Public Release Summary
on

Evaluation of the new active

pyrasulfotole

in the product

Precept Selective Herbicide

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 and Heritage (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 in accordance with accepted scientific principles. Details are outlined in the APVMA's publications *Manual of Requirements and Guidelines (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 Program Manager Pesticides, Australian Pesticides and Veterinary Medicines Authority, PO Box 6182, Kingston ACT 2604.

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LIST OF ABBREVIATIONS AND ACRONYMS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
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
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EUP	End Use Product
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Haematocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OM	Organic Matter
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
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
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
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 the product Precept Selective Herbicide, which contains the new active constituent pyrasulfotole in combination with another currently, approved active MCPA. The product is proposed to be used for the control of broadleaf weeds in barley, oats, cereal rye triticale and wheat.

Responses to this Public Release Summary will be considered prior to registration of the product. They will be taken into account by the Australian Pesticides and Veterinary Medicines Authority (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 pyrasulfotole, 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 located at the APVMA offices, 18 Wormald Street, Symonston ACT 2609.

Written comments should be received by the APVMA by **19 October 2007**. They should be addressed to:

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Applicant
Bayer CropScience Pty Ltd

Product Details
It is proposed to register Precept Selective Herbicide containing 25g/L of pyrasulfotole as an emulsifiable concentrate. The product will be formulated in Australia using pyrasulfotole manufactured in Germany. The product will be packaged in 20L and 110L containers.

Precept Selective Herbicide contains members of the pyrazolone and phenoxy groups of herbicides. The product inhibits 4-hydroxyphenylpyruvate deoxygenase and also acts by disruption of plant cell growth. For weed resistance management Precept Selective Herbicide is a Group F & I Herbicide.

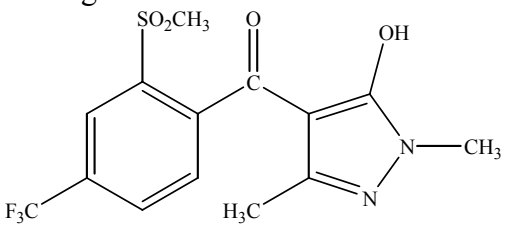
The rate of product use is 1L to 2L/ha. Precept Selective Herbicide is proposed for registration in all States.

CHEMISTRY AND MANUFACTURE

Active Constituent

Pyrasulfotole belongs to the pyrazolone family of compounds, and is a post-emergent herbicide.

The active constituent pyrasulfotole has the following properties:

Common name:	Pyrasulfotole
IUPAC name:	(5-Hydroxy-1,3-dimethylpyrazol-4-yl)(α,α,α-trifluoro-2-mesyl-*p*-tolyl)methanone
CAS Registry Number:	365400-11-9
Molecular formula:	$C_{14}H_{13}F_3N_2O_4S$
Molar mass:	362.3 $gmol^{-1}$
Structure:	

Appearance:	Beige powder with no characteristic odour
Melting point:	201 °C
Density:	1.53 g/cm^3 (20 °C)
Water solubility:	pH 4: 4.2 g/L; pH 7: 69.1 g/L; pH 9: 49.0 g/L (20 °C)
Octanol/water partition coefficient ($logK_{OW}$):	pH 4: 0.276; pH 7: -1.362; pH 9: -1.580
Vapour pressure:	2.7×10^{-7} Pa (20 °C); 6.8×10^{-7} Pa (25 °C)
Safety properties:	Not flammable, not oxidising, not heat, friction or shock sensitive, and not classifiable as a dangerous good
Chemical family:	Pyrazolone
Mode of action:	Inhibition of carotenoid biosynthesis at the phytoene desaturase step

The Chemistry and Residues Program (CRP) of the APVMA has evaluated the chemistry aspects of pyrasulfotole (physico-chemical properties, spectral data, stability, manufacturing process, quality control procedures, batch analysis results and analytical methods).

Pyrasulfotole is a new active constituent and approval is pending. On the basis of the data provided, it is proposed to establish the following Active Constituent Standard for pyrasulfotole:

Constituent	Specification	Level
Pyrasulfotole	Pyrasulfotole	Not less than 960 g/kg
Cyanide	Cyanide	Not more than 50 mg/kg

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

Formulated Product

The CRP has evaluated the chemistry aspects of the product, Precept Selective Herbicide (physico-chemical properties, formulation process, quality control procedures, batch analysis results, stability, analytical methods and packaging).

Precept Selective Herbicide has the following properties:

Appearance:	Clear amber to dark brown liquid with a slight naphthalene odour
Formulation type:	Emulsifiable concentrate
Active constituent concentrations:	25 g/L (pyrasulfotole); 125 g/L (MCPA as the 2-ethylhexyl ester)
Specific gravity:	1.047-1.057 (20 °C)
pH (1% dilution):	3.0- 5.0 (20 °C)
Safety properties:	Not oxidising or reducing, flash point 96 °C, autoignition temperature >450 °C, mildly corrosive to steel, incompatible with strong oxidising agents, strong acids and bases, and peroxides.

The manufacturing and quality control procedures, including compliance with the release specifications, are acceptable.

The applicant provided the results of real time and accelerated stability testing conducted using samples stored in epon lined steel cans (one of the proposed commercial container types). Testing of all of the important parameters for emulsifiable concentrate formulations was conducted. The results indicate that the formulated product is expected to be stable for at least two years when stored under normal conditions in the proposed commercial packaging.

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

Other characteristics of Precept Selective Herbicide (toxicology, occupational health and safety etc) are covered in subsequent sections of this Public Release Summary.

TOXICOLOGICAL ASSESSMENT

Evaluation of toxicology

The toxicological database for pyrasulfotole containing primarily toxicological studies conducted on 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 that such effects will 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. Nevertheless, possible species specific mechanisms are considered in assessing the relevance of animal data to human hazard. Also, consideration of the risks to human health must take into account the likely human exposure levels compared with those which produce adverse effects in animal studies. Toxicity tests should indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the no observed effect level (NOEL) are used to develop acceptable limits for dietary intakes (ADI and ARfD) at which no adverse health effects in humans are expected.

Toxicokinetics and metabolism Studies

The test substance was absorbed readily via the oral route in male rats. Following oral administration, approximately 60% of the pyrasulfotole was absorbed and excreted in the urine within 6 h. Based on these data, the test material is absorbed rapidly following oral dosing. Only a small amount of the administered dose (<2%) remained in the residual carcass and tissues at sacrifice (48 or 52 h). The highest residues were found in the liver and kidney. The compound was found to be poorly metabolized in male rats. A desmethyl derivative was the most abundant, being present at less than 5% in the urine and faeces. Following oral administration, approximately 70% of the radioactive dose was excreted in the urine and approximately 30% in the faeces by 48 or 52 h. In the case of intravenous administration, approximately 90 % of the dose was excreted in the urine and approximately 10% was found in the faeces over 48 h, the latter indicating biliary excretion.

Only male rats were studied; only one dose level was employed; and no repeat dose studies were undertaken.

Percutaneous absorption

No studies were provided.

Acute studies

Active

Pyrasulfotole has low acute oral toxicity in female rats with an LD_{50} >2000 mg/kg bw. It has low dermal toxicity (LD_{50} >2000 mg/kg bw) and low inhalational toxicity (LC_{50} >5030 mg/m^3) in male and female rats. It is not a skin irritant in rabbits or a skin sensitiser in guinea pigs. However it is a moderate eye irritant in rabbits.

Product

The product, "AE 0317309 05 EC 15 A1" (Precept Selective Herbicide), contains pyrasulfotole at 25 g/L (2.28% w/w). This product has low acute oral toxicity in female rats with an LD_{50} >2000 mg/kg bw. It has low dermal toxicity (LD_{50} >2000 mg/kg bw) and low inhalational toxicity (LC_{50} > 4345 mg/m^3) in male and female rats. It is a moderate skin irritant in rabbits but was not found to be a skin sensitiser in a murine local lymph node assay (LLNA). It was however a severe eye irritant in rabbits.

Short-term studies
Pyrasulfotole was incorporated into rodent diet to provide concentrations of 0, 200, 1000, and 5000 ppm and administered *ad libitum* to groups of mice for 28 days. The short-term toxicity of the test substance in the mouse was limited. The treatment-related effects observed in this study were limited to gritty content in the urinary bladder of 2/10 males at 5000 ppm, and histopathological findings of urothelial hyperplasia, diffuse submucosal granulation tissue and diffuse suburothelial mixed-cell infiltrata in the urinary bladder of 3/10 males at 5000 ppm. There were no findings in females at any dose level. Based on treatment-related changes affecting the urinary bladder in male animals at the highest dose level of 5000 ppm (equivalent to 961 mg/kg bw/d) the NOEL of the test substance was considered to be 1000 ppm (equivalent to 192 mg/kg bw/d).

Pyrasulfotole was moistened with tap water and applied under a semi-occlusive bandage to the shorn skin of rats randomly allocated to four treatment groups at 0, 10, 100, and 1000 mg/kg bw/d for 4 weeks. There were few effects of repeated dermal application of test substance to rats. There were no signs of skin irritation or increase in skin thickness. On this basis the NOEL for skin responses was determined to be 1000 mg/kg bw/d. Based on increased incidence of histopathological alterations in the pancreas of both sexes at and above 100 mg/kg bw/d, the NOEL for systemic effects was 10 mg/kg bw/d.

Pyrasulfotole was incorporated into ground diet to provide dietary concentrations of 0, 5000, 13000, and 26000 ppm and administered to groups of 3 male and 3 female Beagle dogs for 28 days. There was intense yellow urine in two females at 26000 ppm, dose-related increase in serum triglyceride levels commencing at 5000 ppm, and elevated liver weight at all doses. Gritty content and/or stones were found in the urinary tract at 13000 and 26000 ppm, accompanied in the kidneys by histopathological findings at 13000 and 26000 ppm. Based on a dose-related increase in serum triglyceride levels commencing at 5000 ppm (174 and 171 mg/kg/d in males and females, respectively), and elevated liver weight at all doses, a NOEL could not be established in this study. (NOEL <171 mg/kg bw/d).

Subchronic studies
Mice were randomly assigned to five groups of 20 (10/sex) and fed treated diet at 0, 100, 1500 and 3000 ppm for 90 days. The only possible treatment-related finding was an increase in urinary pH in females at 3000 ppm. However it is doubtful if this is of toxicological significance and therefore the NOEL in this study was 3000 ppm (500 mg/kg bw/d).

Rats were randomly assigned to six groups of 20 (10/sex) and fed treated diet at 0, 2, 30, 1000, 7000 and 12000 ppm for 90 days. Based on increased liver weights, corneal opacity and neovascularisation, and microscopic renal abnormalities at 1000 ppm and above, the NOEL was 30 ppm (equivalent to 2.3 mg/kg bw/d). However the dose range 30 to 1000 ppm remained unexplored for its capacity to induce treatment-related effects. The dose range used was not therefore the most appropriate for establishing a NOEL (OECD Test Guideline 409).

Corn oil at 1% by weight of the diet and acetone were used as vehicle to suspend the test substance which was then mixed in the diet to achieve concentrations of test substance of 0, 1500, 9000 and 18000 ppm. It was intended to administer the test substance in diet for 90 days to Beagle dogs, but the study was terminated after 29 days. One male dog at 9000 ppm was euthanized for humane reasons on study day 23, while two males at 18000 ppm were euthanized on study day 28 in moribund condition. The remaining dogs were euthanized on study day 29 because of urinalysis findings and the likelihood of urinary tract findings in the dogs unaffected to that point. The dietary administration of test substance to male beagle dogs apparently produced precipitation of test substance in the urinary tract, with the precipitate forming into urinary tract stones. The moribundity, clinical signs, and necropsy

findings in the moribund dogs were clearly due to the presence of these urinary tract stones. Because of the incomplete data set for this study, no NOEL could be established.

Corn oil at 1% by weight of the diet and acetone were used as vehicle to suspend the test substance which was then mixed in the diet to achieve concentrations of test substance of 0, 100, 500, and 1000 ppm. The selection of the concentrations of test substance used in this study was based on the findings of the "90-day dog study" which used concentrations in diet of 0, 1500, 9000 and 18000 ppm and was terminated on study day 29 due to excessive toxicity. In the absence of any findings in this 90-day study, the NOEL was the highest concentration of the test substance tested, 1000 ppm, (40 mg/kg bw/d in males and 33 mg/kg bw/d in females). The fact that this high dose did not induce any treatment-related effects indicates that it was too low (OECD Test Guideline 409). The dose range used was not the most appropriate for establishing a NOEL.

Chronic studies

Mouse

Pyrasulfotole was incorporated into rodent diet and administered at 0, 100, 1000 or 4000 ppm to groups of 60 male mice. Groups of 60 females received 0, 100, 1000, and 6000 ppm for the first 11 weeks of the study. However, mortality at 6000 ppm was considered to be excessive and this dose was decreased to 4000 ppm from week 12 onwards. These concentrations resulted in doses of 0, 13.6, 137, and 560 mg/kg bw/d for males and 0, 16.7, 168, and 713 mg/kg bw/d for females. After 52 weeks, 10/sex from each group allocated to the chronic phase of the study were sacrificed and necropsied. The remaining 50 animals/sex/group, allocated to the carcinogenicity phase of the study, continued to receive treatment until the scheduled final sacrifice of the study after at least 78 weeks of treatment. Decreased body weight was largely confined to the high dose, although there were indications of decreased body weight gain at the mid dose as well as the high dose. Increased relative liver weight associated with centrilobular hepatocellular hypertrophy was observed in males at 1000 ppm and above. As well as these liver effects at the mid and high dose, there were effects in the kidney ("atrophy/ fibrosis/scar: cortex/medulla: unilateral" in females). Also, there was an increased incidence of stones in the urinary tract at 4000 ppm, with accompanying and probably associated clinical signs such as hardness in the urinary bladder area and red urine. Of greatest significance was an increased incidence of gallstones in all treated groups, meaning that no systemic NOEL could be established for this study (NOEL <14 mg/kg bw/d). Urinary tract cancers occurred in both sexes at the high dose only. Therefore the NOEL for carcinogenicity in this study was established as 1000 ppm (137 mg/kg bw/d). It should be noted that this study was technically deficient as a carcinogenicity study since the mortality in the high dose females was above 50% by the end of the study, which is in breach of the relevant OECD guidelines. This mortality was largely due to renal effects. However the study meets relevant USEPA guidelines, which require 25% survival rates in the study groups.

Rat

Pyrasulfotole was incorporated into rodent diet at concentrations of 0, 25, 250, 1000, and 2500 ppm and administered for up to 24 months to groups of 75 male and 75 female Wistar rats (equivalent to approximately 0, 1.0, 10, 41, and 105 mg/kg bw/d for males and 0, 1.4, 14, 57, and 141 mg/kg bw/d for females, respectively). There were indications of depressed body weights and body weight gains at and above 250 ppm in males and females. A range of effects of the test substance on the eyes at 25 ppm were observed in the study. There were histopathological changes in the liver associated with increased liver weights, but the effects were only prevalent at 250 ppm and above. Chronic progressive nephropathy was a common finding in all animals, including the controls; however there was a tendency for treated males to show a higher incidence of chronic progressive nephropathy earlier in the study. It is possible that the test substance has accelerated its development. Kidney weights tended to be

increased in males at higher doses (250 ppm and above), particularly later in the experiment. Increased levels of protein in the urine were seen in all treated males suggesting effects on the kidney. Hyperplasia of the collecting ducts in the kidneys was somewhat more common in all treatment groups of males at 24 months, although this did not reach statistical significance at the lower doses. A somewhat increased incidence of colloid alteration in the thyroid was observed from 6 months onwards in all treated males. Also, there was a dose-related effect associated with increased occurrence in all treated groups of brown pigment in the thyroid in both sexes at 24 months; with the effect tending to be greater at higher doses. There were some indications of a dose-related increase in thyroid weight in the present study at 6 and 12 months, but not at 24 months. These effects appeared at the lowest dose in the present study. However these effects in the thyroid were probably species specific. The incidence of diffuse acinar degeneration/atrophy in the pancreas was raised at higher doses throughout the study. Squamous cell tumors of the cornea were observed in the highest dose group. A NOEL of 1 mg/kg bw/d can be established for this study, based on a range of effects at the next highest dose including corneal and retinal lesions, increased liver weight and centrilobular hepatocellular hypertrophy, and raised plasma cholesterol.

According to the OECD Guideline 453, which is cited in the study, negative findings in a carcinogenicity test in rats are only acceptable if survival in each dose group is 50% or more at 24 months. In the present study, survival at 24 months was less than 50% in four of the five male study groups, including controls, as well as in the female control group. On the other hand the study meets USEPA requirements for 25% survival in study groups.

