fold safety factor.

RESIDUES ASSESSMENT

Metabolism

Wheat plants were treated with a foliar or seed treatment application of phenyl-^{14}C-prothioconazole **(1)**. Total radioactive residues (TRR) were predominantly found in the forage, hay or straw, with virtually no (<1%) of the TRRs located in the wheat grain. In peanut plants treated with ^{14}C prothioconazole, the majority of the extractable TRRs were located in the hay. The TRRs or identified metabolites in the grain or nutmeat, respectively, comprised a relatively small proportion of all residues. When absorbed by the plant, prothioconazole was extensively metabolised to form a number of compounds, the major one being prothioconazole-desthio **(2)**.



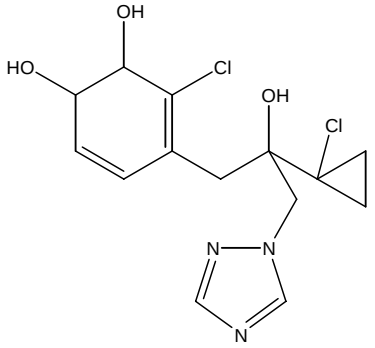
(1) **(2)**

Laying hens were dosed at 10 mg/kg bw for 3 consecutive days with phenyl-^{14}C-prothioconazole. Excretion of radioactivity over the period of the study was greater than 78%. Radioactivity in eggs accounted for 0.01% of the total dose. Radioactive residues in tissues were highest in kidney (4.537 mg equiv./kg) followed by liver (4.081 mg equiv./kg), egg from ovary/oviduct (0.597 mg equiv./kg), subcutaneous fat (0.433 mg equiv./kg), skin (0.383 mg equiv./kg), leg muscle (0.107 mg equiv./kg) and breast muscle (0.058 mg equiv./kg).
Prothioconazole was the major residue in liver and fat (25-30%). Metabolites accounting for greater than 10% of the TRR were prothioconazole-desthio in fat (28%) and egg (19%), and at concentrations of 4-6% in other matrices. Other metabolites were extracted from hen tissues, including the glucuronide of prothioconazole, in the muscle, liver and egg, at concentrations of 16%, 12% and 17%, respectively.

A **Lactating goat** was dosed with phenyl-^{14}C-prothioconazole at 10 mg/kg bw for 4 consecutive days. Total radioactive residues in excreta were 66% of the administered dose. Total ^{14}C-residues accounted for 0.97% of the administered dose in the milk and tissues. Of these, the total radioactivity was 6.762 mg equiv./kg in kidney, 6.092 mg equiv./kg in liver, 0.172 mg equiv./kg in omental fat, 0.162 mg equiv./kg in perirenal fat, 0.149 mg equiv./kg in subcutaneous fat, 0.106 mg equiv./kg in flank muscle, 0.100 mg equiv./kg in loin muscle, 0.084 mg equiv./kg in round muscle and 0.061 mg equiv./kg in milk at sacrifice. The parent compound was a significant residue in liver, muscle, kidney and fat, present at concentrations of 12-18% of the total radioactive residues (TRRs). Prothioconazole-desthio was not a significant metabolite, being present at concentrations of only 1.2-3.3% of the TRRs, except for fat, where this compound was accounted for 19% of the TRRs. The 3-hydroxy desthio-glucuronide of JAU6476 was the major metabolite isolated from the muscle and kidney, respectively accounting for 0.013 mg a.i. equiv./kg and 2.32 mg a.i./equiv./kg.

Phenyl-^{14}C-prothioconazole-desthio was administered to lactating goats. Total radioactive residues in urine and faeces were over 73% of the administered dose. Less than 0.05% of the total dose was present in the milk. Total ^{14}C residues in other tissues accounted for 1.87% of the administered dose, with 18.986 mg equiv./kg in kidney, 18.422 mg equiv./kg in liver, 0.262 mg equiv./kg in combined muscle samples and 0.230 mg equiv./kg in combined fat samples.

Prothioconazole-desthio was the major compound isolated from the liver (31% of the TRRs), and a significant compound present in the fat, accounting for 13% of the TRRs. The compound was in muscle and kidney, comprising 1.88% and 7.66% of the TRRs respectively, but was not isolated from the milk. Sulfate conjugate compounds were isolated from the milk, accounting for over 44% of the TRRs. Desthio-3,4-dihydroxy-dienyl glucuronide **(**unconjugated version shown, **3)** was the major metabolite isolated from the muscle with 12.78% of the TRRs, kidney with 13.75% of the TRRs and fat with 15.15% of the TRRs.



(3)

Analytical methods

Analytical methods to determine prothioconazole residues in wheat matrices, animal tissues and milk were provided.

Prothioconazole and prothioconazole-desthio residues in wheat materials and prothioconazole and prothioconazole-desthio prothioconazole-3-hydroxy-desthio (2-(1-chlorocyclopropyl)1-(2-chloro-3-hydroxy-phenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol) and prothioconazole-4-hydroxy-desthio (2-(1-chlorocyclopropyl)1-(2-chloro-4-hydroxy-phenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol), in animal tissues are determined by RP-HPLC with mass spectrometric detection following extraction in aqueous acetonitrile. For animal matrices, acid hydrolysis was also employed to liberate non-aromatic precursor compounds and those conjugated by glycosidic linkages. The LOQ was 0.05 mg/kg in wheat matrices, 0.01 mg/kg in cattle meat, liver, kidney and fat and was 0.004 mg/kg in cattle milk.

Storage stability

The stability of residues of prothioconazole and prothioconazole-desthio was tested. Residues of prothioconazole were shown to be stable in wheat forage for up to 4 months, 6 months in grain and 13 months in straw. It is recommended to avoid storage intervals exceeding these time periods prior to residues analyses.

Residues of prothioconazole-desthio were shown to be stable in wheat forage, grain and straw for up to 18 months.

Storage stability information was also provided for animal tissues. Residues of prothioconazole-desthio, prothioconazole-3-hydroxy-desthio and prothioconazole-4-hydroxy-desthio in fortified samples of bovine muscle, liver, and kidney were stable after storage for 3 weeks in kidney and four weeks in milk, meat, liver and fat.

The data suggest that any crops with incurred prothioconazole residues should be analysed relatively quickly and not stored for prolonged periods. Tissues and milk from livestock that may be exposed to prothioconazole should be similarly analysed within three-four weeks of sample collection.

Residue definition

Prothioconazole and the prothioconazole-desthio were significant components of the total residue in plant matrices. In animal matrices, prothioconazole-desthio, prothioconazole-3-hydroxy-desthio and prothioconazole-4-hydroxy-desthio are recommended for inclusion in the residue definition for commodities of animal origin as analyses of these compounds are included in the analytical methods provided. Separate residue definitions are recommended for commodities of plant origin and commodities of animal origin:

For commodities of plant origin: "*sum of prothioconazole and prothioconazole desthio (2-(1-chlorocyclopropyl)1-2(-chlorophenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol), expressed as prothioconazole*".

For commodities of animal origin: "*sum of prothioconazole, prothioconazole desthio (2-(1-chlorocyclopropyl)1-2(-chlorophenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol), prothioconazole-3-hydroxy-desthio (2-(1-chlorocyclopropyl)1-(2-chloro-3-hydroxy-phenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol) and prothioconazole-4-hydroxy-desthio (2-(1-chlorocyclopropyl)1-(2-chloro-4-hydroxy-phenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol), expressed as prothioconazole*".

