Public Release Summary
on

Evaluation of the new active

PYROXSULAM

in the product

CRUSADER Herbicide

Australian Pesticides and Veterinary Medicines Authority

April 2008

Canberra
Australia

ISSN1443-1335

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FOREWORD

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

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Aging, Office of Chemical Safety (OCS), Department of the Environment, Water, Heritage and the Arts (DEWHA), and State Departments of Primary Industry.

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

The information and technical data required by the APVMA to assess the safety of new chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in the APVMA's publication *Ag Manual: The Requirements Manual for Agricultural Chemicals* and *Ag Requirements Series.*

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

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

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

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LIST OF ABBREVIATIONS AND ACRONYMS

ABBREVIATIONS

Time

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

Length

cm	Centimetre
M	Metre
µm	Micrometre
mm	Millimetre
Nm	Nanometre

Volume/Area

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

Weight

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

Dosing

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

Concentration

m	Molar
ppb	Parts per billion
ppm	Parts per million

Clinical chemistry, haematology

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

Anatomy

CNS	Central nervous system
GIT	Gastro-intestinal tract
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal

Chemistry

GC	Gas chromatography

GLC	Gas liquid chromatography
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
MS	Mass spectrometry
RIA	Radioimmunoassay
TGAC	Technical grade active constituent
TLC	Thin layer chromatography

Terminology

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

Organisations & publications

AGCS	Advisory Group on Chemical Safety
AHMAC	Australian Health Ministers Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
CAC	Codex Alimentarius Commission
DEW	Department of the Environment and Water Resources
ECETOC	European Chemical Industry Ecology and Toxicology Centre
FAO	Food and Agriculture Organisation of the UN
FAISD	First Aid Instructions & Safety Directions

IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
JECFA	FAO/WHO Joint Expert Committee on Food Additives
JMPR	Joint Meeting on Pesticide Residues
NCI	National Cancer Institute
NDPSC	National Drugs and Poisons Scheduling Committee
NHMRC	National Health and Medical Research Council
NOHSC	National Occupational Health & Safety Commission
NTP	National Toxicology Program
OCS	Office of Chemical Safety
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
US EPA	United States Environmental Protection Agency
WHO	World Health Organisation

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of *CRUSADER* Herbicide (*CRUSADER*), which contains the new active constituent pyroxsulam and the existing safener cloquintocet-mexyl. The product is proposed for use in wheat only (excluding durum varieties) from 3 leaf up to first node for the post emergence control of certain grass and broadleaf weeds.

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

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

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

Written comments should be received by the APVMA by 18 May 2008. They should be addressed to:

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Applicant

Dow AgroSciences Australia Ltd

Details of Product

It is proposed to register *CRUSADER*, containing pyroxsulam at 30g/L and cloquintocet-mexyl at 90g/L as an oil dispersible liquid formulation.

Pyroxsulam is a new active constituent. It is in the triazolopyrimidine sulfonamide class of herbicidal compounds. Pyroxsulam inhibits the plant enzyme acetolactate synthase (ALS), which is essential for the synthesis of branched-chain amino acids valine, leucine, and isoleucine. Inhibition of amino acid production subsequently inhibits cell division and causes death in susceptible plants. Pyroxsulam is a systemic, phloem and xylem mobile herbicide that is absorbed via leaves, shoots, and roots.

Pyroxsulam is for use in wheat as a post emergence herbicide against a wide range of grass and broadleaf weeds. Other active constituents from this class with products registered containing them include imazamox, imazapyr and imazethapyr.

The active constituent cloquintocet-mexyl is used in the *CRUSADER* formulation as a safener. It is already contained, for the same purpose, in the formulations of other products registered by the APVMA.

CRUSADER is proposed for use in Australia as a post emergence herbicide for the control of grass weeds (wild oats, brome grass, phalaris and annual ryegrass) and broadleaf weeds (bedstraw, turnip weed, capeweed, wild radish, Indian hedge mustard, climbing buckwheat, milk thistle, volunteer crops [canola, chickpea, faba bean, lentil, field pea, lupin], medics, subclover and vetch in wheat (excluding durum varieties).