Histopathological sections of the thyroid from this rat chronic study were examined by an independent panel of senior pathologists to determine whether the morphologic changes observed in the thyroid represented an adverse effect of pyrasulfotole in the thyroid. It was the opinion of the pathology expert group that the colloid alteration and pigment deposition observed in rats administered pyrasulfotole for two years were representative of normal age-related physiologic changes specific to the rat, and that these findings were not adverse. While noting this opinion that the changes resemble normal ageing effects in the thyroid, it may nonetheless be significant that the test substance appears, in a number of studies, to accelerate and increase the effects relative to controls. For example, it was clear that in the rats sacrificed on schedule at 24 months in the chronic study, the percentage incidence of brown pigment deposition was higher in the treated groups (including at 25 ppm) in both sexes.

Dog

Pyrasulfotole was incorporated into diet and administered to groups of 4 male and 4 female beagle dogs at 0, 250, 1000, or 3000 ppm for one year. These concentrations provided doses of 0, 7, 34, and 101 mg/kg bw/d for males and 0, 9, 33, and 93 mg/kg bw/d for females, respectively. There were increased liver, kidney and thyroid weights, particularly at the high dose. The increases did not reach statistically significance, although there were some indications of dose-response relationships. These increases were also associated with histopathological effects in the liver and kidney. The incidence and severity of tubular dilatation in the kidney was dose-related in males, being observed at and above 1000 ppm. This effect could be correlated with the apparent dose-response effect on the kidney weight in males. Given the increased incidence and severity of tubular dilatation in the kidneys of males at 1000 ppm and above, a NOEL of 250 ppm was established (7 mg/kg bw/d).

Reproduction study

Test substance was incorporated into diet at concentrations of 0, 30, 300, and 3000 ppm and provided to male and female rats in the F_0 generation throughout pre-mating, mating, gestation, and lactation periods. Following weaning of the F_1 generation, the weanlings were maintained in their same dietary groups through adolescence, mating, gestation, and lactation.

In the premating phase of the study, 0, 2.5, 26.3, and 272.4 mg/kg bw/d of test substance was ingested by the F_0 males, 0, 3.7, 34.1, and 353.6 mg/kg bw/d by the F_1 males, 0, 3.1, 32.6, and 345.7 mg/kg bw/d by the F_0 females, and 0, 4.2, 38.9, and 393 mg/kg bw/d by the F_1 females. During gestation, doses on day 14 to 20 post coitum inclusive were 0, 2.0, 22.3, 228.6 mg/kg bw/d for the F_0 females and 0, 2.2, 23.2, 250.4 mg/kg bw/d for F_1 females. In the lactation period, the intakes on days 0 to 4 post partum were 0, 3.1, 30.9, 294.2 mg/kg bw/d for F_0 females and 0, 3.2, 29.9, 263.2 mg/kg bw/d for F_1 females.

A number of effects were observed in the adult rats at 300 ppm and above, including corneal effects, eosinophilic inclusions in the anterior pituitary of males, hepatocellular hypertrophy, cellular alteration and slight increases in periportal fat accumulation in the liver, and increased incidence and/or severity of basophilic tubules and tubular dilation in the kidneys. Based on these observations, a parental systemic NOEL was established at 30 ppm (2 mg/kg bw/d). Pups in both generations exhibited treatment-related corneal effects at 300 ppm and above. There was also a treatment-related delay in balano-preputial separation in F_1 weanlings at 300 ppm and above. Therefore a NOEL for offspring of 30 ppm (2 mg/kg bw/d) was established. Reproductive indices, insemination, fertility, gestation and live birth percentages, were not influenced by treatment with the test substance up to 3000 ppm. Therefore, the NOEL for reproductive toxicity was 3000 ppm (equivalent to 229 mg/kg bw/d).

Developmental studies

Pyrasulfotole was suspended in 0.5% aqueous methylcellulose and administered by gavage to groups of female sperm-positive rats at 10, 100, and 300 mg/kg bw/d on gestation days 6 to 20. Increased salivation was observed in the dams at 100 mg/kg bw/d and above, increasing in a dose-related manner. Additionally, a dose-related increase in enlarged placenta was seen at and above 100 mg/kg bw/d. Based on these findings, the maternal NOEL was established at 10 mg/kg bw/d. Foetal weights were decreased at and above 100 mg/kg bw/d and there were some indications of an increased incidence of foetal skeletal variations at and above the same dose. Therefore the NOEL for foetotoxicity was also 10 mg/kg bw/d.

Pyrasulfotole was formulated in 0.5% aqueous methylcellulose and administered by oral gavage to groups of time-mated female rabbits at 0, 10, 75, and 250 mg/kg bw/d from gestations days 6 to 28, inclusive. As well as showing reduced food consumption and increased loss of body weight at 250 mg/kg bw/d, dams at this dose had increased liver weight. The maternal NOEL was therefore set at 75 mg/kg bw/d. There were a number of skeletal effects (variations) which showed increased foetal and/or litter incidence with a dose-response relationship, being beyond the historical control range at the mid dose (75 mg/kg bw/d) and above. The foetal NOEL was therefore established at 10 mg/kg bw/d. Accordingly there was some foetotoxicity in the absence of maternotoxicity.

Genotoxicity studies

The test substance was evaluated as not mutagenic in the Ames *Salmonella*/microsome-mediated mutagenicity assay. It was also found not to be clastogenic in Chinese hamster V79 cells *in vitro* and an *in vitro* mutagenicity study in the same cells was also negative. The test substance was not clastogenic in the *in vivo* mouse micronucleus study.

Neurotoxicity studies

Pyrosulfotole was suspended in an aqueous solution of 0.5% methylcellulose/0.4% Tween 80 and administered by oral gavage to rats at 0, 200, 500, and 2000 mg/kg bw. There were no clinical signs indicative of neurotoxicity. A generally dose-related incidence of stained fur was seen in both sexes. This was attributed by the study authors to the excretion of pyrasulfotole leading to colouring of the urine and the spread of this discoloration by way of grooming activity. However this was not confirmed by any analysis of the urine. There was evidence of an ongoing diminution in motor and locomotor activity in all treated females,

albeit without clear indications of a dose-response relationship; possibly indicating systemic toxicity. These observations on activity were not associated with any other indications of neurological abnormality or any histopathological observations. Because of the uncharacterised staining of the fur in all dose groups in both sexes and the effects on activity in females in all dose groups, it is arguable that no NOEL can be established for systemic toxicity. However, gavage administration of the test material at dose levels up to 2000 mg/kg bw did not produce any neurotoxic effects.

Pyrasulfotole was incorporated into rodent meal at concentrations of 0, 500, 2500, and 5000 ppm and provided to rats for 90 days. These dietary concentrations provided doses of approximately 0, 32, 166, and 345 mg/kg bw/d for males and 0, 42, 206, and 416 mg/kg bw/d for females. There were no indications of neurotoxic effects. Because of the occurrence of corneal effects at the low dose in this study (42 mg/kg bw/d), no NOEL could be established for systemic toxicity.

Pyrasulfotole in diet at concentrations of 0, 45, 450, and 4500 ppm was administered to groups of 30 sperm-positive female rats on gestation day 6 to lactation day 21. Dietary concentrations were adjusted during lactation to provide for a constant dosage throughout the treatment period. These concentrations provided an average daily intake of 0, 3.8, 37, and 354 mg/kg bw/d. Based on decreased food consumption during lactation and ocular opacities in dams at 450 and 4500 ppm, the maternal systemic NOEL was 45 ppm (3.8 mg/kg bw/d). There were no maternal neurotoxic effects. Possible reproductive toxicity was limited to decreased fertility indices at 450 ppm and 4500 ppm, which did not reach statistical significance. Neonatal toxicity included decreased postnatal weights, delayed preputial separation and retinal degeneration in the offspring at 450 and 4500 ppm. The NOEL for neonatal systemic toxicity was therefore 45 ppm (3.8 mg/kg bw/d). There were decreased absolute brain weights, decreased cerebrum length and decreased cerebellum height in male and/or female offspring on postnatal day 21 at 450 and 4500 ppm. There was also diminished performance in males in the passive avoidance test at these doses. Therefore the NOEL for neonatal developmental neurotoxic effects was 45 ppm (3.8 mg/kg bw/d). These developmental neurotoxic effects occurred at maternotoxic dose levels.

Other studies

2-(2-nitro-4-fluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) was used as a model inhibitor of the 4-hydroxyphenylpyruvate dioxygenase (HPPDase) enzyme and was dissolved in DMSO for incubation with liver cell preparations from rat, mouse, dog, rabbit, and human. Liver cells were incubated with buffer, buffer plus NTBC (30 µM), buffer plus tyrosine (550 µM), or buffer plus tyrosine (550 µM) plus NTBC (30 µM). After addition of NTBC or solvent (DMSO only) to the incubation buffer, the plates were incubated for 0, 2, or 4 h at 37°C. Tyrosine concentrations in the incubation medium did not change over the incubation time, nor was there any effect on tyrosine of adding NTBC to the medium. In basal conditions (no added tyrosine), the concentration of HPLA was below the limit of quantification in the absence and the presence of NTBC in the rat, dog, and rabbit incubations. Concentrations of HPLA were below the limit of quantification in incubations with human liver cells in basal conditions; however incubation with NTBC for 2 or 4 h increased HPLA concentration to quantifiable limits in a time-dependent manner. In the mouse incubation, low levels of HPLA were detected in basal conditions but did not increase with time of incubation. Addition of NTBC to the mouse incubation markedly increased HPLA concentrations in a time-dependent manner. When tyrosine was added to basal medium, HPLA concentrations were below the limit of quantification in rat, dog, rabbit, and human. Low levels of HPLA, similar to those observed in basal conditions, were observed in mouse liver cell incubations. Addition of both tyrosine and NTBC to the incubation medium increased the production of HPLA in nearly all species. However, production of HPLA was low in rat and rabbit, and no HPLA was observed at any time point in dog incubations. By

contrast, HPLA concentrations were markedly increased in both mouse and human incubations.

NTBC and L-tyrosine were administered singly or in combination to pregnant female rats. NTBC was suspended in demineralized water and administered by oral gavage at 10 µg/kg bw/d on gestation days 6 through 20 inclusive, while L-tyrosine was incorporated into the diet at a concentration of 20000 ppm, and the tyrosine-containing diet was provided to the relevant groups on gestation days 6 through 21. The control group and the group receiving only L-tyrosine were administered demineralized water by oral gavage on gestation days 6 through 20 as a control for NTBC administration. In the treatment groups (tyrosine alone, or NTBC alone), in which maternal plasma tyrosine was somewhat elevated relative to controls, there was some effect on foetal skeletal parameters. In the group administered both tyrosine and NTBC, in which maternal plasma tyrosine was markedly increased, there was generally a stronger increase in skeletal findings.

L-tyrosine was incorporated into rodent diet at 0%, 2%, and 5% and fed to groups of 5 male and 5 female CD rats, Brown Norway rats, and CD-1 mice for a period of 14 days. No corneal opacities were observed in female rats or in either male or female mice. Corneal opacities were not seen in male rats of either strain at 2% dietary tyrosine. In CD rats, all male rats at 5% tyrosine showed corneal opacities by day 7, with progression of the opacity over time. One male Brown Norway rat at 5% tyrosine had a slight corneal opacity only visible on day 14. In all cases, the corneal opacities were characteristic "snow flake" opacities.

In a 14-day dietary study, pyrasulfotole was administered at 18000 ppm in the diet to two groups of 5 male beagle dogs. One group received 300 g of a diet including pyrasulfotole and 450 mL tap water ("wet feed"), while the other group received 300 g of a diet including the pyrasulfotole without added water ("dry feed"). The intake of test substance was somewhat higher in the dry feed group, being 318 mg/kg bw/d on days 1-7 and 479 mg/kg bw/d on days 8-16, compared with the wet feed group with 272 mg/kg bw/d on days 1-7 and 388 mg/kg bw/d on days 8-16. Treatment-related clinical signs were limited to red urine in two dogs of the dry-feed group, in one dog on study day 7 and in another dog on study days 7, 8, 10, and 12, and a tan substance was noted in the faeces of all wet feed dogs. There was a treatment-related increase in BUN and blood in the urine in both dietary groups. Two dogs in the dry-feed group showed calculi in several locations in the urinary tract, and the urinary bladders of these animals showed moderate thickening. There were no findings in the other dogs in this group, and no findings in any of the dogs in the wet-feed group. Dogs in the wet-feed group had slightly higher plasma concentrations of pyrasulfotole at 2 and 4 h after the last feeding than did the dogs in the dry group. However, by 6 h after dosing, plasma concentrations were similar. Urine concentrations of the test substance were higher in the dry-feed group at nearly all urine collection time points. There was no significant difference in urine volume between the treatment groups.

Studies on a benzoic acid derivative

Studies on a benzoic acid metabolite of pyrasulfotole showed that it has low acute oral toxicity (LD_{50} > 5000 mg/kg bw in rats). A 28-day dietary study on rats did not identify any toxic effects and a NOEL of 1118 mg/kg bw/d was established. Likewise a 90-day dietary study in the same species disclosed no toxic effects and a NOEL of 769 mg/kg bw/d. The compound was negative for mutagenicity in a reverse mutation assay (Ames test) and in a CHO/HGPRT forward mutation assay. It was also negative for the induction of chromosomal aberrations in Chinese hamster ovary (CHO) cells and for cytogenic damage in the *in vivo* mouse micronucleus assay. Finally, a developmental toxicology study in the rat found maternal toxicity in the form of clinical signs (salivation), decreased food consumption and

decreased body weight with a maternal NOEL of 75 mg/kg bw/d. However there were no treatment-related effects on foetal development, with a foetal NOEL being established at the highest dose of 750 mg/kg bw/d.

Discussion of toxicity data

Pyrasulfotole is readily absorbed by the oral route in male rats. Approximately 60% is absorbed and excreted in the urine within 6 h. By 48 h, about 70% of an oral dose has been excreted in the urine and 30% in the faeces, with less than 2% of the dose remaining in the body. Studies using the intravenous route found that 10% of the subsequent excretion was via the faeces, indicating some biliary excretion. The compound is poorly metabolised in male rats at least, with the most abundant metabolite, a desmethyl derivative, being present at less than 5% in the urine and faeces.

Pyrasulfotole has low acute toxicity by the oral, dermal and inhalational routes, and it is not a skin irritant or sensitiser. However it is a moderate eye irritant.

Pyrasulfotole was found to have a wide range of effects in short-term and long-term repeat dose studies. Target organs included the eyes, thyroid, liver, kidney, gallbladder and urinary system. As well, the compound has been found to have foetotoxic effects in the rabbit in the form of increased incidence of skeletal variations in the absence of maternotoxicity. Carcinogenicity studies have found an incidence of eye neoplasms in the rat and urinary tract neoplasms in the mouse at relatively high doses. In both species, the tumours observed could be attributed to non-genotoxic proliferative mechanisms (secondary to urinary tract stones in the mice and corneal effects in the rats). There is no evidence that pyrasulfotole is genotoxic.

In the chronic rat study, liver weights were increased and centrilobular hepatocellular hypertrophy and raised plasma cholesterol levels were observed in males with a NOEL of 1 mg/kg bw/d. Similar effects (increased liver weights and centrilobular hepatocellular hypertrophy) were observed in male mice, with a higher NOEL of approximately 14 mg/kg bw/d.

Ocular toxicity was observed at relatively low doses in a 90-day dietary study in the rat (with a LOEL of 77 mg/kg bw/d and a NOEL of 2.3 mg/kg bw/d), and this was confirmed in a two year rat study (with a NOEL of 1 mg/kg bw/d). Corneal effects were observed in both cases, with retinal histopathology as well in the chronic study. Ocular effects were also observed in a postnatal developmental neurotoxicity study in the rat, with ocular opacities in the dams (LOEL of 37 mg/kg bw/d, NOEL of 3.8 mg/kg bw/d) and retinal degeneration in the pups (same LOEL and NOEL as the dams). Corneal effects were observed as well in a rat reproductive study in both dams and pups with a NOEL of 2 mg/kg bw/d.

The applicant has argued that effects on the cornea are related to tyrosinaemia secondary to inhibition of 4-hydroxyphenylpyruvate dioxygenase (HPPDase) by pyrasulfotole, and that they are specific to rats. They propose that rats are especially sensitive to inhibition of this enzyme because they lack the capacity to produce p-hydroxyphenyl lactic acid (HPLA), a "diversionary metabolite" that enables reduction of plasma tyrosine concentrations when HPPDase is inhibited. In a mechanistic study provided in the database, the study authors propose that rat, dog and rabbit have a very low ability to produce HPLA by comparison with mice and humans. However, the data in the study indicate that HPLA is indeed capable of being formed in the rat. It is also noteworthy that dogs do not appear to be capable of producing HPLA, but despite this a chronic toxicity feeding study in the dog did not disclose any corneal lesions. This is not consistent with the study author's hypothesis associating corneal lesions with inability to produce HPLA as a "diversionary metabolite".