Residue trials

A total of 12 residue trials for wheat and barley were provided. Trials were conducted in Australia (SA (one barley trial), NSW (one trial each barley and wheat) and Vic (one wheat trial)), and eight sites across the EU (all wheat trials). Australian trials were conducted at rates of up to 6 × the nominal application rate (5 g a.i./100 kg seed), and European trials were conducted at rates of 2-3 × the nominal Australian application rate. Prothioconazole was applied as a single application seed treatment.
In wheat and barley grain collected at the time of commercial harvest, residues of prothioconazole were all less than the limit of quantitation, 0.05 mg/kg.

Based on the data, an MRL of *0.05 mg/kg is appropriate for wheat. The MRL incorporates the parent compound and the desthio metabolite. The WHP: "Not Required when used as directed" is supported by the data provided.

Processing data were not provided with the application, however, as residues are not likely to be quantifiable from the proposed use pattern, it is unlikely that there will be any quantifiable residues present in any processed fractions (bran, shorts, germ, etc).

Straw samples were collected at the time of commercial harvest. In the Australian trials, residues of prothioconazole and prothioconazole-desthio were <0.05 mg/kg (assuming that there would be negligible quantities of the parent compound present). From the European studies, residues of prothioconazole-desthio only in straw were all <0.05 mg/kg. It is

recommended that a Table 4 entry in the *MRL Standard* for prothioconazole in wheat straw be established at *0.05 mg/kg.

Forage samples were collected between 35 and 73 DAT in the European studies and between 41-73 days in the Australian studies. A 5-week grazing/cutting for stockfood withholding period for use of prothioconazole treated seed was proposed. In the Australian trials, residues of prothioconazole and prothioconazole-desthio were <0.05 mg/kg (assuming that there would be negligible quantities of the parent compound present) at a WHP of 41-42 days. From the European studies, residues of prothioconazole-desthio only in forage were all <0.05 mg/kg, with the shortest WHP of 35 days. It is recommended that a Table 4 entry in the *MRL Standard* for wheat forage (fresh weight) be established for prothioconazole at *0.05 mg/kg.

Animal commodity MRLs

Cattle and other grazing livestock could consume forage from failed crops or straw and stubble from harvested crops. Poultry could be exposed to prothioconazole and prothioconazole-desthio in the diet from consumption of grain from treated crops.

Residues in the forage and straw were all less than the limit of quantitation (0.05 mg/kg) at 5 weeks after planting (forage samples) and at the time of commercial harvest (straw samples).

Dairy cattle were dosed at 5.1 ppm (0.16 mg/kg bw), 29 ppm (0.95 mg/kg bw) and 125 ppm (3.93 mg/kg bw) in the diet for 28 consecutive days. From the 5.1 ppm dosing, detectable residues of prothioconazole-3-hydroxy-desthio, prothioconazole-4-hydroxy-desthio and prothioconazole-desthio were observed only in the liver (maximum 0.05 mg/kg) and kidney (maximum 0.03 mg/kg). Residues were <0.01 mg/kg in muscle and fat. At this feed level, residues in milk were <0.004 mg/kg.

Residues present in the forage and straw grown from treated seed were less than 0.05 mg/kg 35 days after treatment (forage) or at the time of commercial harvest (straw).

Given that the feeding of treated produce would give rise to an exposure of <0.05 ppm in the diet, it is considered unlikely that quantifiable residues of prothioconazole would be observed in milk or tissues of livestock consuming feed grown from treated seed.

It is appropriate to establish the following MRLs for mammalian animal commodities:

MO 0105	Edible offal [Mammalian]	*0.05 mg/kg
MM 0095	Meat [Mammalian][in the fat]	*0.01 mg/kg
ML 0106	Milks	*0.01 mg/kg

A poultry feeding study was not provided. However, likely residues in poultry tissues as a result of eating grain grown from treated seed are expected to be similar to those in the reported dairy cattle feeding study. Also, residues in wheat grain and processed wheat fractions from prothioconazole treated seed are likely to be less than the reported LOQ of 0.05 mg/kg. The following MRLs are recommended for poultry tissues:

PE 0112	Eggs	*0.01 mg/kg
PM 0110	Poultry meat	*0.05 mg/kg
PO 0111	Poultry, edible offal of	*0.05 mg/kg

Estimated dietary intakes

The chronic dietary exposure to prothioconazole is estimated by the National Estimated Daily Intake 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 *Guidelines for predicting dietary intake of pesticide residues (revised)* [World Health Organisation, 1997].

The NEDI for prothioconazole is equivalent to 2% of the ADI. It is concluded that the chronic dietary exposure is acceptably low.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR using 97.5th percentile food consumption data from the 1995 National Nutrition Survey of Australia. NESTIs were in the range <2.5% of the ARfD for children 2-6 years old and <1% of the ARfD for the general population 2 years old and above.

The NESTIs for all relevant commodities are less than the ARfD. It is concluded that the acute dietary exposure is acceptably low.

Recommendations

MRL changes

The following amendments will be made to the *MRL Standard*:

Table 1

Compound	Food		MRL (mg/kg)
ADD: Prothioconazole			
	MO 0105	Edible offal [mammalian]	*0.05
	PE 0112	Eggs	*0.01
	MM 0095	Meat [mammalian][in the fat]	*0.01
	ML 0106	Milks	*0.01
	PM 0110	Poultry meat	*0.05
	PO 0111	Poultry, edible offal of	*0.05
	GC 0654	Wheat	*0.05

Table 3

Compound	Residue
ADD: Prothioconazole	For commodities of plant origin: sum of prothioconazole and prothioconazole desthio (2-(1-chlorocyclopropyl)1-2(-chlorophenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol), expressed as prothioconazole. For commodities of animal origin: sum of prothioconazole, prothioconazole desthio (2-(1-chlorocyclopropyl)1-(2-chlorophenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol), prothioconazole-3-hydroxy-desthio (2-(1-chlorocyclopropyl)1-(2-chloro-3-hydroxy-phenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol) and prothioconazole-4-hydroxy-desthio (2-(1-chlorocyclopropyl)1-(2-chloro-4-hydroxy-phenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol), expressed as prothioconazole.

Table 4

Compound	Animal feed commodity	MRL (mg/kg)
ADD: Prothioconazole		
	Wheat forage (fresh weight)	*0.05
	Wheat straw and fodder	*0.05

The MRL recommendations indicated above will be conveyed to Food Standards Australia New Zealand (FSANZ) for consideration for incorporation into Standard 1.4.2 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:

HARVEST: NOT REQUIRED WHEN USED AS DIRECTED.

GRAZING: DO NOT GRAZE PLANTS GROWN FROM TREATED SEED OR CUT FOR STOCK FOOD WITHIN 5 WEEKS OF SOWING.

The following protection of livestock statement is recommended:
DO NOT feed treated grain to animals, including poultry.

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Relevant Export Commodities, Overseas Registration Status and MRLs, and Potential for Undue Risk to Australian Trade

Commodities exported

Export commodities potentially affected by the use of Redigo Fungicidal Seed treatment are wheat grain and livestock. Wheat and all livestock species are considered to be major export commodities. Residues in these commodities have the potential to unduly prejudice trade.