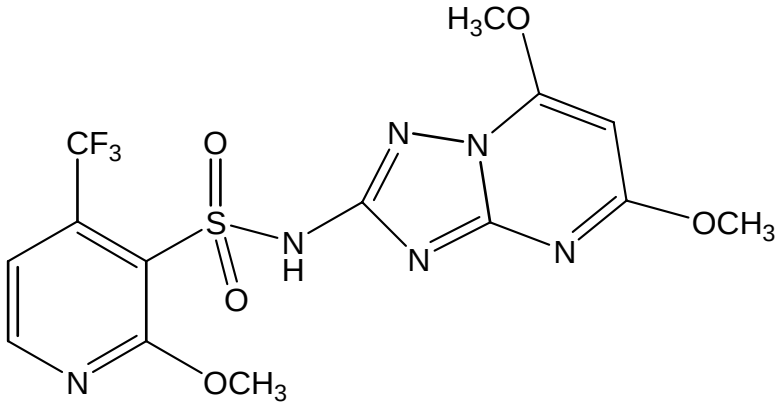
Pyroxsulam formulations are new to the world herbicide market. This submission is being assessed under a workshare arrangement where registrations for the same formulation and uses have been submitted concurrently in Canada, USA and Australia. The registrations in Canada and USA have been granted.

Active Constituent

The active constituent pyroxsulam is manufactured by Dow Agrosciences LLC at 680/1000 Building, Midland, MI 48667, USA and has been approved by the APVMA (Approval Number: 61286).

Chemical Characteristics of the Active Constituent

Common Name:	Pyroxsulam
IUPAC Name:	*N*-(5,7-dimethoxy[1,2,4] triazolo[1,5-a]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)pyridine-3-sulfonamide
CA Name:	*N*-(5,7-dimethoxy[1,2,4] triazolo[1,5-a]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)-3-pyridinesulfonamide
CAS Number:	422556-08-9
Manufacturer's Codes:	X666742, XR-742, BAS 770H, XDE-742
Minimum Purity:	980 g/kg
Molecular Formula:	$C_{14}H_{13}F_3N_6O_5S$
Molecular Weight:	434.354
Structure:	



Chemical Family:	Triazolopyrimidine sulfonamide
Mode of Action:	Inhibition of acetolactate synthase (ALS)

Physical and Chemical Properties of Pure Active Constituent and Technical Material

Colour	White (pure) Off white (tech)
Physical state	Crystals, odourless (pure) Powder at 22.6 ºC, spicy odour (tech)
Melting point	208.3 ºC (pure)
Dissociation constant (pKa)	4.67 ± 0.01 (pure)
Vapour pressure at 20°C	$<1 \times 10^{-7}$ (pure)
Density	Relative: 1.618 g/cm^3 (20 °C) (pure) Bulk: 0.383 g/ cm^3 (22.6 °C) (tech)
UV/Vis absorption maxima and molar absorptivity	Neutral: λ_{max}297; ε = 8000 Acidic: λ_{max}297; ε = 7600 Basic: λ_{max}292; ε = 11100
Octanol/water partition co-efficient (K_{ow}) at 20°C	
pH 4	12.1
7	0.097
9	0.024

Solubility (g/L) at 20°C:	
Water	
pH 4	0.0164
7	3.20
9	13.7
purified	0.0626
Solubility (g/L) at 20°C:	
Acetone	2.79
Dichloromethane	3.94
Ethyl acetate	2.17
n-Heptane	<0.001
Methanol	1.01
1-Octanol	0.073
Xylene	0.0352
Flammability	Not highly flammable
Explosive properties	Not explosive
Relative self-ignition temperature for solids	None below 400 ºC
Oxidising properties	Not oxidising
Oxidising/reducing action	Not oxidising, reducing or chemically incompatible when mixed with solutions of potassium permanganate, ammonium phosphate, zinc dust and water
Stability in presence of metals after 2 weeks	Product is stable in the presence of 304 stainless steel, 316 stainless steel, brass & copper. Product is stable when mixed with CuCl, $NiCl_2$, & $FeCl_3$. No significant degradation.
Stability at 54ºC after 2 weeks	No degradation.
Photochemical properties	Samples were stored under illumination for up to 15 days using a xenon lamp at a light intensity of 615 W/m^2) in sterile buffer at pH 7. The application rate was nominally 1 mg/mL. No degradation took place in the dark controls. The expected half life at 40 ºN latitude in summer sunlight was 3.2 days. Two photoproducts exceeded 10% (742-sulfinic acid and 742-ADTP [aminotriazole pyrimidine]).
Corrosion characteristics	Study in progress. Data to be submitted upon completion.