Corneal lesions have been reported in humans treated with doses of 1-2 mg/kg bw/d of 2-(2-

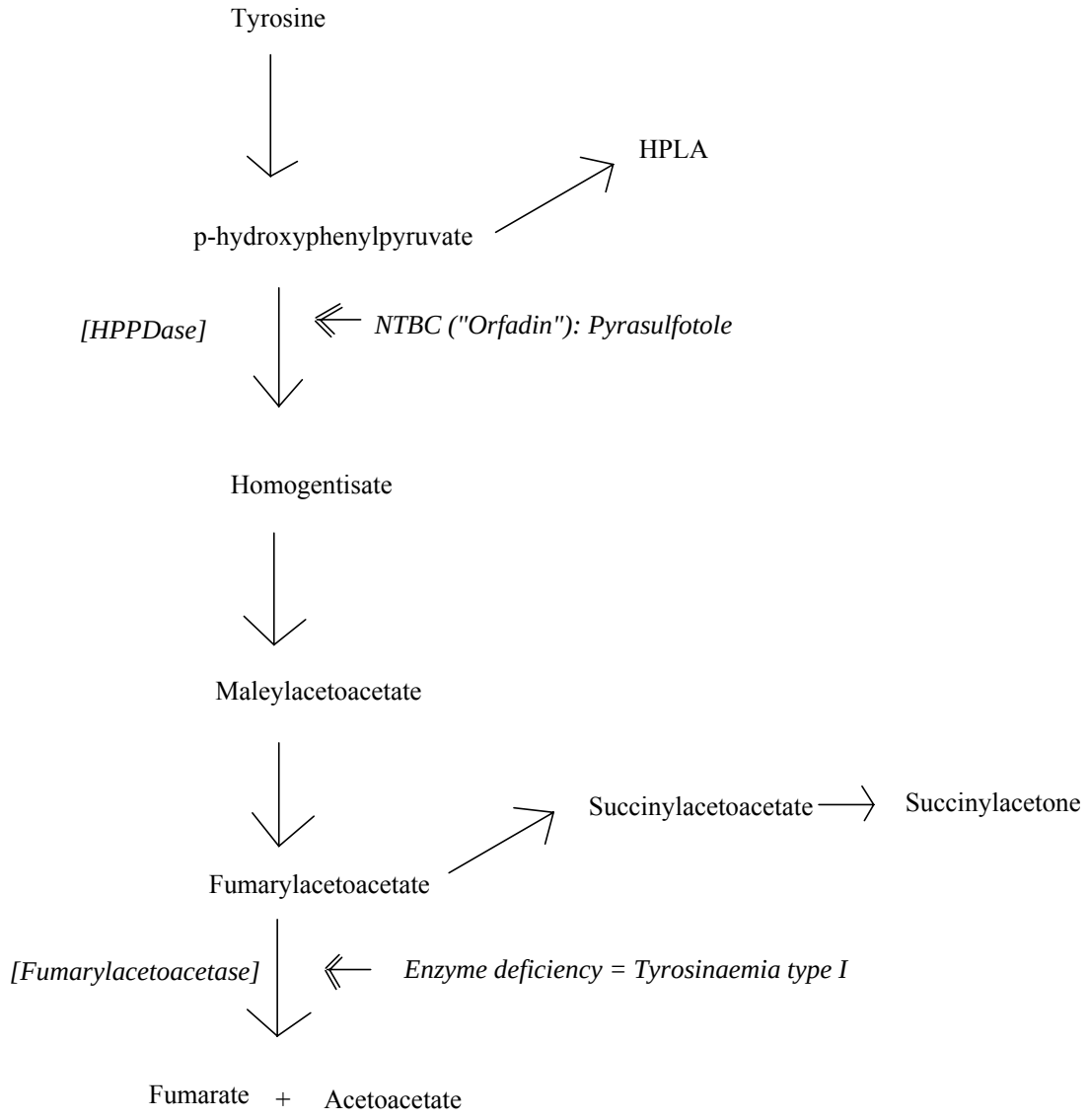
nitro-4-fluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC), which resembles pyrasulfotole in being an inhibitor of HPPDase. In a clinical trial of 207 patients treated with NTBC for hereditary tyrosinaemia type I, ocular side-effects were observed in some individuals, including corneal opacity in 2% of cases (US FDA, 2002).

It has been reported that treatment of beagle dogs with doses as low as 0.1 mg/kg bw/d for 11 weeks produced corneal opacities. On the other hand, treatment of rhesus monkeys with 10 mg/kg bw/d for 12 weeks did not, although tyrosine values were "markedly increased". It was concluded that the production of corneal lesions in experimental animals exposed to NTBC did not appear to be simply related to the concentration of tyrosine in ocular fluid.

The following diagram indicates the metabolic pathway of tyrosine. In human tyrosinaemia type I, there is a deficiency in fumarylacetoacetase. This leads to a buildup of the toxic metabolites succinylacetoacetate and succinylacetone, which are responsible for the liver toxicity which is the most serious effect of this hereditary condition. This condition is treated with NTBC (tradename Orfadin), which prevents the buildup of succinylacetoacetate and succinylacetone by inhibiting metabolism "upstream" at the point indicated, viz. HPPDase. Pyrasufotole also inhibits HPPDase.

Since NTBC (Orfadin) as a treatment for tyrosinaemia type I results in corneal opacity in a percentage of individuals, it is possible that exposure to pyrasulfotole (which inhibits the same enzyme, HPPDase) would also cause corneal effects. Although individuals with tyrosinaemia type I are not typical of the normal population, because they are deficient in the enzyme fumarylacetoacetase, the effect on them and on normal individuals of an inhibitor of HPPDase (in terms of tyrosinaemia, for example) would be expected to be similar. This is because HPPDase precedes fumarylacetoacetase in the metabolic pathway of tyrosine and under conditions of HPPDase inhibition the level of fumarylacetoacetase activity will probably be irrelevant. Therefore the sideffects on the cornea observed in some patients with tyrosinaemia type I following treatment with NTBC raise concerns about the exposure of the general population to such HPPDase inhibitors, which include pyrasulfotole.

Metabolism of Tyrosine: Enzyme inhibitors and enzyme deficiencies



Some evidence on the relative inhibitory efficiency of mesotrione (another herbicide that inhibits HPPDase) compared with NTBC is available. The magnitude and duration of effects on plasma tyrosine levels were compared for the two chemicals in human male volunteers. NTBC had a considerably longer half-life in the plasma than mesotrione and its effects on plasma tyrosine levels were more long-lasting. Following a dose of NTBC of 1 mg/kg bw, the concentration of tyrosine in the plasma reached approximately 1100 nmol/ml, whereas with administration of a dose of 4 mg/kg bw of mesotrione, plasma tyrosine levels reached 300 nmol/ml. These results suggest that in humans mesotrione is at least an order of magnitude less effective as an inhibitor of HPPDase than NTBC. Nevertheless, corneal effects were observed in male rats treated with mesotrione at 0.48 mg/kg bw/d, with a NOEL of 0.16 mg/kg bw/d.

No data on the comparative inhibitory effect on HPPDase of NTBC and pyrasulfotole appear to be available. However pyrasulfotole is apparently less effective at inducing corneal lesions than mesotrione in the rat at least, with a LOEL of 10 mg/kg bw/d for the former compared with a LOEL of 0.48 mg/kg bw/d in the latter case. Therefore it can be argued that pyrasulfotole is likely to be considerably less effective than mesotrione as an inhibitor of HPPDase. Since it appears that mesotrione is itself less effective than NTBC as an inhibitor of human HPPDase, it seems safe to conclude that pyrasulfotole is considerably less inhibitory of this enzyme than NTBC. This also implies that pyrasulfotole is likely not to produce corneal lesions at as low a dose level as has been observed in people treated with NTBC.

It has been hypothesised that tyrosinaemia leads to accumulation of tyrosine in the anterior aqueuous humour of the eye and tyrosine crystals are then deposited in the cornea. A similar mechanism might explain the retinal effects observed with pyrasulfotole. Retinal atrophy was observed at a higher rate in treated groups of rats sacrificed at 24 months in the rat chronic study. The increase was statistically significant in males and females from approximately 10 mg/kg bw/d. Retinal degeneration was also observed in female offspring in the postnatal developmental neurotoxicity study at 37 mg/kg bw/d and above with a NOEL of 4 mg/kg bw/d. It may also be relevant that a rat reproduction study on isoxaflutole, which has a similar mode of action to pyrasulfotole, as well as a similar chemical structure, disclosed some incidence of retinal bleeding in the F2 pups with a NOEL of 20 mg/kg bw/d.

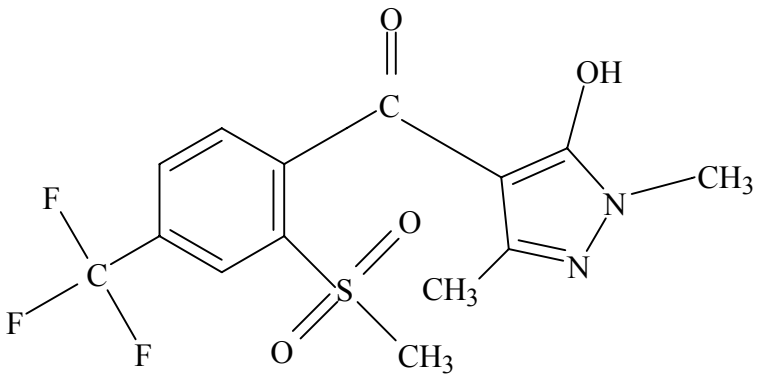
Effects on the thyroid were also observed at relatively low doses in several studies: in the 28 dermal study in rats (LOEL of 100 mg/kg bw/d, NOEL of 10 mg/kg bw/d), in the two year study in rats (LOEL of 1 mg/kg bw/d, with no NOEL established), and in the parental rats in the two generation reproduction study (LOEL of 2 mg/kg bw/d, with no NOEL established). However the rat thyroid is known to be particularly susceptible to sulfur-containing compounds such as pyrasulfotole.
Another effect of interest was the occurrence of gallstones (containing cholesterol) in mice during an 18 month chronic study, in which there was an increased incidence in all treated mice (LOEL of 14 mg/kg bw/d, with no NOEL established).

Although it did not occur at very low doses, a noteworthy finding was stones in the urinary system causing renal failure during the chronic mouse study at 560 mg/kg bw/d. Stone formation in the urinary tract also occurred in a 28-day dog study at 469 mg/kg bw/d and at 454 mg/kg bw/d in a 90-day study in the rat. The stones were attributed by the study authors to concretions of test substance. This would seem biologically plausible.

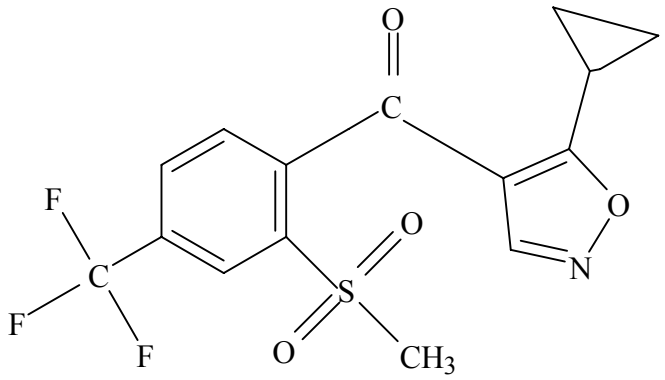
There were no effects of pyrasulfotole on reproductive indices. The test substance was not found to be a teratogen. However some foetotoxicity was observed, namely an increased incidence of skeletal variants, in the absence of maternotoxicity in a rabbit developmental study. Neurotoxic effects were observed in pups in a rat postnatal developmental toxicity study, but they occurred in conjunction with maternotoxicity.

Comparison with a similar compound

Pyrasulfotole



Isoxaflutole



The effects of pyrasulfotole may be compared to those observed in studies previously assessed by OCS on isoxaflutole, which as the illustrations above indicate resembles pyrasulfotole chemically, as well as in its mode of action as an inhibitor of HPPDase. Isoxaflutole also produced corneal opacity, with a NOEL of 2 mg/kg bw/d from a chronic rat study. Retinal bleeding in the F2 pups in a rat reproduction study using isoxaflutole, with a NOEL of 20 mg/kg bw/d, has already been mentioned. Thyroid effects (follicular cell hyperplasia) were observed with this test substance in rats with a NOEL of 2 mg/kg bw/d. Isoxaflutole also had similar effects to pyrasulfotole on the liver, namely increased liver weight and hepatocytic hypertrophy in a chronic rat study with a NOEL of 2 mg/kg bw/d. In terms of developmental effects, isoxaflutole gave rise to low foetal weights with a NOEL of 10 mg/kg bw/d in the rat in the absence of maternotoxicity and increased minor anomalies and absent or reduced ossification with a NOEL of 5 mg/kg bw/d in the rabbit also in the absence of maternotoxicity. This may be compared to the increased incidence of skeletal variants in the absence of maternotoxicity observed with pyrasulfotole in a rabbit study with a NOEL of 10 mg/kg bw/d. Isoxaflutole was placed in Schedule 5 of the SUSDP.

Modes of action of pyrasulfotole

It is arguable that many of the effects of pyrasulfotole in the test species are the result of three separate modes of action, as follows:

1. Increased levels of tyrosine in the blood – tyrosinaemia – due to the effects of pyrasulfotole as an inhibitor of HPPDase. Inhibition of this enzyme limits the normal metabolism of tyrosine and leads to a build up of tyrosine. At sufficiently high levels in the blood, tyrosine is known to cause corneal inflammation and damage. The corneal effects observed in the present database can be related to this effect. It is possible that effects in other

tissues and organs, for example the retinal effects, may also be directly or indirectly due to high blood tyrosine levels.

Corneal tumours were observed in 2 out of 55 rats at the highest dose (105 mg/kg bw/d) in the chronic (carcinogenicity) study. Corneal hyperplasia, inflammation and neovascularisation were common in animals at this dose – being found in the two animals with corneal tumours – and it is likely that the tumours observed were associated with these effects. Pyrasulfotole has not been found to be genotoxic, and it is reasonable to conclude that the corneal tumours observed were the result of a non-genotoxic proliferative mechanism.

2. Pyrasulfotole precipitating out in the tissues. At high dose levels, urinary tract concretions formed in the mouse, rat and dog, probably due to precipitation of the test substance, pyrasulfotole. In the mouse, these urinary stones were associated with urothelial hyperplasia and the development of urinary tract tumours. Tumours were noted in the urinary tracts of male mice subjected to a dose level of 560 mg/kg bw/d. Urothelial hyperplasia and stones were common in the urinary tract at this dose and it is reasonable to conclude that the tumours observed were associated with these effects, being the result of a non-genotoxic proliferative mechanism.

3. A direct toxic effect of pyrasulfotole. Pyrasulfotole inhibits HPPDase. Human tyrosinaemia type III involves a defect in this enzyme and has not been associated with effects on the cornea or the liver. However, when NTBC is used in human medicine as an inhibitor of HPPDase to treat tyrosinaemia type I (which involves a genetic defect in an enzyme further down the metabolic pathway of tyrosine than HPPDase, namely fumarylacetoacetase), corneal lesions and liver effects are among those reported as adverse reactions. However liver effects are a feature of the genetic condition itself and it is not clear that these are actually side-effects. Therefore these observations do not necessarily help explain the liver abnormalities observed in the animal studies using pyrasulfotole.

Effects of pyrasulfotole at low doses on the liver included increased liver weight and centrilobular hepatocellular hypertrophy in the rat chronic study, along with a raised plasma cholesterol which may have been related. Also, in the mouse chronic study, gallstones containing cholesterol were observed in all treated groups, together with increased relative (although not absolute) liver weights, and centrilobular hepatocellular hypertrophy in the mid and high dose mice. Clinical chemistry, including plasma cholesterol levels, was not covered in the mouse chronic study.

Pyrasulfotole has also been observed to have effects on the rat thyroid, including colloid alteration, pigment deposition, loss of colloid, follicular cell hypertrophy, follicular cell hyperplasia and increased follicular diameter. In the case of isoxaflutole, there were also effects observed on the rat thyroid, including follicular cell hyperplasia (NOEL of 2 mg/kg bw/d) and neoplasia (follicular cell adenomas) at a high dose (500 mg/kg bw/d) with a NOEL of 20 mg/kg bw/d. Thyroid effects (follicular epithelial hypertrophy) were also observed in dogs at 460 mg/kg bw/d. In the case of isoxaflutole, it was suggested that the effects on the rat thyroid were secondary to effects on the liver. That is, that isoxaflutole induces liver enzyme activity that is likely to enhance thyroxine conjugation and excretion, thereby lowering T_4 (thyroxine) levels and stimulating TSH activity. It is known that constant TSH stimulation can lead to the sequence of thyroid hypertrophy, benign neoplasia and eventually malignant neoplasia. Sulfur-containing chemicals such as isoxaflutole and pyrasulfotole are known to frequently affect the rat thyroid, and the similarity of the structure of pyrasulfotole to isoxaflutole suggests that it is likely to have a similar mode of action on the thyroid, probably by way of the liver.