Proposed Australian use-pattern

The Australian use pattern is for the treatment of seed prior to planting to control common bunt.
Use in treated seed is likely to result in residues less than the limit of quantitation (LOQ) in wheat grain.
Although unlikely, livestock could be exposed to prothioconazole-desthio in the diet through consumption of grain, forage or straw from treated crops. Detectable residues resulting from any of the exposure scenarios are not likely. The predicted residues are expected to be low, potentially even below the limit of detection, when based on worst-case assumptions.

Overseas registrations

The applicant indicated that prothioconazole products are registered for use in Germany as a foliar application, and a seed treatment use is registered in the United Kingdom.

Comparison of Australian MRLs with Codex and overseas MRLs.

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods.

Prothioconazole has not been considered by Codex.

The following overseas residue MRLs/tolerances have been established:

Country	Commodity	Tolerance, mg/kg (expiry date)	Reference
UK	Barley	T0.05	https://secure.pesticides.gov.uk/MRLs/EC/MRLlist.asp
	Rape seed	T0.05	
	Rye	T0.01	
	Wheat	T0.01	

The applicant has stated that the above uses are as a seed treatment. The applicant has also stated that prothioconazole is registered for foliar use in Germany, however no MRLs pertaining to this use were located.

No overseas animal commodity MRLs/tolerances have been identified for prothioconazole.

Potential risk to Australian export trade

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

Residues above quantifiable levels are not expected to occur in wheat grain, forage or straw treated with prothioconazole as a seed treatment. Therefore the expected risk to trade in wheat commodities is expected to be small.

The overall risk to trade in animal commodities is considered to0 be small, as it is expected that any residues present in the relevant commodities will be less than the limit of quantitation.

The APVMA welcomes comment with regard to whether the proposed use of prothioconazole on wheat seed, wheat grain grown from treated seed and its processed commodities, or livestock fed on commodities produced from crops grown from seed treated with prothioconazole, poses an undue prejudice to Australia's trade in these commodities.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Assessment of Occupational Health and Safety

Prothioconazole was of low acute oral, dermal, and inhalation toxicity in rats. The compound was neither an irritant for eye and skin in rabbits, nor a skin sensitiser in guinea pigs. Prothioconazole is not on the NOHSC *Hazardous Substances Information System* (NOHSC, 2005). Based on the information provided, OCS classified prothioconazole as a non-hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances*.

Redigo Fungicidal Seed Treatment has low oral, dermal and inhalation toxicity in rats. The product was non-irritating to eyes and skin in rabbits, but was a skin sensitiser in guinea pigs (Maximization Test). Based on the submitted toxicology information, Redigo Fungicidal Seed Treatment is determined to be a hazardous substance, in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances*.

Formulation, Packaging, Transport, Storage and Retailing

The product will be formulated in Germany and imported into Australia in ready-for-sale package of 10 L high-density polyethylene containers with 63 mm neck size. Transport workers and store persons will handle the packaged product and could only become exposed to the product if packaging were breached.

Use and Exposure

Redigo Fungicidal Seed Treatment is intended for the control of the fungal disease, common bunt (*Tilletia spp.*) in seed wheat. The rate of application of the product, Redigo Fungicidal Seed Treatment, is 50mL per 100 kg seed, diluted to 400mL (water plus product). The product will be used in either commercial seed treatment facilities or farms. Mobile seed treatment units (mobile treaters) or other on-farm equipment will be used for product application.

Workers may become contaminated with the product/treatment mixture during mixing/loading, treating seed, cleaning up spills and maintaining equipment and handling treated seed prior to planting. The main routes of exposure to the product are dermal and inhalation.

The main acute hazard associated with the Redigo Fungicidal Seed Treatment is skin sensitisation. Therefore, cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves, are recommended when opening the container, preparing and using the prepared treatment mix to protect against skin sensitisation.

The applicant has provided a study conducted in Germany to determine worker exposure during seed treatment with Redigo Fungicidal Seed Treatment and bagging of the treated seed. These exposure estimates in conjunction with toxicology data demonstrated that the use of cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves are required when opening the container, preparing and using the prepared treatment mix.

Exposure During Re-handling

Workers re-handling treated areas can be exposed to product residues during bagging and loading into planting equipment.

The applicant has provided a study on worker exposure during loading of seed wheat treated with Redigo Fungicidal Seed Treatment. These estimations in conjunction with toxicology data demonstrated that the risk to workers re-handling treated seed is low. Therefore, OCS does not recommend a re-handling statement.

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 opening the container, preparing and using the prepared treatment mix.

The PPE recommended should meet the relevant Australian Standards.

Conclusion

The registration of prothioconazole at 100 g/L in Redigo Fungicidal Seed Treatment, as a flowable concentrate for seed treatment formulation, for the control of the fungal disease, common bunt (*Tilletia* spp.) in seed wheat, is supported.

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

ENVIRONMENTAL ASSESSMENT

Environmental Chemistry and Fate

Hydrolysis

The experimental half-life of prothioconazole at pH 7 and 9 was calculated to be >1 year while at pH 4 it was 120 days at 50°C. Hydrolysis is not expected to be a major degradation route of prothioconazole in the environment.

Photolysis

Aqueous: Photodegradation may contribute to removal of prothioconazole in the environment. The compound was completely photodegraded with a mean half-life of 47.7 hours corresponding to a predicted environmental half-life under solar summer conditions of 7.1-11 days. The main metabolite was M04, found at a maximum level of 56% applied radioactivity. Two further major photodegradation products were identified as M12 (15%) and M13 (12%).

Quantum yield measurements for prothioconazole and M04, and subsequent modelling to predict environmental half-lives showed that for prothioconazole, direct photodegradation is expected to contribute to elimination of the chemical in the environment where the pH is above the pK_a of 6.9. Direct photodegradation is not expected to be a major removal mechanism for M04. Based on experimental degradation kinetics, the aqueous photolytic half-life of M12 was calculated to be 125-212 indicating photolysis will not significantly contribute to further degradation of M12 under environmental conditions.

Soil: One study considering photolysis of prothioconazole in soil was provided. The results of this test indicate that degradation is rapid on soil surfaces irradiated by simulated sunlight. However, there was fast degradation in the dark control soil indicating the breakdown was not a result of photolysis.

Degradation in Soil and Water

Soils aerobic: Testing on soils with a pH range of 5.9-7.2 and OM% range of 1.36-3.69 resulted in rapid degradation and some mineralisation was observed with up to 18% CO_2 found after one year in one of the tests. M04 was the most significant metabolite found in both tests and peaked at 40-45% of applied radioactivity (AR) in all soils except one where it peaked at 21%. In one test, M01 was another major metabolite peaking at 10-15% AR. Bound residues generally increased throughout the tests peaking at 40-45% AR in one test and 38-56% AR in the other. The degradation pattern appeared to be bi-phasic. However, the first half-life was rapid and ranged from 0.3-1.27 days and very little parent compound remained after this initial degradation. Microbial biomass may impact on the degradation rate with the slowest half-lives being found in the soil with the lowest microbial carbon. However, even these half-lives were quick.
Breakdown of the main metabolites, M01 and M04 was further considered on four soil types. M01 was degraded and partly mineralised. Half-lives ranged from 6-46 days. Six further metabolites were detected but none were >10% AR and were not characterised. Mineralisation was between 25-54%AR with one exception where one soil only returned 5.2%AR. M04 was degraded and mineralised with up to 62% AR being found as CO_2. Half-lives ranged from 7-34 days. Two other metabolites were found but were <10% AR and not characterised.