Summary and establishment of ADI and ARfD

The most significant endpoints observed in the database on pyrasulfotole were corneal and retinal lesions, increased liver weight and centrilobular hepatocellular hypertrophy, and raised plasma cholesterol, all of which were observed in the chronic rat study, with a NOEL of 1 mg/kg bw/d. Applying a 100-fold safety factor to this figure leads to an ADI of 0.01 mg/kg bw/d. A further consideration is that, as noted above, a dose of 1 mg/kg bw/d of another HPPDase inhibitor, namely NTBC which is used in human medicine, can lead to corneal lesions in some individuals. If pyrasulfotole is assumed to be equally effective as NTBC as an HPPDase inhibitor (as indicated above, this would be a conservative assumption), it is arguable that 1 mg/kg bw/d, which produces corneal lesions in a small percentage of human subjects, could be treated as a LOEL for pyrasulfotole in humans. Applying a 10-fold safety factor because of the use of a LOEL rather than a NOEL and a 10-fold safety factor to allow for individual variation among humans would lead to an appropriate ADI of 0.01 mg/kg bw/d. This is the same ADI as that derived from the animal studies, indicating an adequate margin of safety for such an effect.

Further support for this ADI of 0.01 mg/kg bw/d is derived from other studies in the pyrasulfotole database. For example, the ADI figure is also supported by the LOEL related to the occurrence of gallstones at the low dose in the chronic mouse study (14 mg/kg bw/d), which would lead to an ADI of approximately 0.01 mg/kg bw/d - using a 1000 fold safety factor because of the use of a LOEL. Likewise, given that foetal effects occur in the rat and rabbit developmental studies with a NOEL of 10 mg/kg bw/d in both cases, the application of a 1000 fold safety factor because of the extra level of safety used in the case of developmental effects would also give rise to an ADI of 0.01 mg/kg bw/d. In summary, an ADI of 0.01 mg/kg bw/d appears to be robust.

An acute neurotoxicity study on rats indicated decreased motor and locomotor activity in females at all dose levels following treatment, as well as uncharacterised staining of the fur in all dose groups in both sexes. Since these effects were observed following a single dose, with a LOEL of 200 mg/kg bw, an ARfD of 0.2 mg/kg bw can be established, using a 1000-fold safety factor.

PUBLIC HEALTH STANDARDS

Poisons scheduling

The National Drugs and Poisons Schedule Committee (NDPSC) considered the toxicity of pyrasulfotole. The Committee agreed to include pyrasulfotole in Schedule 5 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) on the basis that it is a moderate eye irritant, while being of low acute toxicity by the oral, dermal and inhalational routes and not being a skin irritant or sensitiser.

The NDPSC recommended that no pyrasulfotole product for domestic use should be registered, and that any product labelling for pyrasulfotole include the statement "not for home garden use" or a similar statement.

First Aid Instructions and Safety Directions

First Aid Instructions and Safety Directions have been established for Precept Selective Herbicide, which contains pyrasulfotole as one of the actives.

Acceptable Daily Intake (ADI)

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. The NOEL is then divided by a safety factor, which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

The ADI for pyrasulfotole was established at 0.01 mg/kg bw/d based on a NOEL of 1 mg/kg bw/d in a 24-month rat study and using a 100-fold safety factor.

Acute Reference Dose (ARfD)

The acute reference dose (ARfD) is the maximum quantity of an agricultural 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 ARfD for pyrasulfotole was established at 0.2 mg/kg bw based on a LOEL of 200 mg/kg bw in a rat acute neurotoxicity study. A 1000-fold safety factor was used to derive this ARfD since it was based on a LOEL rather than a NOEL.

RESIDUES ASSESSMENT

Metabolism

Plants

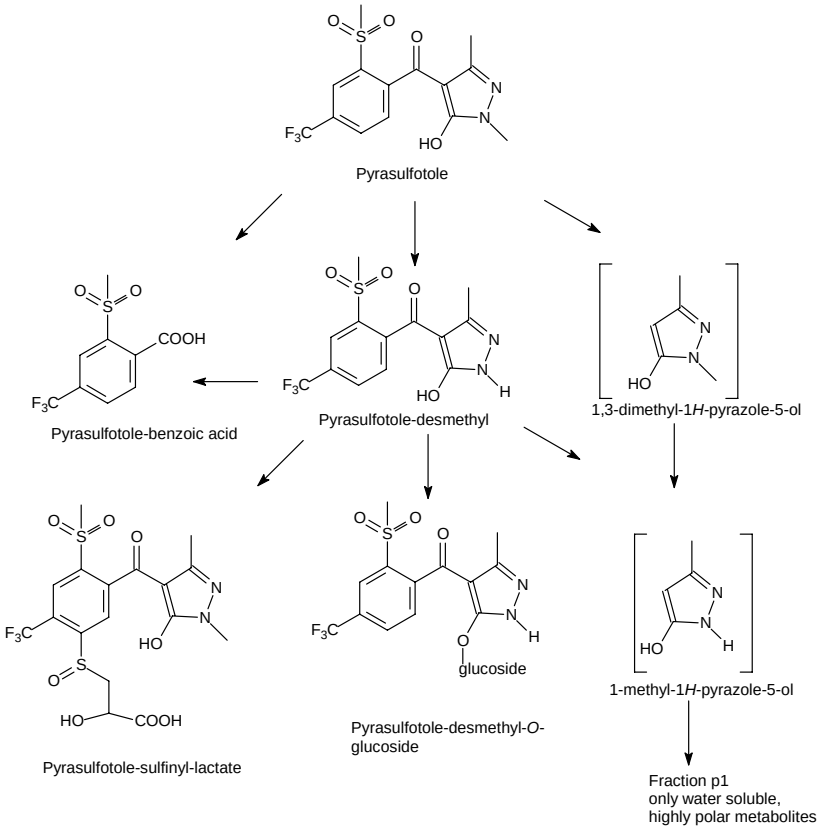
The metabolism of the herbicide pyrasulfotole (labelled as either phenyl-U-^{14}C or pyrazole-3-^{14}C-pyrasulfotole) was investigated in spring wheat.

At maturity, the overall distribution of radioactivity from the whole plant was 74.4-95.1% of the TRR in straw, and 4.9-25.6% of the TRR in grain. In the phenyl-label study polar components were characterised at levels of ~5-36% of the TRR. The predominant residue was pyrasulfotole-benzoic acid in all wheat matrices with levels increasing as the plant matured (~25-90% of the TRR). Pyrasulfotole-desmethyl-*O*-glucoside was also a major component in wheat forage (~34% of the TRR) and hay (~10% of the TRR), and a minor component in straw. In the pyrazole-label study many polar components were characterised (~38-77% of the TRR) in wheat matrices. Pyrasulfotole-desmethyl-*O*-glucoside was the only metabolite identified in forage, hay, straw (~22% of the TRR), and grain (<1% of the TRR). Several unknown metabolite fractions of varying polarity were detected in wheat matrices, none of them exceeding <8% of the TRR.

In a second metabolism study, in addition to application of pyrasulfotole labelled as phenyl-U-^{14}C, the safener mefenpyr-diethyl was performed in parallel, in order to investigate the influence of the safener on the metabolism of pyrasulfotole.

There are two main metabolic pathways for pyrasulfotole in wheat matrices. The first pathway involves the demethylation of pyrasulfotole yielding pyrasulfotole-desmethyl. This intermediate metabolite is glucosylated (pyrasulfotole-desmethyl-O-glucoside), or conjugated with glutathione leading to pyrasulfotole-sulfinyl-lactate. The second pathway is the result of cleavage of the pyrazole moiety leaving the pyrasulfotole-benzoic acid and multiple polar constituents. The use of a crop safener, mefenpyr-diethyl in conjunction with pyrasulfotole did not yield any qualitative difference in the residue profile of wheat resulting from the use of pyrasulfotole alone.

Figure 1. Metabolic profile of pyrasulfotole in wheat.



Livestock

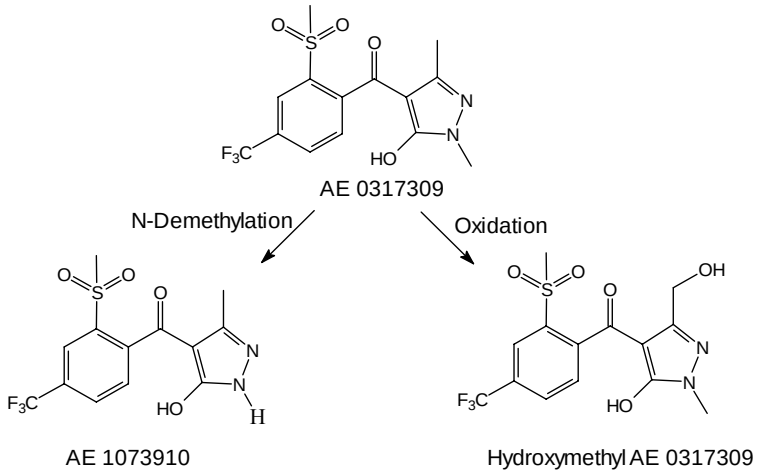
Goats

The metabolism of pyrasulfotole in lactating goats was investigated in two separate studies using different radiolabels; [phenyl-U-^{14}C] and [pyrazole-3-^{14}C]-pyrasulfotole. More than 67% of the administered dose was recovered in urine and faeces, with less than 2% in tissues, and 0.2% in milk.

The majority of the residue in tissues was comprised of pyrasulfotole (≥80% of the TRR), with lesser amounts identified as pyrasulfotole-desmethyl metabolite (≤2% of the TRR), and hydroxymethyl pyrasulfotole (≤9% of the TRR). The majority of the residue in milk was comprised of pyrasulfotole (38-83% of the TRR), with lesser amounts identified as pyrasulfotole-desmethyl metabolite (≤12% of the TRR), and hydroxymethyl pyrasulfotole (≤5% TRR).

The metabolic fate of [phenyl-U-^{14}C] and [pyrazole-3-^{14}C]-pyrasulfotole in lactating goats involved either *N*-demethylation of pyrasulfotole to afford pyrasulfotole-desmethyl, or oxidation of pyrasulfotole to afford pyrasulfotole-hydroxymethyl. The proposed metabolic profile of pyrasulfotole in lactating goats is presented in Figure 2.

Figure 2. Metabolic profile of pyrasulfotole in lactating goats.



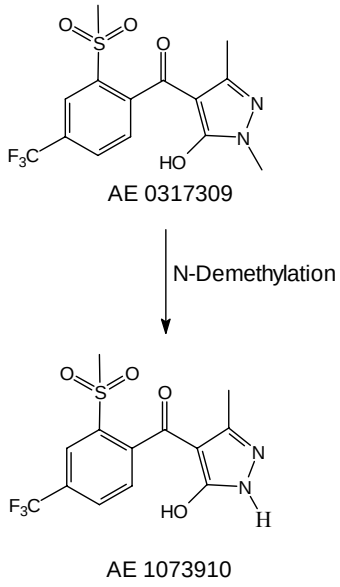
Poultry

The metabolism of pyrasulfotole in laying hens was investigated in two separate studies using different radiolabels; [phenyl-U-^{14}C] and [pyrazole-3-^{14}C]-pyrasulfotole

More than 85% of the administered dose was recovered in the excreta, with less than 0.4% in tissues and eggs. The predominant residue in tissues was pyrasulfotole (≥93% of the TRR), with lesser amounts of the pyrasulfotole-desmethyl metabolite (≤7% of the TRR). Residues in eggs were characterised, but not identified.

The metabolic fate of [phenyl-U-^{14}C] and [pyrazole-3-^{14}C]-pyrasulfotole in laying hens involved the *N*-demethylation of pyrasulfotole to yield the pyrasulfotole-desmethyl metabolite. The proposed metabolic profile of pyrasulfotole in laying hens is presented in Figure 3.

Figure 3. Metabolic profile of pyrasulfotole in hens.



Analytical methods

Plant matrices.
Bayer CropScience has developed a HPLC/MS/MS method for the detection and quantitation of residues of pyrasulfotole, pyrasulfotole-desmethyl, and pyrasulfotole-benzoic acid in crop matrices.

The crop matrices were extracted with a mixture of acetonitrile/water/concentrated hydrochloric acid. The sample extracts were heated, then cooled and a mixture of isotopic internal standards added. A small aliquot was purified by C18 solid phase extraction (SPE) and concentrated for analysis by HPLC/MS/MS. The limit of quantitation (LOQ) is 0.01 mg/kg for each analyte in each matrix. The method was validated in soybean grain, corn grain, corn stover, wheat forage, barley hay, and barley grain. A successful independent laboratory validation (ILV) was completed with samples of wheat grain and soybean grain.

Alternative methodology was used for the detection and quantitation of residues of pyrasulfotole, pyrasulfotole-desmethyl, and pyrasulfotole-benzoic acid in the Australian residues trials. Homogenised test samples were extracted with methanol:0.1% formic acid in water following the addition of internal standards. The extract was filtered and diluted with methanol:0.1% formic acid in water. Samples extracts were analysed by HPLC/MS/MS. To demonstrate recovery of residues from test samples, untreated control test samples of wheat, barley and oats (forage, grain and straw) were fortified with pyrasulfotole, pyrasulfotole-desmethyl, and pyrasulfotole-benzoic acid at the proposed LOQ (0.02 mg/kg) and at 1 mg/kg (5x LOQ).

Animal matrices.
A residues method for the determination of pyrasulfotole in tissues and milk was provided. The livestock tissues were extracted using ACN/H_2O. The sample extracts were heated and then cooled prior to the addition of a stable isotopic internal standard purification by C18 SPE. The solvent was removed from the samples and the residues were reconstituted for analysis using HPLC/MS/MS.

Milk samples were diluted with water and the stable isotopic internal standard added. The diluted samples were syringe filtered and analysed by HPLC/MS/MS. For cream, the samples were extracted with ACN and centrifuged and the stable isotopic internal standard added. The extract was partitioned with n-hexane. The ACN layer was drained into a glass vial and the n-hexane phase was discarded. An aliquot of the ACN phase was concentrated prior to analysis using HPLC/MS/MS. The analytical method for the determination of residues of pyrasulfotole in livestock tissues and whole milk was validated by ILV.
The APVMA sought the advice of the National Residues Survey (NRS) in relation to the capability of this method to detect and quantify residues of pyrasulfotole-desmethyl.

Residue definition
In lactating goats the predominant residue in tissues and milk was pyrasulfotole. Pyrasulfotole was also the predominant residue in poultry tissue and eggs. The metabolism of pyrasulfotole was by *N*-demethylation of pyrasulfotole to form pyrasulfotole-desmethyl. In goats, oxidation of pyrasulfotole to form pyrasulfotole-hydroxymethyl was also observed.
There are two main metabolic pathways for pyrasulfotole in wheat matrices. The first pathway involves the demethylation of pyrasulfotole yielding pyrasulfotole-desmethyl. The second pathway is the result of cleavage of the pyrazole moiety leaving the pyrasulfotole-benzoic acid and multiple polar constituents.

Based on the toxicological evaluation of pyrasulfotole and its metabolites by the Office of Chemical Safety (OCS), pyrasulfotole and pyrasulfotole-desmethyl should be part of the residue definition. Pyrasulfotole-benzoic acid, the major metabolite in wheat and rotational crop studies, is not of toxicological concern, thus the inclusion of the benzoic-acid metabolite in the residue definition is not considered necessary.

Methods capable of the detection and quantitation of pyrasulfotole and pyrasulfotole-desmethyl in plant and animal matrices are available.

Based on the metabolism of pyrasulfotole in crops and animals, its toxicological profile and the suitability of the analytical methods for the detection of pyrasulfotole and pyrasulfotole-desmethyl residues, the following residue definition is recommended for inclusion in Table 3 of the MRL Standard; the sum of pyrasulfotole and (5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)[2-mesyl-4-(trifluoromethyl)phenyl]methanone, expressed as pyrasulfotole.

Freezer storage stability.
Residues of pyrasulfotole, and pyrasulfotole-benzoic acid were stable in all crop matrices during 11 months (336 days) of frozen storage. Residues of pyrasulfotole-desmethyl were stable in soybean grain and wheat grain for up to ll months (336 days) of frozen storage. However, residues of pyrasulfotole-desmethyl were found to decline in wheat forage and hay (ca. 0.12% per day) in frozen storage. In forage and hay samples analysed after 180 and 336 days in frozen storage, recovery of the desmethyl metabolite was ~62% and ~54%, respectively.

Residues trials
Four Australian studies (16 trials in total) to determine residues of pyrasulfotole, pyrasulfotole-desmethyl and pyrasulfotole-benzoic acid in cereal crops following application of *Precept* were provided. Residues trials were conducted at 1 and 2 L of product/ha. The higher rate (2 L product/ha) is the maximum proposed application rate on the draft product label and corresponds to an application rate of 50 g pyrasulfotole + 250 g MCPA + 12.5 g mefenpyr-diethyl/ha.

The application timing proposed on the label for wheat, oat, cereal rye and triticale crops is between the 3-leaf and first node stages (Z13-Z31). For barley, application should be made between the 5-leaf and first node stages (Z15-Z31). A single application is recommended. The residues data reported below relate to the maximum label rate and reflect the proposed application timing. The full trial details are summarised in the appendices of this report.

Forage samples were stored frozen 23-59 weeks prior to analysis. Grain and straw samples were stored for 7-41 weeks. A validated method was used for the preparation, extraction, detection and quantitation of residues of pyrasulfotole and its metabolites in cereal matrices (forage, fodder and grain). All components of the residue were expressed as ‘pyrasulfotole equivalents’.

The residues data package provided in support of the proposed use pattern included grain, forage and fodder data for barley, oats and wheat. On the basis of the data provided, it is acceptable to extrapolate MRLs to cover minor crops such as cereal rye and triticale.

Cereal Grains
In all 16 Australian residues trials, residues of pyrasulfotole and pyrasulfotole-desmethyl in grain were <0.02 mg/kg (LOQ). On the basis of these data, it is appropriate to establish a group MRL for cereal grains. As the individual components of the residue were <LOQ in all grain samples, it is appropriate to set the MRL for GC 0080 at the LOQ (0.02 mg/kg) for the individual components.

In grain fractions, residues of pyrasulfotole and pyrasulfotole-desmethyl have been shown to concentrate in the bran and aspirated wheat grain fractions at ~1.6x and ~33x, respectively. No concentration in other grain fraction was observed. As cereal bran may be made available for human and animal consumption, an MRL for Cereal bran, unprocessed is required.

Assuming residues in wheat bran are representative of residues in the bran of other cereal grains, applying the processing factor of 1.6x to the proposed MRL of *0.02 mg/kg, gives a residue of 0.032 mg/kg. Given most of the residues in bran were pyrasulfotole-desmethyl, and residues of parent were <LOQ, an MRL of 0.032 mg/kg is appropriate for CM 0081 Bran, unprocessed of cereal grains.

The WHP statement of "NOT Required when used as Directed" is appropriate for the harvest of cereal grains.

Forage, straw and fodder of cereal grains.
In the trials provided, forage samples were stored frozen for 23-59 weeks prior to analysis. Straw samples were stored for 7-41 weeks. The storage stability data provided indicates that parent pyrasulfotole is stable in forage and hay for up to 11 months, however residues of pyrasulfotole-desmethyl may have decreased by up to 47% during frozen storage. As residues in forage have been estimated on a dry weight basis, it is likely that correction for dry weight would have resulted in an overestimate of total residues, as residues in many samples were <LOQ on a wet weight basis. As such no correction of residues to account for instability in frozen storage is required.

Residues of pyrasulfotole and pyrasulfotole-desmethyl in barley, oat and wheat forage 14 DAT were estimated at (in rank order) 0.24 (4), 0.25 (3), 0.26 (2), 0.28, 0.30 (2), 0.34, 0.49, 0.92 and 1.37 mg/kg (n = 16, median = 0.26 mg/kg) following correction for dry weight. The three highest residues in forage were all from barley samples, which were the only samples that contained quantifiable residues of pyrasulfotole and/or pyrasulfotole-desmethyl in the fresh sample. In these three samples the ratio of pyrasulfotole to pyrasulfotole-desmethyl were 1.5:1, 1:2.5 and 1:6 respectively.

Residues of pyrasulfotole and pyrasulfotole-desmethyl in barley, oat and wheat forage 28 DAT were estimated at (in rank order) 0.24 (4), 0.25 (3), 0.26 (2), 0.28, 0.30 (2), 0.34, 0.40, 0.49 and 0.52 mg/kg (n=16, median=0.26 mg/kg) following correction for dry weight. Only one of the samples contained quantifiable residues in the fresh sample, the ratio of pyrasulfotole to desmethyl-pyrasulfotole being 1:1.5.

In the animal transfer study provided, only pyrasulfotole was fed to livestock. Tissue and milk samples were analysed for pyrasulfotole only. Given the limited nature of animal transfer data provided in support of this application, it is preferable to set a WHP such that the residues of pyrasulfotole-desmethyl are at or about LOQ in the feed (at least on a wet weight basis), and the ratio of pyrasulfotole and pyrasulfotole-desmethyl is at, or close to 1:1, assuming the transfer of pyrasulfotole and pyrasulfotole-desmethyl into animal commodities is similar.

In wheat and oat forage, the ratio of pyrasulfotole: pyrasulfotole-desmethyl residues was 1:1 14 DAT. In barley, the ratio of residues was 1:1 ratio 28 DAT. At a WHP of 14 days for wheat and oats, and 28 days for barley, the available data support an MRL of 0.5 mg/kg for AF 0081 Forage of cereal grains.

For cereal forage (except barley) the WHP statement of "DO NOT GRAZE OR CUT FOR STOCKFOOD FOR 2 WEEKS AFTER APPLICATION" is appropriate. For barley, the

WHP statement "Barley DO NOT GRAZE OR CUT FOR STOCKFOOD FOR 4 WEEKS AFTER APPLICATION" is appropriate.

Residues of pyrasulfotole and pyrasulfotole-desmethyl in the fodder (straw) of barley, oat and wheat were <0.02 mg/kg at harvest. Due to the high proportion of dry weight (~88%) in the harvested material correction of residues to account for moisture was not required. No correction of residues was undertaken to account for the possible degradation of pyrasulfotole-desmethyl, as residues in straw stored for 7-9 weeks were at the LOQ, as were residues in samples stored for up to 41 weeks. The available data support an MRL of *0.02 mg/kg for AF 0081 Fodder and straw of cereal grains and a WHP of "NOT REQUIRED WHEN USED AS DIRECTED".

Animal commodity MRLs.

Cattle, sheep and pigs
Based on the MRL for the forage of cereal grains, the estimated combined dietary intake of pyrasulfotole and pyrasulfotole-desmethyl for cattle and sheep is 0.02 mg/kg bw/day. Given the maximum dietary exposures of cattle and sheep are equivalent, mammalian MRLs will be based on cattle, for which a feeding study was provided. Due to the relatively low dietary exposure in pigs, it is expected that MRLs established on the basis of the dietary burden of cattle will be adequate to account for residues in pigs resulting from the feeding of treated grain.

In the animal transfer study provided, tissue and milk samples from cattle were analysed for residues of pyrasulfotole only. As livestock may consume feed that contains residues of pyrasulfotole and pyrasulfotole-desmethyl, the feeding study may underestimate residues in animal commodities. Nor does the feeding study account for possible metabolism of pyrasulfotole and pyrasulfotole-desmethyl as observed in the livestock metabolism study. This may lead to residues in animal commodities being underestimated. The applicant has submitted argument that on the basis of structural similarity it is reasonable to assume that the transfer factors for parent pyrasulfotole and pyrasulfotole-desmethyl are similar.

Assuming residues of pyrasulfotole and pyrasulfotole-desmethyl will be present in the feed at a ratio of ~1:1, and in order to account for any metabolism of pyrasulfotole to pyrasulfotole-desmethyl (up to 10% in milk), livestock MRLs will be based on a feeding level of 1 mg/kg, rather than the 0.5 mg/kg which is anticipated in feed.

Based on the data provided, at a feeding level of 1.0 ppm, an MRL of *0.01 mg/kg for MM 0095 Meat (mammalian) and ML 0106 Milks are recommended. Accepting liver as an indicator tissue of other components of edible offal, based on a feeding level of 1.0 ppm, an MRL of 0.5 mg/kg for MO 0105 Edible Offal (mammalian) is recommended.

No depuration data for pyrasulfotole in livestock were submitted, thus an Export Slaughter Interval (ESI) cannot be recommended at this time.

Poultry
A metabolism study was available in which pyrasulfotole was fed to hens and residues of pyrasulfotole and pyrasulfotole-desmethyl analysed. This study was used to estimate residues in poultry commodities. Due to the low dietary burden of poultry and likely similarity in transfer factors for pyrasulfotole and pyrasulfotole-desmethyl, the hen metabolism study provides a reasonable approximation of the likely residues in poultry. Based on the theoretical dietary burden of poultry, which is equivalent to 0.0044 ppm bw/day, the poultry metabolism studies were conducted at ~185-fold the anticipated dietary burden (assuming only pyrasulfotole-desmethyl is fed).

Based on the poultry metabolism study, it is unlikely that quantifiable residues of pyrasulfotole and pyrasulfotole-desmethyl will be detected in eggs or poultry meat. MRLs at the LOQ (0.01 mg/kg) are recommended for PE 0112 Eggs, PO 0111 Poultry Offal and PM 0110 Poultry Meat.

Crop rotation

The accumulation and nature of pyrasulfotole residues were studied in confined rotational crops following an application of either [phenyl-UL-^{14}C] pyrasulfotole or [pyrazole-3-^{14}C] pyrasulfotole to soil. Wheat, Swiss chard (leafy vegetable), and turnips (root crop) were planted approximately 120 DAT. Wheat was also planted approximately 300 DAT. Based on the characterisation of residues in wheat matrices at 120 and 301 DAT, residues of pyrasulfotole in the harvested commodities are below the LOQ and there were no detectable residues of the desmethyl metabolite

Accumulation of pyrasulfotole in the field was also investigated. Pyrasulfotole was applied to wheat planted in silty loam and following harvest and/or crop of corn and soybeans were planted 114 to 123 days following the application to wheat. The harvested samples were analysed for residues of pyrasulfotole and the metabolites pyrasulfotole-benzoic acid and pyrasulfotole-desmethyl. Following a plant back interval of 114-123 days, residues of pyrasulfotole in the harvested commodities were below the LOQ, and there were no detectable residues of the desmethyl metabolite.

Re-cropping intervals, relating to possible phototoxicity and yield reductions, are recommended on the Precept selective Herbicide label. The shortest recommended re-cropping interval is 3 weeks, for wheat, barley and oats, and 5 weeks for sweet corn (provided 125 mm of rain has fallen). Used according to the proposed label directions, it is unlikely that any of these crops will be re-sown within this period, unless the previous cereal crop has failed. On the basis of the proposed Good Agricultural Practices (GAP) and the recommended plant back periods, it is considered unlikely that residues of pyrasulfotole or pyrasulfotole will be present at detectable levels in rotational crops.

Fat solubility and potential for bioaccumulation

The very low Log(K_{ow}) of pyrasulfotole (-1.362 at pH 7) and its relatively high solubility in water and polar solvents indicate that it is unlikely to partition preferentially into fat.

On the basis of the information available, pyrasulfotole and pyrasulfotole-demethyl are unlikely to partition preferentially into fat or bio-accumulate.

Spray drift

With respect to livestock feeding on pasture contaminated by spray drift, required no spray zones were calculated to achieve the maximum feeding level (MFL) of 0.5 mg/kg in the dry feed.

The potential for spray drift of Precept was determined using AgDRIFT®. In the absence of specific advice on the product label, parameters representative of realistic application situations have been used in the estimation of the no spray zone (a droplet size of 200-300 microns (fine/medium spray quality) as defined by Standard S572 of the ASAE in combination with a spray volume of 20L/ha and 20km/h). The resulting out put from AgDRIFT show that a down wind no spray zone of 300 m is required.

For ground based application, it is recommended that a spray volume of 50-80 L/ha is used in conjunction with a droplet size of 200-300 microns (a fine/medium spray quality) as defined by Standard S572 of the ASAE. Flat fan nozzles are recommended. Using these parameters in AgDRIFT a no spray zone distance of 20 m is required.

The following no spray zone is required on the label: DO NOT apply within 300 m (aerial application) or 20 m (ground application) when there are livestock, pasture or any land that is producing feed for livestock downwind from the application area.

Dietary exposure assessment

The chronic dietary exposure to pyrasulfotole is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines[1] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for pyrasulfotole is equivalent to <2% of the ADI.

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[5] with 97.5th percentile food consumption data derived from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of acute exposure (24 hour period) to chemical residues in food.

The NESTIs for all relevant commodities were estimated at <1% of the ARfD. It is concluded that the acute dietary exposure is acceptable.

It is concluded that both the acute and chronic dietary exposure to pyrasulfotole are acceptable.

Standards

Upon granting of the application, the following amendments will be made to the MRL Standard. MRLs in Tables 1 and 3 will be recommended for inclusion in the Food Standards Code:

Table 1

Compound	Food		MRL (mg/kg)
ADD:			
Pyrasulfotole	CM 0081	Bran, unprocessed of cereal grains	0.03
	GC 0080	Cereal grains	*0.02
	MO 0105	Edible Offal (mammalian)	0.5
	PE 0112	Eggs	*0.01
	MM0095	Meat (mammalian)	*0.01
	ML 0106	Milks	*0.01
	PO 0111	Poultry, edible offal	*0.01
	PM 0110	Poultry, meat	*0.01

Table 3

Compound	Residue
ADD:	
pyrasulfotole	The sum of pyrasulfotole and (5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)[2-mesyl-4-(trifluoromethyl)phenyl]methanone, expressed as pyrasulfotole

Table 4

Compound	Animal Feed Commodity		MRL (mg/kg)
ADD:			
pyrasulfotole	AS 0081	Fodder and straw of cereal grains	*0.02
	AF 0081	Forage of cereal grains	0.5

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

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Commodities exported, destination and value of exports

As a commodity group, cereal grains (including wheat, oats, cereal rye, triticale and barley) are a major export commodity. Pyrasulfotole MRLs are recommended at the limit of quantitation for cereal grains (*0.02 mg/kg) and 0.03 mg/kg in bran of cereal grains. As no detectable residues are expected in grain, residues are expected to comply with the standards of key export markets. No information is available for the export of processed grain fractions.

MRLs have also been recommended for fodder and straw of cereal grains (*0.02 mg/kg) and forage of cereal grains (0.5 mg/kg).

Oaten hay is also considered to be a major export commodity. No information on the export of oaten hay is available. In broad terms, the export market for Australian hay has grown from 423,000 tonnes in 2001 to a projected 646,000 tonnes in 2006, with the majority going to Japan's dairy industry.

Detectable residues of pyrasulfotole are not expected in poultry meat, poultry offal or eggs. As such, consideration of trade of these commodities is not required.

The MRLs for meat (mammalian) and milks are *0.01 mg/kg. Residues of up to 0.5 mg/kg may be present in edible offal, mammalian. No depuration data for pyrasulfotole in livestock were submitted, thus it is not possible to recommend an ESI.

Stakeholder advice in relation to other pesticides has been that if detectable residues are present in offal, even if there are none expected or present in meat, the potential exists for disruption to or suspension of exports. Thus detectable residues in offal may impact on the trade of meat and livestock.

The value and destination of livestock and dairy exports are detailed in Tables 1, 2 and 3 below.

Table 1. Value of Beef Exports and Importing Country.