Soils anaerobic: No anaerobic soils data were provided. This is acceptable. Some anaerobic data for water/sediment systems were provided. However, the wheat seed treatment use pattern proposed is such that anaerobic soils are unlikely to be exposed.

Water aerobic: One study was provided investigating two aerobic water/sediment systems with prothioconazole radiolabelled in either the phenyl or triazole ring. In both systems, water was aerobic for the majority of the study. However, in the sediments, one system showed mainly anaerobic sediments while the other showed mainly aerobic sediments. The application rate was based on a field spray rate of 200 g ac/ha with a nominal water concentration of 67 ppb (water depth of 30 cm). Prothioconazole was shown to dissipate rapidly in both systems with a half-life in the whole system of <3 days. The evolution of CO_2 increased continuously until the termination of the experiment although it was much slower in the triazole labelled samples. M04 was the only metabolite found at levels >10% AR in both water and sediment. M01 was found in one of the systems at concentrations of 5-10% AR in the (anaerobic) sediments at several sampling points.

Water anaerobic: One study considering degradation in an anaerobic water/sediment system was provided with prothioconazole radiolabelled in the phenyl ring. Redox measurements confirmed both water and sediments remained anaerobic throughout the test. Application was to the water at a concentration of 33.6 ppb. The only metabolite detected in significant amounts was M01. This substance was found up to 8.6% AR in the water, although after 91 days was not detected in this medium. In the soil, it was found up to 77% AR with 76% AR still found in sediments after 360 days. The dissipation of the parent compound from the water column was fast with a half-life of 2.5 days. Degradation in the whole system was slower with a half-life of around 72 days. Whole system degradation was based on total detections of both parent and the M04 metabolite, a possible explanation for the slower decline compared with aerobic conditions.

Mobility

Volatility: The calculated Henry's Law Constant for prothioconazole suggests very low volatility from water. Modelling indicates that where prothioconazole is present in the atmosphere, it is unlikely to persist with calculations indicating it would degrade rapidly by reaction with hydroxyl radicals (DT_{50} around 1.14 hours). Further modelling with M04 indicates a longer residence time in the atmosphere with a predicted half-life of 14.2 hours, although again, partitioning of this chemical to the atmosphere is expected to be very slight.

Adsorption/desorption: Mobility of prothioconazole was estimated using HPLC and comparing retention times to several reference compounds. Based on the retention time and compared to the reference compounds, the Koc values were estimated to be 32 and 1383 at pH 6.0 and 2.5 respectively. These values indicate mobility will be very high at pH 6.0 and low at pH 2.5.

Adsorption/desorption of the major degradation product M01 and M04 were tested in standard batch equilibrium tests on four soils with the compounds labelled in the phenyl ring. The range of %OC values in the tested soils was 0.79-2.02. The M01 test showed strong adsorption on the soils tested with a Koc range of 1974-2995, classed as low to slight. Mobility of the M04 metabolite was higher with a Koc range of 523-625, and a mobility classification bordering on being medium to low.

Leachability: Leaching potential of prothioconazole was tested in soil columns when applied freshly to the top of the column as a 250 g EC formulation. The application rate was equivalent to a field spray rate of 200 g ac/ha and the column was "irrigated" with the

equivalent of 200 mm rain over a 48 h period. Prothioconazole degraded quickly in four tested soils over the leaching period. This compound along with its degradation products showed a low tendency to migrate through the columns with almost all radioactivity remaining in the top 6 cm of 3 columns, and in the top 12 cm of the sandiest soil.

A further column leaching experiment was performed with aged residues of prothioconazole in a loamy sand (86.8% sand). Residues were aged for up to 30 hours (around 1.5 half-lives) and transferred to the top of a 30 cm soil column and leached by overhead irrigation for about 5 days with the equivalent of 508 mm rain. Following the initial incubation period, prothioconazole was shown to move only to a limited extent below the aged soil segment. The two main metabolites, M01 and M04 both moved to the 0-6 cm layer (below the aged soil layer) and to a lesser extent, to the 6-12 cm soil layer.

Modelling the leachability of prothioconazole, M01 and M04 to groundwater using the FOCUS-PELMO model and the 9 standard European FOCUS scenarios indicated none of the analytes would be expected to leach significantly with estimations that no concentration in groundwater in the percolate at 1 m depth would exceed 0.001 ppb.

Field Dissipation

Soils: One field dissipation study provided summarised 8 different trials in typical agricultural regions of northern Europe. Half the trials were cropped with spring barley in the first and grass in the second year, and half were conducted without vegetation. No differences in translocation or degradation behaviour were observed for cropped or bare soil trials with parent and the metabolites being non-persistent or mobile. Average temperatures during these studies ranged from 12^{o}C (four trials) to 20^{o}C (1 trial). Half-lives for the parent compound ranged from 1.3-2.8 days (mean of 1.7 days) while those for M04 ranged from 16.3-72.3 days (mean of 42.0 days).

Prothioconazole was not mobile in these 8 trial sites with no residues moving past the 0-10 cm layer at any time up to the limit of detection. Of the metabolites tested for, only M04 was detected. This metabolite formed rapidly following application. Again, this metabolite was never detected below the top 0-10 cm soil.

A second study considered the dissipation of prothioconazole from treated wheat seed with testing performed at two sites, both with an early drilling and late drilling period. Seed was dressed at a rate of 10 g ac/ha and seeded at a rate of 500 g/6 m^2 test plot. Precipitation played a major role in dissipation times. While all dissipation of the parent compound was fast (0.2-1.5 days), the longer residence time in drier conditions resulted in much more conversion to M04 rather than complete dissipation from the plot. In drier conditions, the concentrations of M04 reached a maximum of around 20 mg/kg compared to less than half this in the wetter plots. There was no appreciable degradation of M04 during the short 10 day experiments.

Accumulation/Bioaccumulation

Both prothioconazole and M04 were tested for bioaccumulation and metabolism in separate studies using Bluegill sunfish. In both cases, steady state concentrations were not well defined. However, it was demonstrated that depuration was rapid once exposure ceased. The depuration half-life for prothioconazole and M04 was <1 day and <0.5 days respectively. The steady state BCF for prothioconazole was calculated to be 19 when normalised to a fish with 6% lipid content, while that for M04 was calculated to be 45. These both indicate the chemicals are only slightly concentrating. In the prothioconazole experiment, the main

compound detected in fish was unchanged parent compound (40-57%) with prothioconazole-glucuronide (M05, M06 and M07) being the most prominent metabolite. M01 and M04 were found to a lesser extent along with M08. In the M04 study, between 91-94% of the total radioactivity was identified, most of which was unchanged M04. Only negligible amounts of 5 minor metabolites were detected.

Modelling using FOCUS-PELMO and the nine standard FOCUS scenarios indicates that, when applied as a seed treatment at 30 g ac/ha followed by three consecutive sprays each at 200 g ac/ha, maximum soil concentrations of prothioconazole, M01 and M04 will be 0.225, 0.036 and 0.163 mg/kg respectively. Therefore, they are not expected to accumulate in agricultural soil. The major photolysis product, M12, was shown through modelling to be unlikely to be found in surface waters at 1% or more of the original amount of active substance reaching surface water under realistic environmental conditions.