Value of beef exports	1998	1999	2000	2001	2002	2003	2004	2005
	$m	$m	$m	$m	$m	$m	$m	$m
Beef and veal								
Americas								
Canada	104.6	128.0	148.1	204.4	320.2	110.9	38.1	32.6
United States	735.2	805.1	1 172.8	1 699.7	1 593.6	1 332.3	1 374.4	1 186.4
Asia								
Chinese Taipei	108.2	123.2	116.7	132.6	152.3	126.7	124.2	148.3
Hong Kong, China	23.6	16.6	18.2	17.8	17.1	15.0	27.3	18.7
Indonesia	6.1	33.3	40.8	37.2	46.1	38.4	26.7	33.6
Japan	1 312.4	1 369.7	1 537.3	1 728.2	1 237.7	1 384.4	2 189.8	2 244.8
Korea, Rep. of	87.6	201.9	221.7	228.9	320.4	250.7	434.4	494.8
Malaysia–Singapore	66.7	68.7	70.6	78.7	91.4	86.8	74.4	48.9
Philippines	40.4	38.5	34.3	55.8	36.1	23.0	4.3	5.9
Europe								
European Union	58.6	61.3	37.4	48.4	53.5	49.2	62.8	56.8
CIS	58.2	18.1	3.8	14.4	2.9	0.7	2.0	4.6
Eastern Europe	43.6	6.9	6.3	1.2	9.1	4.5	1.3	0.4
Middle East								
Kuwait	3.6	1.6	0.3	4.6	1.8	9.8	3.4	1.0
Saudi Arabia	7.4	3.3	2.1	23.0	11.6	7.8	3.1	1.7

United Arab Emirates	5.4	2.5	4.4	11.6	10.9	7.8	12.0	13.7
Oceania								
New Zealand	4.5	5.0	11.1	6.3	25.6	15.9	9.8	8.8
Pacific Isles	6.2	4.1	5.2	7.2	7.4	5.4	4.5	4.0
Papua New Guinea	12.3	14.1	14.1	11.5	9.8	4.9	5.2	4.3
Total beef and veal	2 768.3	2 963.3	3 464.1	4 357.3	4 002.6	3 475.3	4 390.2	4 346.7
Live cattle								
Asia								
Indonesia	18.0	68.5	143.1	171.8	254.0	203.4	207.3	209.1
Japan	11.6	7.8	9.8	12.7	11.2	16.6	14.6	20.5
Malaysia	15.3	29.9	25.7	38.5	45.1	38.9	25.2	20.1
Philippines	87.7	126.7	117.8	58.4	65.8	39.1	30.1	11.6
Middle East								
Egypt	61.6	131.2	129.7	153.8	94.9	5.0	0.0	3.8
Israel	5.7	3.8	9.0	15.4	23.9	22.8	11.9	20.6
Jordan	7.7	15.7	18.1	6.7	2.4	12.9	15.3	10.2
Libya	64.9	13.5	0.0	0.0	0.0	0.0	0.0	0.0
Saudi Arabia	0.0	0.0	0.0	14.9	32.5	9.4	0.0	11.0
Total live cattle	280.3	409.2	471.7	514.4	580.8	376.5	327.7	337.1

Table 2. Value of Sheep Exports and Importing Country.

Value of sheep exports	1998	1999	2000	2001	2002	2003	2004	2005
	$m	$m	$m	$m	$m	$m	$m	$m
Mutton								
Canada	3.2	3.1	4.6	6.8	5.2	3.6	5.8	5.4
Chinese Taipei	29.1	27.6	26.3	36.9	48.9	32.2	41.9	34.8
CIS	9.2	0.9	3.1	3.7	5.4	1.3	5.8	13.5
European Union	44.8	28.2	34.1	42.0	41.4	28.1	43.2	48.3
Japan	37.9	32.6	34.0	42.7	51.1	29.9	47.1	38.1
Korea, Rep. of	2.3	2.1	1.7	2.3	3.3	2.2	3.1	3.1
Malaysia	11.6	13.7	16.5	21.7	22.9	15.9	22.6	18.5
Papua New Guinea	8.0	7.5	6.2	7.4	6.6	6.1	5.1	5.2
Saudi Arabia	37.4	36.8	43.9	90.1	77.5	65.0	53.0	63.9
Singapore	16.4	16.5	18.4	23.4	23.2	20.4	22.0	18.6
South Africa	34.6	35.3	46.3	30.9	17.6	11.1	14.1	18.7
United States	40.3	37.1	43.9	56.4	64.7	67.9	48.6	44.4
Other	77.9	84.2	97.1	146.3	152.0	91.7	113.4	119.7
Total	352.5	325.8	376.3	510.6	519.7	375.3	425.9	432.0
Lamb								
European Union b	48.2	52.3	74.3	105.7	89.3	96.9	93.4	83.9
Japan	22.9	25.1	30.7	37.0	40.7	42.3	53.5	79.1
Papua New Guinea	12.0	13.0	16.0	18.0	15.7	14.4	17.3	19.4
South Africa	9.7	10.0	15.3	5.5	1.2	2.1	3.5	5.3
United Arab Emirates	18.1	18.2	24.2	27.4	31.6	29.9	27.0	32.8
United States	97.6	103.2	150.2	219.9	218.2	257.5	259.9	324.2
Other	87.2	96.3	137.0	165.7	169.5	159.7	184.7	233.1
Total	295.6	318.0	447.7	579.1	566.2	602.8	639.3	777.8
Live sheep c								
Middle East	187	177	204	349	395	330	223	275
Bahrain	13	15	13	20	25	29	33	35

Egypt	1	6	12	14	9	1	0	0
Jordan	32	35	24	28	39	35	58	53
Kuwait	53	47	61	79	101	105	84	60
Oman	18	17	20	26	24	19	20	25
Qatar	17	13	15	16	21	13	10	12
Saudi Arabia	0	0	27	120	127	104	0	74
United Arab Emirates	49	35	29	34	30	16	13	15
Other	2	3	2	5	7	8	3	4
Total	189	180	206	355	402	338	225	279

Table 3 Value of Dairy Exports and Importing Country.

Value of dairy exports	Unit	1999-00	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06
Cheese								
Japan	$m	306.6	338.8	429.2	272.0	299.6	378.9	298.5
Philippines	$m	16.4	18.6	20.0	15.7	11.1	18.2	13.7
Saudi Arabia	$m	94.1	123.6	148.2	98.9	69.0	81.5	103.5
United Kingdom	$m	23.9	38.7	21.5	15.2	18.3	20.5	20.1
United States	$m	28.8	39.1	48.3	36.1	33.9	45.4	54.8
Other	$m	336.8	391.0	366.3	361.9	306.6	330.9	345.5
Total	$m	806.6	949.9	1 033.4	799.8	738.4	875.4	836.1
Butter and butterfat								
Egypt	$m	33.7	34.6	23.5	18.9	6.4	10.5	12.5
Malaysia	$m	15.8	14.7	14.4	12.7	13.5	11.6	15.8
Philippines	$m	11.9	8.6	5.1	3.7	1.9	2.8	5.1
Singapore	$m	19.4	16.7	20.4	15.5	18.2	16.8	21.1
Thailand	$m	27.3	19.8	23.0	13.2	12.7	13.5	12.0
Other	$m	182.6	196.6	211.0	160.0	129.4	133.0	157.6
Total	$m	290.5	291.0	297.4	224.0	182.1	188.3	224.1
Skim milk powder								
Japan	$m	56.2	48.9	53.7	29.6	13.3	10.6	12.5
Malaysia	$m	78.3	87.4	88.4	51.4	52.7	64.2	77.1
Philippines	$m	102.0	181.4	143.5	69.0	59.8	49.4	72.0
Singapore	$m	26.7	51.8	52.8	38.4	41.3	57.7	56.1
Thailand	$m	55.1	67.2	69.1	33.2	20.0	21.7	76.8
Other	$m	159.8	257.5	290.5	184.1	198.8	216.3	234.3
Total	$m	478.1	694.2	697.9	405.6	386.0	419.9	528.9
Casein								
Japan	$m	15.3	19.9	26.7	20.6	23.3	23.1	30.4
United States	$m	62.6	56.7	80.5	81.4	68.8	56.6	27.3
Other	$m	15.3	23.4	15.5	26.4	30.4	36.4	31.3
Total	$m	93.2	100.1	122.6	128.4	122.5	116.1	88.9
Whole milk powder								
Malaysia	$m	27.0	26.9	39.2	22.3	28.9	33.1	23.8
Singapore	$m	15.7	31.7	29.7	25.2	21.4	30.9	44.6
Taiwan	$m	49.2	54.9	54.1	44.9	40.0	31.5	22.8
Thailand	$m	28.8	24.9	22.6	14.0	12.0	8.6	10.5
Other	$m	282.8	441.8	425.5	273.4	218.9	220.3	231.9
Total	$m	403.4	580.2	571.1	379.8	321.1	324.4	333.6
Other products								

Fresh milk	$m	81.4	82.0	98.1	98.1	104.0	108.7	107.3
Other fresh products	$m	20.2	12.7	7.9	5.5	9.6	9.1	6.3
Condensed milk	$m	87.6	111.5	123.7	133.3	121.0	139.8	147.5
Other powders	$m	182.2	223.2	276.6	272.1	253.9	244.9	241.2
Total	$m	371.5	429.4	506.2	509.1	488.6	502.6	502.3

Approximately $300 million worth of edible offal were exported during 1999/2000. Australia exports about 80% of its offal production to premium markets throughout the world - Japan being the single largest market[2].

Comparison of Australian MRLs with Codex and overseas MRLs.

Currently there are no international MRLs for pyrasulfotole. The registration submission presented to the APVMA is part of a joint review being undertaken in collaboration with Canada and the United States. Australia, Canada and the United States will be the first countries to register products containing pyrasulfotole. The proposed residue tolerances for Canada and the United States are presented in Table 4 below.

Table 4. Overseas MRLs/Residue Tolerances.

Country	Commodity	Recommended Tolerance (mg/kg)
United States &Canada	Wheat, grain	0.02
	Wheat, straw	0.20
	Wheat, forage	0.20
	Wheat, hay	0.80
	Wheat, aspirated grain fractions	0.40
	Oat, grain	0.08
	Oat, straw	0.20
	Oat, forage	0.10
	Oat, hay	0.50
	Barley, grain	0.02
	Barley, straw	0.20
	Barley, hay	0.30
	Triticale, grain	-
	Rye, grain	0.02
	Rye, straw	0.20
	Rye, forage	0.20
	Milk	0.01
	Cattle, meat	0.02
	Cattle, fat	0.02
	Cattle, meat byproducts	0.06
	Cattle, liver	0.35
	Goat, meat	0.02
	Goat, fat	0.02
	Goat, meat byproducts	0.06
	Goat, liver	0.35
	Hog, meat	0.02
	Hog, fat	0.02
	Hog, meat byproducts	0.02
	Sheep, meat	0.02

[2] http://www.mla.com.au/TopicHierarchy/InformationCentre/Coproducts/Types+of+Co-products.htm

	Sheep, fat	0.02
	Sheep, meat byproducts	0.06
	Sheep, liver	0.35
	Horse, meat	0.02
	Horse, fat	0.02
	Horse, meat byproducts	0.06
	Horse, liver	0.35
	Poultry, meat	0.02
	Poultry, fat	0.02
	Poultry, meat byproducts	0.02
	Eggs	0.02

Potential risk to trade

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

Commodities relevant to the current application are exported and detectable residues may occur above the standards of key export markets. Accordingly, a determination of undue prejudice to trade or commerce should be made following the completion of the public consultation process. Any areas of concern and possible management strategies have been outlined in the Public Release Summary.

The relevant industry groups should be given the opportunity to comment on the perceived level of risk and whether any industry-initiated strategies are required to manage the risk.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Product use pattern
Precept Selective Herbicide (AE 0317309 05 EC15 A1; containing 25 g/L pyrasulfotole and 195 g/L 2-ethylhexyl ester of MCPA [i.e. 125 g/L of pure MCPA] as the active constituents and 6.25 g/L of mefenpyr-diethyl as crop safener) will be supplied in 20 L and 110 L (returnable) containers.

Precept is to be used for post-emergent control of weeds during the production of wheat, oats, cereal rye, triticale and barley. For ground application, it is recommended that the product be applied with 50 to 80 L of water/ha, with a droplet size of 200 to 300 microns (that is, not in the respirable range) using ground boom apparatus. No work rates were supplied, therefore a default value of 50 ha/d for ground application was assumed.

Aerial application was also proposed, with a maximum area to be treated of 2000 ha/d. The applicant advised that the maximum amount of active ingredient (pyrasulfotole) handled per day would be 225 kg.

The product is not intended for home/garden use and bystander exposure to spray is unlikely to be a significant concern. Farmers and their employees will be the main users of the product. Workers may be exposed to the product when opening containers, during mixing and loading, during application and when cleaning up spills and equipment. The main route of exposure to the product and its diluted spray will be dermal and inhalational.

Risk assessment
In the absence of exposure data for the proposed modes of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (2002) was used to estimate exposure. Given the likely length of seasonal occupational exposure, a NOEL derived from a subchronic study was considered appropriate, and a 90-day oral rat study was selected in which endpoints of particular concern (ocular effects) were observed.

Comparison of predicted exposure levels with the NOEL selected led to the conclusion that the use of gloves during the mixing and loading stage of ground application led to an acceptably low level of exposure. However, in the case of aerial application, unacceptably high exposure levels were reached in the mixing and loading stage even with the use of gloves. Accordingly, aerial application cannot be supported.

No re-entry period was established in the case of ground application, since re-entry modeling for pyrasulfotole indicated that exposure levels would be low enough from Day 0 following application.

Besides repeat dose risks, there are acute hazards associated with the product, namely severe eye irritation and moderate skin irritation. However these acute hazards are not of concern during the application phase, that is when using the spray, since the product is diluted in the spray down to a maximum of 4%.

Conclusions from the acute and repeat dose risk assessments are that, when preparing the spray for ground application, users should wear cotton overalls buttoned to the neck and wrist and a washable hat, as well as elbow-length chemical resistant gloves and goggles.

ENVIRONMENTAL ASSESSMENT

Introduction

Bayer CropScience Australia Ltd has applied for the registration of a new product Precept Selective Herbicide, containing the new active constituent (ac) pyrasulfotole at 25 g ac/L, for use in wheat, oats, cereals, rye, triticale and barley for the control of cape weed, deadnettle, Indian hedge mustard, wild radish, wild turnip and wireweed as well as canola, chickpea, faba bean, lupin, medic and sub clover volunteers. The product will be marketed as an emulsified concentrate formulation with a proposed maximum application rate of 50 g ac/ha.

Environmental Exposure & Fate

Hydrolysis

Pyrasulfotole did not degrade significantly at pH 5, 7 and 9 at 25ºC and no major transformation products were found in the study.

Photolysis

^{14}C-pyrasulfotole did not degrade significantly in aqueous solution under continuous irradiation or in dark control solutions. No major transformation products were formed with minor degradates not exceeding 4% of the administered radioactivity. A similar observation was made for the photolysis of ^{14}C-pyrasulfotole on soils.

Degradation in Soil and Water

Soils aerobic: Degradation of ^{14}C-pyrasulfotole in loamy sand, sandy loam and silt loam soils was studied. The data indicate that pyrasulfotole is degradable in microbially active soil under aerobic conditions, producing a major metabolite 2-methylsulfonyl-4-trifluoromethylbenzoic acid AE B197555 (maximum of 9.3% AR), CO_2 (maximum of 40.5% AR) and non-extractable residues (maximum of 50.1% AR). Residues of pyrasulfotole were found up to 358 days (maximum of 29.3% AR). The DT50s of pyrasulfotole in the soils studied were determined to be in the range of 30-99 days by non-linear regression, with significant slowing over time and concomitant formation of non-extractable residues. Transformation of pyrasulfotole involves hydrolytic cleavage of the phenyl and pyrazole moieties to yield the benzoic acid derivative, AE B197555, plus several unidentified minor compounds, with steady formation of bound soil residues and moderate levels of mineralization to CO_2.

Water aerobic: Degradation of ^{14}C-pyrasulfotole was studied in pond water with sandy loam sediment and water-silty clay sediment for 131-132 days under aerobic conditions. The DT50s were determined to be >90 days in sediment but ranged from 29.6-250 days in the aqueous compartment. The data indicate that pyrasulfotole was persistent and transformed to yield minor levels of the metabolite AE B197555 with the formation of bound sediment residues as the primary dissipation pathway and no evidence of mineralisation of [^{14}C]-residues to CO_2.

Soils anaerobic: Degradation of ^{14}C-pyrasulfotole in loamy sand soil was studied under anaerobic conditions for 120 days after 30 days aerobic. The DT50 was determined to be ≥120 days in soil. The data indicate that pyrasulfotole is degraded in a similar fashion as aerobic transformation except that the levels of pyrasulfotole, AE B197555 and bound residues all remained relatively constant once anaerobic conditions were formed.

Water anaerobic: Degradation of ^{14}C-pyrasulfotole was studied in pond water with silty clay loam sediment and water-silty clay sediment for 365 days under anaerobic conditions. The DT50s were determined to be >365 days under sediment and aqueous conditions. The data indicate that pyrasulfotole was transformed primarily involving the formation of bound

sediment residues with minimal levels of mineralisation to CO_2 and the possible formation of several minor compounds.

Mobility

Adsorption/desorption: The adsorption/desorption of ^{14}C-pyrasulfotole was performed on five soils and one sediment. In the adsorption phase of the study, the active constituent showed Koc values ranging from 21.6 (clay loam) to 715 (sandy loam), demonstrating a very high to low mobility mostly depending on soil pH. The metabolite was shown to be weakly adsorbed to soil. The Koc values obtained indicate potential for high mobility in soil.

Field Dissipation

Soils: Three US field dissipation studies and one Canada field study (3 sites) were provided for pyrasulfotole and it major metabolite (AE B197555). The studies indicate that pyrasulfotole dissipates slowly with residues of up to 16% and 12% found in bare soil and cropped soil, respectively, up to study termination. DT50s were determined to be in the range of 42-16 days and 77-87 days in bare soil and cropped soil, respectively based on all the data. Again degradation slowed over time. The majority of pyrasulfotole and the metabolite residues were confined in the top soil layers of 15 cm depth, however, movement of residues at the limit of quantitation (LOQ) or closer were found in most soils at lower layers. Pyrasulfotole above LOQ was detected in the 60-75 cm soil segment in Saskatchewan and Ontario soils and up to the 120 cm segment in Washington soil.

Accumulation/Bioaccumulation

Pyrasulfotole and the primary metabolite AE B197555 are unlikely to bioaccumulate due to the high water solubility and low log P_{ow}.

Environmental Toxicology

Avian

Pyrasulfotole was found to be practically non-toxic to bobwhite quail in a single oral dose acute study conducted to US EPA requirements, with an LD50 estimated to be greater than 2000 mg/kg, the highest dose tested. Two 5-day dietary studies in bobwhite quails and in mallard ducks, conducted to US EPA requirements, similarly showed that pyrasulfotole was practically non-toxic to the test species, with LC50 values estimated to be greater than 4911 and 5089 ppm respectively, the highest concentrations tested in both cases. Two 21 week multi-generation studies testing chronic toxicity and reproductive effects on bobwhite quails and in mallard ducks fed pyrasulfotole in the diet, found no clear dose-response effects of pyrasulfotole in bobwhite quail and the NOEC to be 205 ppm in the diet. For mallard ducks, there was a slight reduction in male body weight gain at the highest dose (557 ppm), which may not be biologically significant, but was statistically significant, and thus the NOEC was given as 167 ppm.

Aquatic

Acute toxicity studies on bluegill sunfish, (*Lepomis macrochirus*) rainbow trout (*Oncorhynchus mykiss*) and Sheepshead minnow (*Cypriodon variegates*) determined that pyrasulfotole is practically non-toxic to fish, with no effects noted at 93.5 mg ac/L and 96 h LC50s were estimated at greater than 93.5 mg ac/L in limit tests conducted to US EPA and OECD requirements. The main soil metabolite AE B197555 was also rated as non-toxic to rainbow trout.

A chronic study on survival and growth of fathead minnow demonstrated that pyrasulfotole showed toxic effects to fish fry. There were significant effects following 35 days exposure to pyrasulfotole on survival, growth rates, weight and behaviour, when compared to controls. Total length was the most sensitive endpoint and was statistically reduced compared to control at all but the lowest test concentration. This gave the NOEC as 0.58 mg ac/L.

For aquatic invertebrates the acute 48 h daphnia toxicity test conducted according to US EPA and OECD Guidelines using technical pyrasulfotole gave an EC50 of > 93.3 mg ac/L for *Daphnia magna* and pyrasulfotole was rated as practically non-toxic to daphnia. For mysid shrimp, the 96 h daphnia toxicity test gave an EC50 of 1.1 mg ac/L and NOEC of 0.37 mg/L. In the chronic 21 day study using *D. magna*, conducted according to US EPA guideline, the NOEC was 12.8 mg ac/L with the most sensitive effect being on survival, with other effects noted including on reproduction and body length. In an Eastern oyster 96-h study conducted according to USA EPA guidelines, the EC50 of >104 mg/L and NOEC was 104 mg/L and was rated as practically non-toxic with no effect on shell growth noted. The main soil metabolite AE B197555 was rated as practically non-toxic to *D. magna*.

Technical pyrasulfotole was rated as slightly toxic to freshwater green algae (*Selenastrum capricornutum*), a freshwater diatom (*Naviculla pelliculoa*) and a blue-green algae (*Anabaena flos-aquae*) with measured 96-h E_rC50s of 30, 83 and 45.7 mg ac/L respectively and NOECs of 2.6, 51.4 and 40.1 mg ac/L in tests conducted according to USA EPA guidelines. It was also slightly toxic to the marine diatom algae (*Skeletonema costatum*) with an ErC50 of 17.9 mg ac/L and NOEC of 6.4 mg ac/L. The main soil metabolite AE B197555 was rated as moderately toxic to green algae the *Selenastrum capricornutum* with an ErC50 of 9.3 mg ac/L.

Technical pyrasulfotole was rated as very highly toxic to duckweed (*Lemna gibba G3*) with a 7 day ErC50 of 98 µg ac/L and a NOEC of 9.57 µg ac/L in a test based on frond weight and conducted according to OECD guidelines. The formulated product 05 EC15 A130 (Australian formulation) was rated as very highly toxic (expressed as pyrasulfotole) to Lemna with a 72-h ErC50 of 1.0 mg formulation/L, corresponding to 25 µg pyrasulfotole/L, based on frond count and a NOEC of <0.082 mg formulation/L, in a static test conducted according to US EPA and OECD 201 guidelines.

Terrestrial Toxicity:
Honey bees: The acute toxicity of pyrasulfotole to bees was tested according to OECD 213 and 214 guidelines and the LD50s were >120 and >75 µg ac/bee for the oral and contact exposure routes respectively. Pyrasulfotole can be rated as slightly to very slightly toxic to bees.

Earthworms: In tests on the effect of pyrasulfotole technical on earthworms (*Eisenia fetida*) conducted according to OECD guidelines using artificial soil in a limit test, there was no mortality and the LC50 was determined as > 1000 mg ac/kg and the NOEC = 1000 mg ac/kg. The effect of pyrasulfotole is determined to be very slightly toxic to earthworms.

Arthropods: Residues of the formulated product (US formulation containing pyrasulfotole and product safener) when applied to glass plates, were found to be slightly harmful to predatory mites, *Typhlodromus pyri*, with a LR50 of greater than 100 g pyrasulfotole/ha and estimated at 113 g ac/ha in a test conducted to IOBC Guidelines. The NOEC was 18 g pyrasulfotole /ha.

Survival of parasitic wasps *Aphidius rhopalosiphi* was significantly reduced by exposure to the formulated product and the NOEC was 18 g pyrasulfotole/ha and LR50 was 80.3 g pyrasulfotole/ha when tested according to IOBC guidelines. There were also effects on wasp reproduction with an IR50 of 31.1 g pyrasulfotole/ha.

Soil micro-organisms: Technical pyrasulfotole did not show any adverse effects on soil micro-organism nitrogen transformation and respiration in standard OECD soil microbial tests at 50 and 250 g ac/ha, corresponding to 1 and 5 times the maximum field application rate.

Non-target Vegetation: The effect of pyrasulfotole, formulated as 02 SE06 A103 (US/Canadian formulation; a mixture of pyrasulfotole and product safener) was tested on the seedling emergence of monocot (corn, oats, barley and ryegrass) and dicot (cucumber, oilseed rape, soybean, sugar beet, sunflower, tomato) species. Corn and oats were sprayed up to 2.5 kg product/ha, barley up to 1.25 kg product/ha, while the dicots were sprayed at rates up to 0.625 kg product/ha according to US EPA Guidelines. With the exception of soybean, biomass was significantly affected in all dicot species; biomass was not affected in any monocot species. Survival was significantly affected in oilseed rape, sugar beet, sunflower and tomato; survival was not affected in any monocot species or in cucumber and soybean. The most sensitive dicot species, based on dry weight, was tomato with EC50 of 7.8 g pyrasulfotole/ha.

The effect of pyrasulfotole formulated as 02 SE06 A103 on the vegetative vigour of monocot and dicot seedlings, using the same crops as above, was studied at varying nominal application rates. Ryegrass and oat were treated with up to 0.156 kg product/ha, onion and corn were sprayed at up to 2.5 kg product/ha while the dicot seedlings were treated at up to 0.156 kg product/ha. With the exception of ryegrass, the plant dry weight was significantly affected by the formulated product treatment in all species. The most sensitive monocot species, based on dry weight, in the vegetative vigour test was onion with an EC50 of 49.3 g ac/ha and a NOEC of 14 g ac/ha. The most sensitive dicot species, based on dry weight, was tomato with an EC50 of 2.13 g ac/ha and a NOEC of 0.89 g ac/ha.

Mammals: The results showed that pyrasulfotole has no acute toxicity to rats. The chronic toxicity is also relatively low with effects noted being increased liver weight.

Environmental Risk

The environmental risk to birds and mammals are considered acceptable on the basis of the acute toxicity and considering residues on food items.

Our assessment indicates that the main risk is from aerial spray drift impacting non-target vegetation and to a lesser extent aquatic organisms. The risk quotients from a simple worse case scenario indicate some concern for the aquatic environment due to impacts on aquatic plants (duckweed). Taking into account that the most sensitive endpoint ie frond numbers, not lethality, were used in the aquatic risk calculation, a label drift warning is considered acceptable. Therefore, the herbicide spray drift was calculated using AgDRIFT to examine the environmental risk further.

AgDRIFT calculations show that downwind buffer zones of 300 and 40 m, respectively, are required when the fine to medium droplet sizes proposed by the applicant are used. These can be reduced to about 100 and 15 m, respectively, if a coarse droplet size is employed. For ground application small buffer zones of 10 m and <5 m respectively are estimated, where in all cases DEH recommends that an amended label drift warning statement is suitable for an acceptable risk.

There is the potential for an environment risk to aquatic organisms from runoff from application of pyrasulfotole due to its high mobility in some soils. However, based on the field measured runoff of other highly mobile chemicals and that there would be dilution from non-treated areas, the risk was considered acceptable. As the endpoint used was not lethality, it is expected that aquatic plants would recover from short term exposures.

The risk to bees, earthworms, and soil micro-organisms are considered low at the proposed maximum application rate of 50 g ac/ha. While there is unlikely to be an acute risk to

predatory mites and parasitic wasps, there may be some effects on the reproductive rate for both species, but numbers in post-emergent cereal crops are expected to be very low.

Conclusion

As Precept is to be allowed to be aerially applied, the draft label includes additional label statements with regard to droplet sizes for aerial applications and the corresponding spray drift buffers for protection of non-target vegetation, including native vegetation. If Precept is not to be aerially applied, then a statement to that effect should be on the label.

EFFICACY AND SAFETY ASSESSMENT

Purpose of application

Registration of Precept Selective Herbicide is sought for the control of a range of broad leaf weeds commonly found in cereal crops grown in all states of Australia including cruciferous weeds and canola, legume and pulse crop volunteers, capeweed and wireweed either alone or as a tank mix with clopyralid.

Precept Selective Herbicide contains members of the pyrazolone and phenoxy groups of herbicides. As such, Precept is a Group F and Group I herbicide. Resistance to these mode of action chemicals is known to exist in some weed populations, for example, wild radish in Western Australia. This product should be used as part of an integrated weed management program.

Supporting Information

Data sets and reports from over one hundred individual trials covering efficacy trials on a wide range of broadleaf weeds, crop safety evaluation in a range of cereal species and varieties, formulation and adjuvant comparison for efficacy and crop safety and crop plant back studies are covered by the trial data submitted.

Type of Trials

Trials were of a small plot nature in a randomized complete block design with either three or four replications of applied treatments. Treatment number ranged from as low as three treatments in plant-back/re-cropping trials to as many as fourteen treatments with most trials having around twelve treatments.
An untreated control was always included.
In the weed control efficacy trials, the herbicide Tigrex at one or more rates was included as a standard treatment.

Trials were reasonably uniformly distributed between the states of Western Australia, South Australia, New South Wales, Victoria and Queensland and examined three broad areas:

1. Efficacy and crop safety

In this area the trials covered the following fields of investigation and research.

Efficacy of Precept and other formulations, at a range of rates, against a wide range of broadleaf weeds including self sown legume and pulse crops, canola and pasture legume species.
Comparison of various formulations of the active constituent to establish equivalence.
Evaluation of various adjuvants and adjuvant combinations against Precept alone for weed control efficacy.
Evaluation of herbicide tank mixes with Precept to enhance control of the more difficult weeds.
Investigation of the effect of Precept alone at a range of rates, in tank mixes and with adjuvant addition on the safety to cereal crops.
A total of sixty six (66) individual trials were relied on in the review of efficacy and crop safety of Precept.

2. Crop Tolerance

Evaluation of the safety of winter cereal crops to Precept alone and in mixture, with and without adjuvants determined by ratings of discolouration, phytotoxicity and crop vigour and any resultant yield effects.

Trials were mostly conducted in a weed free situation to remove any confounding effect of weed control arising from the applied treatments and were therefore true tolerance trials.
A total of eleven (11) trials were relied on to support the safety of Precept in winter cereal crops.

3. Re-cropping interval for a full range of winter and summer cereals, pulse, legume crops and pasture species, cotton and canola.

A range of winter cereals, grain legume and pulse crops, canola and pasture legumes as well as summer crops including cotton were included in the plant back studies.
Soil types ranged from acid sands (WA) to neutral to high pH clays with a range of plant back intervals and rainfall amounts between treatment application and sowing of the crop species.
A total of twenty five (25) trials were relied on in the review of the re-cropping, plant back studies.

Weed control efficacy trials

Ratings of weed control and crop safety were mainly based on biomass reductions and were conducted at varying intervals after treatment application. Weed counts were also conducted for most trials and generally coincided with the last weed control rating. At least 90% weed control was required to be deemed commercially acceptable control. A minority of trials was taken through to crop yield and some of these had a low yield due to dry seasonal conditions. Crop safety was determined by biomass reduction and crop discolouration ratings.
No aerial application trials were conducted.

Crop Tolerance

Most trials were weed free and taken through to harvested yield. During the growing season the winter cereal crops were rated at various timings after treatment application for discolouration, biomass reduction and vigour.

Re-cropping, plant back trials

Plant establishment counts and ratings of biomass reduction, discolouration and grain or biomass yield were used to determine the soil residual effects of Precept on winter and summer grown, follow crop species.

Suitability of Trials

In terms of the number of trials, their state and regional distribution, treatment selection, trial design, implementation and reporting the overall evaluation of Precept Selective Herbicide has been conducted in a professional and thorough manner. Many of the trials were conducted under testing seasonal conditions which impacted particularly on the harvesting of trials for meaningful yield determination. The weed control efficacy trials addressed all the weeds claimed on the label and many others not on the label. There was adequate evaluation of adjuvants and tank mixes to support label recommendations. More ‘standards’ or a more appropriate standard herbicide treatment should have been used in some of the weed efficacy trials. Crop tolerance of winter cereals to Precept was adequately addressed with mostly weed free trials taken through to harvest. This work was supported by observations and ratings of crop effects in the efficacy trials. Re-cropping and plant back studies covered a wide range of summer and winter crop species and were mostly conducted under ‘worst case scenarios’ situations of higher pH soils and limited rainfall between treatment application and re-cropping. Regenerating legume based pastures comprising clovers and medics, following treated crops, may be at risk.

Summary of Trial Results

Precept Selective Herbicide, or various formulations of the active constituent pyrasulfotole, either alone, in tank mixes with other herbicides and with various adjuvants and adjuvant combinations was evaluated in over one hundred efficacy, crop tolerance and plant back trials throughout the main cereal cropping regions of Australia in the period 2003-2006 inclusive.
The trials demonstrated that Precept Selective Herbicide at rates of 1.0 to 2.0 L/ha with liquid ammonium sulphate or Hasten crop oil, as adjuvants, gave control of a range of cruciferous and other weeds common to winter cereal crops. The weed control spectrum was also demonstrated to be extended to included pulse crops, capeweed and legumes by the addition of Clopyralid as a tank mix. Activity against many other weeds was demonstrated in some of the trials but these are not currently claimed on the proposed label.
Potential was also demonstrated for broadening the weed spectrum further by tank mixing with other selective herbicides.
Trials were predominantly conducted in wheat crops with a lesser number of barley trials and few triticale, cereal rye and oat crops. These latter crops were better represented in the crop tolerance trials.
Precept demonstrated excellent crop safety to winter cereal crops at the highest label rate and in a failed crop situation could be safely reseeded to these same winter cereals. No cereal variety sensitivity was indicated.
While good data was generated for more sensitive follow crops, a conservative approach has been adopted on the proposed label. Excellent crop safety was demonstrated for some, but not all, potential winter and summer follow crops and legume pastures after nine months. Further research is pending and the advice of Bayer Crop Science recommended in the interim.

Conclusions

The control of the specified weeds with Precept Selective Herbicide will be achieved when used in accordance with the label recommendations with respect to application rates, adjuvant additions, tank mixing with Lontrel SG and application timing.

When used according to the proposed label, Precept Selective Herbicide will be safe to apply to a wide range of varieties of wheat, barley, oats, triticale and cereal rye grown throughout the grain belts of Australia.

Failed winter cereal crops, to which Precept has been applied, can be safely reseeded to wheat, barley or oats at three weeks from the Precept application.

Selected crops species, both summer and winter growing, as specified on the label, can be safely seeded the following season.