Environmental Toxicology

While test data on algae, aquatic plants and terrestrial plants were not well represented, the suite of ecotoxicity results supplied for prothioconazole was generally complete and acceptable for the seed treatment use pattern being assessed.

Avian:
Prothioconazole is practically non-toxic to birds based on the acute and dietary values. During reproduction testing, mallard duck proved more sensitive than bobwhite quail. The NOEC of 700 ppm was due to statistically reduced survival of 14-day old hatchlings in the highest test rate of 2000 ppm (87.4% survival compared to 92.9% survival in the control group).

The only metabolite tested was M04. The metabolite was practically non-toxic to birds when exposed acutely. However, the 5 day dietary LC50 determined by probit analysis indicates the chemical is slightly toxic to birds although only one species was tested. Reproductive testing indicated that bobwhite quail was more sensitive than mallard duck. The NOEC of 173 ppm to quail was determined due to a statistically reduced survival rate of 14-d old chicks compared to the control at the next (and highest) treatment level of 500 ppm (87.1% survival compared to the control value of 96.7%).

Aquatic:
Fish: Prothioconazole was moderately toxic to three fish species when tested acutely under static conditions (LC50s from 1.83-6.91 mg/L). Sub-lethal effects found in all tests tended to include quiescence, lying on the bottom of the tank, loss of equilibrium or swimming at the water surface. Early life stage testing was performed on rainbow trout under flow-through conditions for 97 days. Tested concentrations were 35.6, 74.9, 140, 308 and 553 µg/L (ppb) along with a dilution water control. Based on the statistical analyses of egg hatch, time to hatch, fry survival and growth, no chronic effects of prothioconazole were observed up to the highest treatment level. However, swim-up was observed between study days 49 and 64. Between days 61 and 64, swim up was statistically significantly reduced at the 553 ppb group resulting in a NOEC of 308 ppb. Based on this one study, prothioconazole would be classified as slightly toxic to fish (chronic NOEC between 0.1-1.0 mg/L)

One test was performed on M01 with acute, static exposure to rainbow trout where M01 was moderately toxic with a 96 h LC50 of 1.79 mg/L. Sub-lethal effects were observed in large numbers of live fish and included lethargy, laboured breathing, lying on the bottom of the tank and dark colouration. Two acute tests with M04 showed this chemical to be moderately to slightly toxic to fish. Again, many live fish exhibited sublethal effects that included

convulsing, swimming at the bottom of the tank and tumbling during swimming. Of more concern with this metabolite were the results of the early life stage testing on rainbow trout. Test concentrations ranged from 1.9-53.0 ppb (measured). While tested endpoints such as egg hatch and swim-up behaviour did not reveal any statistically significant differences to the control fish at the highest rate, there was a statistically reduced body length and weight in the two highest treatment groups. This reduction was partly due to a deformation of the head and snout length. Based on visual assessments, the NOEC for deformities was 3.34 ppb. The MATC was calculated to be 5.01 ppb.

M13 was practically non-toxic to fish based on one acute test with an LC50 of 760 mg/L. A longer term juvenile growth test resulted in a 28 day NOEC of 100 mg/L for growth, but based on sub-lethal effects, the NOEC was 3.2 mg/L.

Aquatic invertebrates: Based on one acute study to *Daphnia magna* with prothioconazole, this chemical is moderately toxic (bordering on toxic) to aquatic invertebrates. In a reproduction test on this species (tested from 0.56-18.0 mg/L), the 21 d NOEC was determined to be the lowest tested concentration of 0.56 mg/L. At concentrations of 3.2-18.0 mg/L there was no parental survival. Both mean body lengths of surviving parents and the mean number of offspring per parent in the 1.0-1.8 mg/L groups were considered statistically reduced from control values. This NOEC indicates prothioconazole is slightly toxic to aquatic invertebrates through chronic exposure. Sediment dwelling midge were exposed with the chemical applied through the water column that based on previous experience, appears to lead to more sensitive results. At exposure concentrations of 1.14-57.1 mg/L, the number of emerged midges along with their development rate did not differ between the controls and test concentrations. However, due to the low water solubility of the test substance, only those up to 9.14 mg/L could be confirmed by analysis. Therefore, the NOEC was set at this level.

Based on the results of one test exposing *Daphnia magna* to M01, the chemical is considered moderately toxic to aquatic invertebrates. M04 was shown to be at worst, slightly toxic to *Daphnia* from acute exposure, while M13 was practically non-toxic. M04 was also tested chronically to *Daphnia* at concentrations of 0.025-0.80 mg/L. No effects were observed on parental survival at any concentration. Treatment related effects on parental body length were found at the two highest levels of 0.40 and 0.80 mg/L. Reproductive impacts for mean number of offspring per parent and mean offspring per reproduction day were found at the concentrations of 0.20-0.80. Therefore, the NOEC was set at the next lowest test concentration of 0.10 mg/L. M04 can be considered moderately to slightly toxic to aquatic invertebrates based on this result.

M04 was also tested through the water column to sediment dwelling midge larvae. Nominal concentrations tested ranged from 1-32 mg/L and effects on emergence and development were observed. At 8 mg/L upwards, emergence was significantly postponed for at least 2 days, and at the 16 mg/L group, for 7 days. None emerged in the 32 mg/L group. The EC50 for emergence was calculated to be 8.46 mg/L. Based on emergence effects not being considered statistically reduced in the 4 mg/L group, this is considered the NOEC.

Algae and aquatic plants: Only one test using one algal species was provided for prothioconazole, M01, M04 and M13. In terms of the initial measured concentrations, prothioconazole is moderately to highly toxic to the tested freshwater green alga based on 0-72 h results. However, the 96 h biomass result could be considered a chronic result in terms of algae toxicity. The NOEC of 0.37 mg/L indicates the chemical is only slightly toxic. The lack of test data on algae and aquatic plants for prothioconazole is acceptable in terms of this assessment and the use pattern being considered, a seed treatment to wheat, is unlikely to lead to excessive exposure of these organisms. However, given the level of acute toxicity to the

species tested, further results in this area may be required in the future if extensions to the use pattern are sought.

Testing with M01 showed this chemical was moderately toxic over 72 hours based on the biomass result to a single freshwater green alga. In this test, inhibition was statistically reduced compared to the control at all tested concentrations, starting 1.03 mg/L (initial measured concentration). Therefore a NOEC could not be established. In terms of growth rate and biomass, this reduction was 3.2 and 16.5% respectively compared to the controls, while it was 18.9% for cell density reduction.

Biomass was again the most sensitive indicator in the M04 test on a freshwater green alga with a 72 h EC50 of 0.073 mg/L and a NOEC of 0.052 mg/L. The 72 h result (acute toxicity) indicates that this metabolite is very highly toxic to algae. However, 96 h results for algae may be considered as chronic, in which case the derived NOEC is indicative of moderate toxicity.

M13 was shown to be slightly toxic to algae based on the 72 hour EC50 results in one test. The 96 h NOEC from the same test is suggestive of only very slight toxicity.

Terrestrial Toxicity:
When applied in its technical form, or as a 250 EC formulation, prothioconazole was shown to be only very slightly toxic to bees through the contact route with an acute 48 h contact LD50 >71.0 µg/bee. Due to incomplete consumption of doses in the oral part of the tests, doses received showed no effects on bees, but the chemical has to be considered to be at worst slightly toxic to bees with an acute 48 h oral LD50 >48.7 µg/bee.

Several studies were provided addressing toxicity to a range of above-ground and ground-dwelling arthropods. Tests to ground-dwelling animals were undertaken with both the technical prothioconazole and considering exposure through treated wheat seed, with a FS 100 formulation.

Testing on predatory mites, parasitic wasps and ladybirds were undertaken to develop a lethal rate to 50% of the population (LR) from a dose response due to spraying. In all cases, this dose/response was defined and results ranged from 18.7 g/ha to 230 g ac/ha depending on the exposure method. Where the predatory mite was exposed to residues aged for 1 and 15 days, no effect was observed at 300 g ac/ha. Testing on lacewing up to 600 g ac/ha showed no effects on reproductive capacity. However, there was a significant reduction in mortality of 15.2% at the lowest rate tested of 200 g ac/ha with increasing mortality as treatment rates increased. No metabolites were tested on these organisms.

Soil dwelling arthropods tested included carabid beetles, rove beetles, collembola, a soil dwelling mite and spiders. Where prothioconazole was tested in its technical form NOECs were generally shown to be the highest rates tested, and all were in excess of 64 mg/kg dry soil. All these organisms were also exposed to prothioconazole treated seed. The seed was treated in all cases at 10 g ac/100 kg seed (twice the rate proposed in Australia), and then seeded at various rates from about 200 kg seed/ha upwards. Generally, no effects were found with at least a sowing rate of 230 kg seed/ha. However, rove beetles where shown to have statistically reduced reproductive capacity (11.2% reduced compared to the control) with a seeding rate of 198 kg seed/ha and a seed treatment rate of 10 g ac/100 kg seed.

Collembola were also exposed to M01 and M04. One test with M01 produced a NOEC of at least the highest application rate of 31.6 mg/kg soil while the lowest NOEC from treatment with M04 was 62.5 mg/kg soil.

Earthworms were exposed to prothioconazole in its technical form, as a 250 g/L EC formulation (one acute, one reproduction and one field study) and from treated wheat seed. Earthworms were not sensitive to the chemical in any study with NOECs generally being threshold levels of the highest tested rate. In the two acute laboratory studies (technical and 250 g/L EC formulation), the 14 D LC50s were higher than the highest tested rates. When exposed to the technical compound up to 1000 mg/kg, there was a statistically reduced body weight of worms after 14 days at this level resulting in a NOEC of the next highest treatment level of 562 mg/kg dry soil.

M01 and M04 were tested for both acute and reproduction toxicity to earthworms. In the acute studies, rates tested ranged from 1-1000 mg/kg dry soil. For both metabolites, weight alterations at concentrations >100 mg/kg were considered statistically different to the controls. However, there was no difference in mortality rates compared to the controls at any tested rate. In reproduction testing, the number of juveniles produced per adult worm was statistically different to controls in higher tested concentrations allowing NOECs of 100 and 1.0 mg/kg to be defined for M01 and M04 respectively.

Testing for adverse effects on soil respiration and nitrification showed no effects at the maximum tested levels of 2.7 mg/kg dry soil for prothioconazole and M01, and 1.37 mg/kg dry soil for M04 (nitrification tests only for this metabolite). In addition, prothioconazole effects on activated sludge (bacterial toxicity) resulted in 34.2% respiration inhibition at the maximum tested rate of 10000 mg/L (IC50 >10000 mg/L).

Environmental Risk

Prothioconazole is proposed for use in a 100 g/L fungicidal seed treatment formulation for treating wheat seed. No other uses are proposed with the current assessment.

Terrestrial organisms

Birds

The application method (treated seed, soil incorporated) will result in 15 g seed/m^2 (based on 150 kg seed/ha) equating to 0.75 mg prothioconazole/m^2. Based on acute oral toxicity, a 10 g bird would need to consume all seed over a 6.7 m^2 area to consume a lethal dose of prothioconazole, and all seed over a 5.5 m^2 area to consume a lethal dose of M04 assuming full conversion of parent compound to M04. A risk quotient (RQ) may be calculated by dividing the exposure rate (mg/m^2) by the acute LD50. This results in RQs of <<0.001 for both prothioconazole and M04 indicating the risk to birds from use as a seed treatment at the proposed rate is considered low.

Bees and other terrestrial invertebrates

Exposure to bees should be negligible based on the seed treatment use of this compound. In any event, the equivalent spray rate of prothioconazole based on a wheat seeding rate of 150 kg seed/ha is 0.075 µg/cm^2. This is some 650 times lower than the most sensitive NOEC of >48.7 µg ac/bee with no sublethal effects observed, assuming that a honeybee is approximately 1 cm^2 in surface area. The potential risk to honey bees is expected to be low.

Exposure to above ground terrestrial invertebrates will be negligible resulting in low risk to these organisms.

Soil-dwelling invertebrates

Application of 150 kg seed/ha results in an equivalent application rate of 7.5 g ac/ha and possible residues of 0.01 mg/kg soil if distributed through the top 5 cm of soil (density 1.5 g/cm^2). The risk to soil-dwelling invertebrates from exposure to metabolites is predicted to be low. Assuming full conversion of prothioconazole to either M04 or M01, the soil concentration in the top 5 cm was determined to be 0.01 mg/kg soil. The lowest NOEC found for soil invertebrates exposed to metabolites was a threshold concentration of 31.6 mg/kg dry soil. This represents a Q value of <<0.01 based on the NOEC.

Soil microbial processes were shown to not be affected at maximum tested rates of 2.7 mg/kg dry soil for prothioconazole and M01, and a maximum tested rate of 1.37 mg/kg dry soil for M04. The predicted soil concentration in the top 5 cm of soil of 0.01 mg/kg prothioconazole indicates the likely risk to soil microorganisms is low.

Earthworms were not sensitive to prothioconazole. The lowest threshold NOEC found was through exposure to treated seed at a rate equivalent to 115 g ac/ha. No effects were found during reproduction testing (56 days) at the highest tested rate that was over 15 times the rate expected to be used in Australia. The risk to earthworms from exposure to the active constituent is expected to be low.

Similarly for metabolites, $NOEC_{reproduction}$ values for both M01 and M04 were experimentally derived to be 100 and 1.0 mg/kg soil. With a maximum concentration of either metabolite in soil of 0.01 mg/kg in the top 5 cm, the corresponding Q value is 0.01 or less indicating a low risk to earthworms from the metabolites.

Terrestrial Plants

No exposure is likely based on the use pattern assessed so risk to terrestrial plants is low.

Aquatic organisms

Exposure to aquatic systems is unlikely based on the seed treatment use pattern of this chemical. The label prohibits seeding from aircraft, so direct application of treated seed to water bodies is not expected.

As a very conservative scenario, if in applying wheat seeds to field, 10% from 1 ha was blown into a water body with a surface area of 1 ha and a water depth of 15 cm, and all applied prothioconazole was available in the water column, the concentration in the water (1.5 ML) would be 0.5 μg/L.

Risk to fish and aquatic invertebrates through acute and chronic exposure, along with risk to sediment dwelling organisms and algae/aquatic plants were considered in the risk assessment for both prothioconazole and its main metabolites, M01 and M04. In all cases, the most sensitive aquatic endpoint was considered with the predicted water concentration.