Labelling Requirements

MAIN PANEL

CAUTION

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

(label code)

THIS PRODUCT IS NOT RECOMMENDED FOR HOME GARDEN USE

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*20, 110

PRECEPT SELECTIVE HERBICIDE

STORAGE AND DISPOSAL
Store in the closed, original container in a cool, well-ventilated area. Do not store for prolonged periods in direct sunlight.
(20 L containers)
Triple or preferably pressure rinse containers before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and 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.
(110 L returnable containers)
If tamper evident seals are broken prior to initial use then the integrity of the contents cannot be assured.
Empty container by pumping through dry-break connection system. Do not attempt to breach the valve system or the filling point, or contaminate the container with water or other products. Ensure that the coupler, pump, meter and hoses are disconnected, triple rinsed and drained after each use. When empty, or contents no longer required, return the container to the point of purchase. This container remains the property of Bayer CropScience Pty Ltd.

SAFETY DIRECTIONS
Harmful if swallowed. Corrosive, will damage eyes. May irritate the skin. Avoid contact with eyes and skin. If product in eyes, wash it out immediately with water. When opening the container and preparing spray wear cotton overalls buttoned to the neck and wrist and a washable hat, elbow-length chemical resistant gloves and goggles. Wash hands after use.

FIRST AID
If poisoning occurs contact a doctor or Poisons Information Centre (telephone 13 11 26). If swallowed, do NOT induced vomiting. Give a glass of water. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

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.

APVMA Approval No.:

IMPORTANT: READ THE ATTACHED BOOKLET BEFORE USE

FOR 24 HOUR SPECIALIST ADVICE

IN EMERGENCY ONLY

PHONE 1800 033 111

*

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Website: www.bayercropscience.com.au
Technical enquiries: 1800 804 479

Batch Number:
Date of Manufacture:

(label code)

CAUTION

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

PRECEPT SELECTIVE HERBICIDE

ACTIVE CONSTITUENTS:	25 g/L PYRASULFOTOLE
	125 g/L MCPA AS THE 2-ETHYLHEXYL ESTER
CROP SAFENER:	6.25 g/L MEFENPYR-DIETHYL

For the post-emergent control of certain broadleaf weeds in wheat, barley, oats, cereal rye and triticale as specified in the DIRECTIONS FOR USE table.

STORAGE AND DISPOSAL

Store in the closed, original container in a cool, well-ventilated area. Do not store for prolonged periods in direct sunlight.
The method of disposal of the container depends on the container type. Read the "Storage and Disposal" instructions on the label that is attached to the container.

SAFETY DIRECTIONS

Harmful if swallowed. Corrosive, will damage eyes. May irritate the skin. Avoid contact with eyes and skin. If product in eyes, wash it out immediately with water. When opening the container and preparing spray wear cotton overalls buttoned to the neck and wrist and a washable hat, elbow-length chemical resistant gloves and goggles. Wash hands after use.

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APVMA Approval No.:

IMPORTANT: READ THIS BOOKLET BEFORE USE

DIRECTIONS FOR USE

Restraints

DO NOT use if rainfall or irrigation is to occur within 2 hours of application.
DO NOT apply to frost affected weeds or if frosts are imminent.
DO NOT apply without adjuvant/crop oil[#].

[#] See **'Use of Adjuvant/Crop Oil'** under 'General Instructions'.

Note

Precept is a phenoxy (Group I) and pyrazolone (which inhibits 4-HPPD - Group F) herbicide. Precept will substantially reduce the growth of many weeds rather than give complete plant kill. Refer to the Critical Comments in the Directions for Use Table below for directions.

CROP	WEED	STATE	WEED STAGE	RATE L/ha	CRITICAL COMMENTS
Wheat, **oats**, **cereal rye**, **triticale**, 3 leaf (Z13) to first node (Z31); **barley**, 5 leaf (Z15) to first node (Z31)	Capeweed (*Arctotheca calendula*)	All States	2 to 5 leaf	1.0 + 60 g/ha Lontrel® SG	**Adjuvant/Surfactant/Wetting agent** Spray grade liquid ammonium sulphate or a recommended crop oil must be used in conjunction with Precept Selective Herbicide. Recommended adjuvants include spray grade liquid ammonium sulphate, e.g. Liase® (1.2 L/ha) or Hasten® (1% v/v). Consult Bayer Crop Science for information on other adjuvants. DO NOT use non-ionic surfactants, eg. BS1000. **Application** Activity of Precept Selective Herbicide will be reduced if weeds are stressed. Optimum results will be obtained if good soil moisture exists at or soon after application. Where crop or weed density is high, water volume should be increased. **Later weed emergence♣** Precept Selective Herbicide will not reliably control following germinations of weeds. A follow up application of a suitable herbicide may be required to control remaining plants or plants that emerge after application. The use of Precept Selective Herbicide at 2.0 L/ha will provide better control of weed emergence following application.
	Canola, volunteer (*Brassica napus*)		2 to 8 leaf	1.0	
	Chickpea, volunteer (*Cicer arietinum*)		2 leaf to 5 node	1.0 + 60 g/ha Lontrel SG	

CROP	WEED	STATE	WEED STAGE	RATE L/ha	CRITICAL COMMENTS
Wheat, **oats**, **cereal rye**, **triticale**, 3 leaf (Z13) to first node (Z31); **barley**, 5 leaf (Z15) to first node (Z31)	Deadnettle (*Lamium amplexicaule*)	All States	2 to 6 leaf	1.5	**Weed stage**♣ Apply when weeds are actively growing. In most situations the rate specified for each weed size will give satisfactory control. Under certain conditions such as: *high crop or high weed density *later germinations *abnormal weed growth including early flowering, higher rates of Precept Selective Herbicide (the maximum rate of application specified for that weed) may be required.
	Faba bean, volunteer (*Vicia faba*)		2 leaf to 5 node	1.0 + 60 g/ha Lontrel SG	Precept Selective Herbicide may not effectively control: * regrowth of suppressed weeds; * transplanted weeds; * weeds growing under stress from previous herbicide applications.
	Indian hedge mustard (*Sysimbrium orientale*)		2 to 8 leaf	1.0	**Weed density**♣ DO NOT use the 1.0 L/ha rate for the control of dense wild radish populations (>75/m^2). For dense wild radish populations, increasing the rate to 2.0 L/ha will give good control in most situations. Because high weed density may cause shading of weeds lower in the plant canopy a follow up application of a suitable herbicide may be required to control plants remaining after an application of Precept.
	Lupin, volunteer (*Lupinus* spp.)		2 to 8 leaf	1.0	
	Medic (*Medicago* spp.), volunteer		2 to 4 leaf	2.0 L/ha **or** 1.0 L + 60 g/ha Lontrel SG	
	Sub clover, volunteer (*Trifolium subterraneum*)		2 to 6 leaf	1.0 + 60 g/ha Lontrel SG	
	Wild radish (*Raphanus raphanistrum*)		2 to 4 leaf	1.0 or 2.0♣	
			up to 8 leaf	2.0	
	Wild turnip (*Brassica tournefortti*)		2 to 8 leaf	1.0	

CROP	WEED	STATE	WEED STAGE	RATE L/ha	CRITICAL COMMENTS
Wheat, **oats**, **cereal rye**, **triticale**, 3 leaf (Z13) to first node (Z31); **barley**, 5 leaf (Z15) to first node (Z31)	Wireweed (*Polygonum aviculare*)	All States	2 to 8 leaf	2.0	

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/Stockfood

Wheat, Oats, Cereal Rye, Triticale: DO NOT GRAZE OR CUT FOR STOCKFOOD FOR 2 WEEKS AFTER APPLICATION.

Barley: DO NOT GRAZE OR CUT FOR STOCKFOOD FOR 4 WEEKS AFTER APPLICATION.

GENERAL INSTRUCTIONS

Precept is a selective phenoxy and pyrazolone (phenyl pyrazolyl ketone) group herbicide. It is predominantly a foliar herbicide with limited activity via the soil. Precept will not reliably control weeds that emerge after spraying. Results are best under good growing conditions and application to weeds or crop under stress should be avoided.

Use of Adjuvant/Crop Oil

Spray grade liquid ammonium sulfate or a recommended crop oil must be used in conjunction with Precept or Precept tank mixtures with other products in cereals. Recommended adjuvants include spray grade liquid ammonium sulphate at 500 grams active ingredient/ha (e.g. Assist (1.0 L/ha), Boost (1.0 L/ha), Liase (1.2 L/ha)) or Hasten (1% v/v). Consult Bayer CropScience Pty. Ltd. for information on other adjuvants.
DO NOT use non-ionic surfactants, e.g. BS1000.

Crop Safety

Precept Selective Herbicide generally shows good crop selectivity when used as directed. The following will help minimise crop effects.

Selective crops

- DO NOT apply to crops undersown with legumes or to broadleaf pastures.
- DO NOT apply to any crop other than wheat, barley, oats, cereal rye or triticale.
- DO NOT apply to hay crops unless boom overlap growth reduction of approximately 10% is accepted.

Recommended growth stage

- Precept Selective Herbicide contains MCPA 2-ethylhexyl ester. Wheat, oat, triticale and cereal rye should be a minimum 3 leaf stage (Z13 growth stage), before application of Precept Selective Herbicide. Barley should be a minimum 5 leaf stage (Z15 growth stage), before application of Precept Selective Herbicide. Consult your local agronomist for the latest advice on varieties which require later growth stage applications to avoid the effects of MCPA.
- DO NOT apply later than Z31 (first node).

Agronomic and environmental factors

- Some crop yellowing and growth retardation may occur within 2 to 5 weeks of application. Where Precept Selective Herbicide up to 2.0 L/ha is applied, any effects will be negligible and rapidly dissipate except in areas of boom overlap. In boom overlap areas, growth retardation may occasionally remain until spring. Grain yield will not be compromised.
- Growth retardation may be increased if the crop is affected by root disease, (e.g. cereal cyst nematode, rhizoctonia, take-all (haydie)), nutritional stress, waterlogging, drought stress, excessively cold conditions or previous herbicide treatment.
- DO NOT apply to cereals that are physically damaged (e.g. by hail, wind, insect attack).
- Do not apply to crops not actively growing, e.g. due to cold and wet conditions or drought stress.

Crop Rotation Recommendations

Minimum re-cropping intervals apply for all crops following Precept Selective Herbicide application.
To reduce the potential of recropping symptoms, cultivate prior to sowing.
For advice on crops not listed below, contact the manufacturer, Bayer CropScience Pty. Ltd.

Rainfall

For crops listed as requiring a 9 month recropping interval, rainfall of less than 250 mm following use of Precept may result in an extended recropping interval.
Patchy rain, with extended dry periods may also result in an extended recropping interval, even when rainfall exceeds 250 mm. If in doubt, seek specialist advice.

pH

Use on soils with a pH greater than 8.4 (soil in water) has not been tested and is not recommended.
Recropping intervals may be reduced on acid soils (pH < 7).

Recropping Interval – alkaline soil	**Crop – winter sown**
3 weeks	wheat, barley, oats (Transient biomass reduction or discolouration may occur where wheat, barley or oats are recropped following Precept application in the same year. Grain yield is not compromised where transient biomass reduction or discolouration occurs. Wheat , barley or oats may be recropped the year after Precept application without biomass reduction or discolouration.) triticale
9 months	chick pea, field pea, lucerne, lupin (to 1.0 L/ha applied only)

Recropping Interval – alkaline soil	Crop – winter sown
recropping interval not yet available	canola, clover, faba bean, lentil, medic, vetch (recropping interval not determined, not suitable to recrop in the same season on failed crop treated with Precept. Ongoing investigation. For further advice, contact the manufacturer, Bayer CropScience Pty. Ltd.)

Recropping Interval – alkaline soil	Crop – summer sown
5 weeks	maize (Rainfall of less than 125 mm following Precept may result in extended re-cropping intervals. Patchy rain, with extended dry periods may also result in extended re-cropping intervals, even when rainfall exceeds 125 mm. If in doubt, seek specialist advice.)
recropping interval not yet available	cotton, lucerne, mung bean, sorghum, soybean, sunflower (recropping interval not determined, not suitable to recrop in the same season on failed crop treated with Precept. Ongoing investigation. For further advice, contact the manufacturer, Bayer CropScience Pty. Ltd.)

Resistant Weeds Warning **GROUP F I HERBICIDE**

Precept Selective Herbicide contains members of the pyrazolone (pyrasulfotole) and phenoxy (MCPA) groups of herbicides. Precept is a herbicide which inhibits 4-hydroxyphenylpyruvate deoxygenase (4-HPPD) and also acts by disruption of plant cell growth. For weed resistance management Precept is a Group **F** and Group **I** herbicide. Some naturally-occurring weed biotypes resistant to Precept, and other Group **F** and Group **I** herbicides, may exist through normal genetic variability in any weed population. The resistant individuals can eventually dominate the weed population if these herbicides are used repeatedly. These resistant weeds may not be controlled by Precept or other Group **F** and Group **I** herbicides.

Since occurrence of resistant weeds is difficult to detect prior to use, Bayer CropScience Pty Ltd accepts no liability for any losses that may result from the failure of Precept to control resistant weeds.

The pyrazolone component of Precept targets an enzyme, 4-hydroxyphenylpyruvate dioxygenase (4-HPPD), a mode of action that under the European system of classification is defined as Group F2. Under the European system of classification herbicides such as diflufenican (e.g. Brodal) are defined as having an alternative mode of action, Group F1 (inhibitors of carotenoid biosynthesis at the phytoene desaturase step).

Do not rely exclusively on Precept for weed control. Use as part of an integrated weed management program involving herbicides with other modes of action and non-chemical methods of control. CropLife Australia resistance management strategies are available from your local agricultural chemical supplier. Refer to these strategies for details of how to manage the build up of resistant weeds on your farm.

Mixing
Half fill the spray tank with water, then with agitators in motion, add the correct amount of Precept Selective Herbicide directly into the spray tank. Add other relevant compatible herbicides, then adjuvant or crop oil as recommended. Complete filling the tank with agitators in motion. Agitation must continue before and during spraying.

Application
Ensure that complete and even spray coverage of all weeds is achieved.

Equipment
Ground Sprayers – Standard boom sprayers only are recommended and must be fitted with by-pass or mechanical agitation. It is recommended that 50 to 80 L water/ha is applied with a droplet size of 200 to 300 microns (a fine/medium spray quality as defined by Standard S572 of the ASAE). Use flat fan nozzles. Use of air induction nozzles is not recommended.

Aircraft – When aerially applying Precept, use a fine/medium spray quality as defined by Standard S572 of the ASAE. For advice on aircraft application, contact the manufacturer, Bayer CropScience Pty. Ltd.

No spray zones -
DO NOT apply within 300 metres (aerial application) or 20 metres (ground application) when there are livestock, pasture or any land that is producing feed for livestock downwind from the application area.
DO NOT apply within 40 metres (aerial application) of downwind streams, rivers, wetlands or waterways.
DO NOT apply within 300 metres (aerial application) of downwind non-target vegetation. Examples of non-target vegetation include remnant vegetation in road verges, vegetation along public rights-of-ways, and other native plant communities and non-target crops, gardens, parks, reserves and areas of special vegetation.

Misters – DO NOT apply Precept through a mister.

Sprayer Clean Up
The sprayer must be thoroughly decontaminated before being used again to spray crops other than winter cereals.
Ensure that the following operation is carried out in an area that is clear of waterways, desirable vegetation and tree roots, and preferably in an area where drainings can be contained.
Fill the boom tank with water, rinse and repeat this procedure (i.e. fill and rinse the tank twice) then remove and clean all filters (inline and nozzle) separately. This will provide an effective cleaning technique for Precept Selective Herbicide. This should be done immediately after spraying is finished to prevent dried residues adhering to the tank/lines/filters.
A boom cleaner may be used when cleaning.

Compatibility
Precept may be mixed with Lontrel® 750 SG at 60 g/ha without any loss of efficacy or adverse crop effects.
For advice on the compatability of other products, contact the manufacturer, Bayer CropScience Pty. Ltd.

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

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Highly toxic to algae and aquatic plants.
DO NOT contaminate streams, rivers or waterways with this product or used containers.
DO NOT apply under weather conditions or from spraying equipment that could be expected to cause spray to drift onto wetlands, natural surface waters, neighbouring properties or other sensitive areas.

PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS
DO NOT apply under weather conditions, or from spraying equipment, that may cause spray to drift and MCPA volatilization onto nearby susceptible plants/crops, cropping lands or pastures.

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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

APVMA PUBLICATIONS ORDER FORM

To receive a copy of the full technical report for the evaluation of pyrasulfotole in the product Precept Selective Herbicide please fill in this form and send it, along with payment of $30 to:

Verity Scarlett
Pesticides Division
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

Alternatively, fax this form, along with your credit card details, to:
Verity Scarlett 02 6210 4748.

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

Card number _____/_____/_____/_____ Expiry date ...../...../.....

Signature_____ Date _____