The results demonstrated that under worst case exposure, the risk to all aquatic organisms from this use pattern is expected to be low and Q values were generally <0.01 (often much less). The most likely concern will be chronic exposure of fish to metabolites, particularly M04, where the Q-value was 0.17. This is still 6 times less than an acceptable Q-value of 1 when using a chronic NOEC, and assumes full conversion of the active constituent to M04, an unrealistic assumption.

The suite of data for algae was poor, and no aquatic plants were tested. However, based on the worst-case risk assessment outcomes, this is acceptable for this use pattern.

Groundwater

Prothioconazole was shown in field studies to dissipate rapidly, and where it was detected, remained in the top 10 cm of soil. Field studies also demonstrated the retention of the main M04 metabolite in the top 10 cm of soil, and very little formation of M01 under field conditions. Given this, prothioconazole and its main metabolites are not expected to migrate to groundwater. This is supported by modelling.

Conclusion

The proposed use of the chemical will not lead to an unintended effect that is harmful to animals, plants or the environment at the proposed rate and following good agricultural practice.

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EFFICACY AND SAFETY ASSESSMENT

Justification for use and Mode of Action

Prothioconazole is a new fungicide of the new fungicidal class of triazolinthiones. With respect to fungicide resistance, prothioconazole is classed as a Group C fungicide. As a Group C fungicide, Redigo Fungicidal Seed Treatment offers control of common bunt *(Tilletia laevis and T.tritici)* of wheat via application to the seed. Common bunt can occur at low or trace levels and, in the absence of seed treatments has the potential to increase rapidly. There is a nil acceptance level for bunt in wheat. It is widely accepted that cereals should be treated with a smuticide each year (bunt being a smut disease) to avoid yield loss, improve grain quality and to maintain a clean seed source. Seed treatment can used to prevent producing grain that is potentially unsaleable.

Registration is supported by Australian agricultural authorities.

Proposed use pattern

Redigo Fungicidal Seed Treatment will be applied to wheat as a seed treatment for control of common bunt (*Tilletia laevis* and *T.tritici*). The application rate is 50 mL of Redigo Fungicidal Seed Treatment in a mixture of 400 mL (product and water) per 100 kg seed.

Use is proposed for all State and Territories.

It is proposed that the product will be available in 10 L high-density polyethylene containers.

The following Withholding Period statements are recommended for the product:

Harvest:	Not required when used as directed.
Grazing:	Do not graze plants grown from treated seed or cut for stock food within 5 weeks of sowing.

The following protection of livestock statement is recommended:

DO NOT feed treated grain to animals, including poultry.

Evaluation of efficacy

The data presented supports the claim for control of common bunt (*Tilletia laevis* and *T.tritici*) of wheat. Detailed efficacy data was presented including results from a range of Australian field trials. Data from seven trials conducted on three varieties of wheat over 2 seasons were presented in support of the application. Sites were distributed in southern New South Walers, Victoria, South Australia and western Australia. The trials were acceptable on layout, and experimental design. Wheat seed was treated in accordance with commercial conditions with adequate disease levels to demonstrate efficacy. The data supports the claim.

Crop safety

The data demonstrated that Redigo Fungicidal Seed Treatment did not affect the emergence of wheat when planted at depths between 2 and 5 cm.

Resistance management

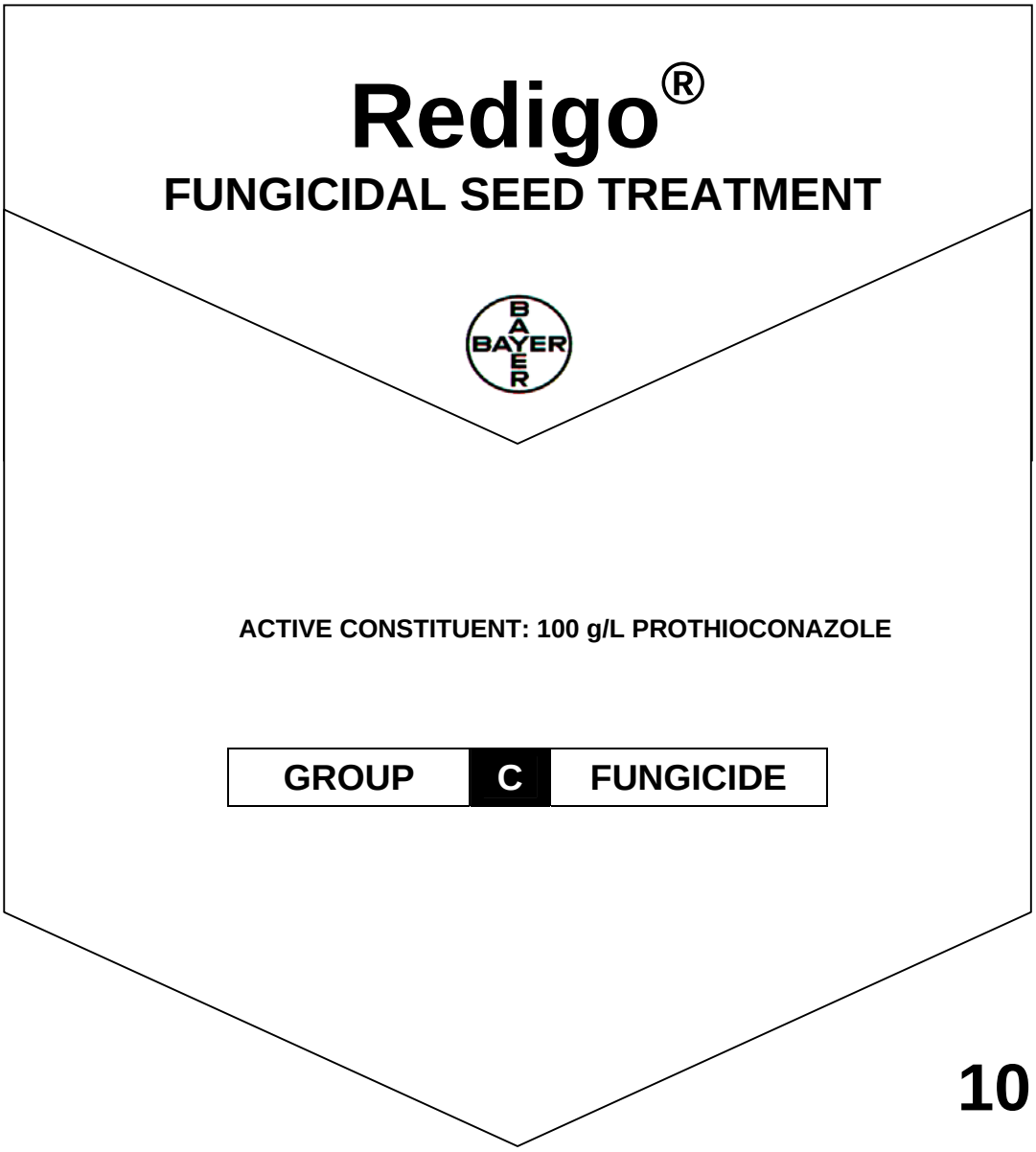
Prothioconazole is a new fungicide of the new fungicidal class of triazolinthiones. With respect to fungicide resistance, prothioconazole is classed as a Group C Fungicide.

Conclusion

Sufficient statistically analysed data from suitably designed and scientifically conducted trials has been presented to substantiate the claim for use shown on the proposed label. The data demonstrate that the product should be suitable for control of common bunt (*Tilletia laevis* and *T.tritici*) of wheat seed when used in accordance with the proposed label instructions and Good Agricultural Practice (GAP).

LABELLING REQUIREMENTS

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



For the control of common bunt in wheat

(label code)

DIRECTIONS FOR USE (All States)

Restraints

DO NOT treat physically damaged seed.
DO NOT apply treated seed from aircraft.

CROP	DISEASE/PEST	RATE	CRITICAL COMMENTS
Wheat	Common bunt (*Tilletia* spp.)	50 mL/100 kg seed	Ensure even and thorough coverage of seed. The quantity of water used for mixing will vary depending on the type of equipment and quality of seed. Use of 400 mL of mixture (water + product) with each 100 kg seed is recommended.

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

WITHHOLDING PERIODS

Harvest: NOT REQUIRED WHEN USED AS DIRECTED
Grazing: DO NOT GRAZE PLANTS GROWN FROM TREATED SEED OR CUT FOR STOCKFOOD WITHIN 5 WEEKS OF SOWING.

PROTECTION STATEMENT
DO NOT FEED TREATED GRAIN TO ANIMALS, INCLUDING POULTRY.

GENERAL INSTRUCTIONS

Protection from bunt will only be achieved if all grains are treated. Therefore, ensure that the application equipment is correctly set up to achieve even application of the product.

Plant establishment may be reduced when sowing seed treated with fungicides, at depths greater than 50 mm, in heavier soils. In these circumstances it is recommended to increase sowing rates to compensate for any such reduction.

Fungicide Resistance Warning **GROUP C FUNGICIDE**

Redigo Fungicidal Seed Treatment is a member of the triazole group of fungicides. For fungicide resistance management Redigo is a Group **C** fungicide. Some naturally occurring individual fungi resistant to Redigo and other Group **C** fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungal population if these fungicides are used repeatedly. These resistant fungi will not be controlled by Redigo and other Group **C** fungicides, thus resulting in a reduction in efficacy and possible yield loss.
Since the occurrence of resistant fungi is difficult to detect prior to use, Bayer CropScience Pty Ltd accepts no liability for any losses that may result from the failure of Redigo to control resistant fungi.

Seed Quality

Redigo seed treatment should not be used on seed with more than 12% moisture content, or on sprung, sprouted, damaged or severely pinched seed, or seed of poor viability. If in doubt, have a germination test carried out on the seed before treatment to ensure that it is of acceptable standard. The use of Redigo at the recommended rate will have no effect on the storage life of treated sound seed.

Mixing

Shake the container well before using. Add the required volume of Redigo to the water whilst agitating.

Compatibility

Do not mix with any other product.

Application
Ensure the application of Redigo provides even and thorough coverage of the seed. For information about suitable application equipment and calibration, contact your supplier of Redigo or a Bayer CropScience representative.

Cleaning Up
Equipment should be thoroughly cleaned with water after application. If changing from this water-based liquid formulation to a solvent-based liquid formulation, it is essential to rinse equipment with methylated spirits after thoroughly cleaning with water. If changing from a solvent-based liquid to this water-based liquid formulation, thoroughly clean with methylated spirits then rinse with water. Failure to do so will result in clogging of equipment.

PRECAUTIONS
Do not store treated seed near food or animal feed. Do NOT allow seed treated with this product to contaminate seed intended for human consumption. Do NOT use treated seed for human consumption.

Storage of Treated Seed
If the seed is not used immediately after treatment it should be stored in a dry, well ventilated place. When treated seed is stored it should be kept apart from other grain and the bags or other containers should be clearly marked to indicate the contents have been treated with this product. Bags which have held treated seed are not to be used for any other purpose.

Although Redigo has no effect on the viability of treated seed, subsequent germination can be adversely affected by poor storage conditions such as high moisture combined with high temperatures. Bayer CropScience therefore accepts no liability for the performance of stored treated seed.

PROTECTION OF LIVESTOCK
Seed treated with this product must not be used for animal consumption or poultry feed or mixed with animal feed. DO NOT allow seed treated with this product to contaminate seed intended for animal consumption.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Do NOT contaminate streams, rivers or waterways with this product, used containers or bags which have held treated seed. Do NOT feed treated seed or otherwise expose to wild or domestic birds. Any spillages of treated seed, however minor, must be cleaned up immediately, preferably by recovery and re-use. If disposal is required, ensure treated seeds are thoroughly buried and not accessible to birds and other wildlife.

STORAGE AND DISPOSAL
Store in the closed, original container in a cool, well-ventilated area. Do not store for long periods in direct sunlight. Triple or preferably pressure rinse containers before disposal. Dispose of rinsings in disposal pit, or use for diluting product to required volume. 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.

Application Equipment
Rinse all application equipment with clean water immediately after use and dispose of rinsings in a dedicated disposal pit, specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots.

SAFETY DIRECTIONS
Repeated exposure may cause allergic disorders. When opening the container and, preparing and the using the prepared treatment mix, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), and elbow length PVC gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

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

MATERIAL SAFETY DATA SHEET
Additional information is listed in the Material Safety Data Sheet, which can be obtained from www.bayercropscience.com.au.

EXCLUSION OF LIABILITY
This product must be used strictly as directed, and in accordance with all instructions appearing on the label and in other reference material. So far as it is lawfully able to do so, Bayer CropScience Pty Ltd accepts no liability or responsibility for loss or damage arising from failure to follow such directions and instructions.

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GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product.
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer.
Chronic	Of long duration.
Codex MRL	Internationally published standard maximum residue limit.
Desorption	Removal of an absorbed material from a surface.
Efficacy	Production of the desired effect.
Formulation	A combination of both active and inactive constituents to form the end use product.
Genotoxicity	The ability to damage genetic material
Hydrophobic	Water repelling
Leaching	Removal of a compound by use of a solvent.
Log P_{ow}	Log to base 10 of octonol water partioning co-efficient.
Metabolism	The conversion of food into energy
Photodegradation	Breakdown of chemicals due to the action of light.
Photolysis	Breakdown of chemicals due to the action of light.
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body.
Toxicology	The study of the nature and effects of poisons.

REFERENCES

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Footnote:
Updated versions of these documents are available on the APVMA website http://www.apvma.gov.au.

APVMA PUBLICATIONS ORDER FORM

To receive a copy of the full technical report for the evaluation of prothioconazole in the product Redigo Fungicidal Seed Treatment, please fill in this form and send it, along with payment of $30 to:

David Hutchison
Pesticides Program
Australian Pesticides and Veterinary Medicines Authority
PO Box E240
Kingston ACT 2604

Alternatively, fax this form, along with your credit card details, to:
David Hutchison, Pesticides Program at 02 6210 4776.

Name (Mr, Mrs, Ms, Dr)_____

Position _____

Company/organisation _____

Address _____

Contact phone number (___) _____

I enclose payment by cheque, money order or credit card for $_____

Make cheques payable to 'Australian Pesticides and Veterinary Medicines Authority'.

___ Bankcard ___ Visa ___ Mastercard

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Signature_____ Date _____