FORMULATED PRODUCT

Distinguishing name:	**Crusader Herbicide**
Formulation type:	Oil dispersion (OD)
Active constituent[s] concentration:	Pyroxsulam 30 g/L Cloquintocet-mexyl 90 g/L

Physical and Chemical Properties of the Product

Appearance (colour, odour, physical state)	Opaque brown, liquid, mild odour
pH	5.13 @ 20^{O}C (neat) 6.21 (1% w/v dilution)
Relative Density	1.0421 g/mL
Viscosity	10 (L/s) 99.67 mPa.s @ 20ºC 10 (L/s) 54.43 mPa.s @ 40ºC
Surface tension	36.3 mN/m (neat @ 25.0 ºC) 30.9 mN/m (diluted at 20.4 ºC)
Flammability	96.1ºC (Flash point)
Explosive properties	No significant exothermic events observed over temperature range 35 – 400 ºC
Oxidizing or Reducing Action	No significant increases (> 5 ºC) in temperature when product mixed with water, zinc dust, monoammonium phosphate, and potassium permanganate. A colour change was noted when mixed with potassium permanganate.
Corrosion characteristics	The product will be packed in FHDPE and PET containers.
Storage stability	Stability data provided by applicant indicates that the product is expected to remain within specification for at least 2 years when stored under normal conditions in PET and FHDPE containers.
Low temperature stability	No separation of the formulation was observed and less than 1 mL sediment (< 1%) was recorded for the product when stored for 7 days at 0ºC.

Recommendation

Based on a review of the chemistry and manufacturing details provided by the applicant, registration of *CRUSADER* is supported.

TOXICOLOGICAL ASSESSMENT

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

Toxicokinetics and Metabolism

In rats, pyroxsulam was rapidly absorbed and excreted *via* the urine and faeces with the majority of the compound being eliminated by 12 and 24 hr post-dosing, respectively. The urine accounted for 30-78% of the administered dose while the faeces accounted for 45-69%, following 48 hours post-dosing. Metabolism is not extensive and most of the administered dose was excreted rapidly as parent. 2'-demethyl-pyroxsulam is the only significant metabolite. Similar results were seen in a mouse metabolism study.

Acute Studies

Pyroxsulam has low acute oral (LD_{50} >2000 mg/kg bw), dermal (LD_{50} >2000 mg/kg bw), and inhalational (LC_{50} = 5120 mg/m^3) toxicity in rats. It is not a skin and eye irritant in rabbits, but was a moderate to severe skin sensitiser in the guinea pig maximisation test.

*CRUSADER*Herbicide, which contains 30 g/L pyroxsulam and 90 g/L cloquintocet-mexyl as the active constituents, has low acute oral (LD_{50} =3129 mg/kg bw), low dermal (LD_{50} >5000 mg/kg bw) and low to moderate inhalational (LC_{50} >1100 mg/m^3) toxicity in rats. It is a moderate skin and severe eye irritant in rabbits and was a skin sensitiser in local lymph node assay.

Repeat-dose studies

Little toxicity was observed in the toxicology studies on pyroxsulam. No treatment-related adverse effects were observed in the subchronic oral studies (mice, rats, or dogs), chronic/carcinogenicity study in rats, chronic study in dogs, chronic neurotoxicity study in rats, the developmental and reproduction studies in rats, or the 14-day dermal toxicity study in rats up to the limit dose of 1000 mg/kg bw/day. The developmental study in rabbits contained dose groups up to 300 mg/kg bw/day. There were no maternal or offspring effects at the highest dose tested. Pyroxsulam is not mutagenic and not likely to be carcinogenic to humans. In the available pyroxsulam toxicity studies, there was no estrogen-, androgen-, and/or thyroid-mediated toxicity.

The only clinical sign observed in the toxicology database was an increased incidence of perineal urine soiling in rats (males and females) in the subchronic and chronic oral studies at doses as low as 100 mg/kg bw/day up to 1000 mg/kg bw/day. This effect was interpreted to be non-adverse based on the lack of any corresponding histopathologic urinary tract effects and the absence of alterations in the urinalysis parameters. The biological significance is unknown.

The liver appeared to be the target organ in mice in the carcinogenicity study, where both absolute and relative liver weights were increased in males. Microscopic examination of the male mouse livers showed an increased incidence of clear cell foci of alteration. These effects were noted at the limit dose only (1000 mg/kg bw/day). The NOAEL is 100 mg/kg bw/day. There was an increase in tumour incidence (hepatocellular adenomas and carcinomas) in male mice in the low- and high-dose groups (10 mg/kg/day and 1000 mg/kg/day), but not at the mid-dose (100 mg/kg/day).

The Cancer Assessment Review Committee determined that the tumour incidence was unrelated to treatment because of: 1) the highly variable nature of liver tumours in mice, especially males; 2) the lack of a clear dose response; 3) SAR comparison, none of the triazolopyrimidine sulfonamides are likely carcinogens; 4) pyroxsulam is not mutagenic; 5) the mouse metabolism study showed a dose-response in internal exposure, but there was no clear tumour response; 6) there was no increase in basophilic foci of alteration, which is more commonly linked to tumour formation than the clear cell foci of alteration; and 7) there was no tumour response in females.

The 90-day studies in mice, rats, and dogs suggested that the liver might be the target of toxicity. In each study, the high-dose group animals exhibited slight increases in the mean absolute (mice and dogs) and relative (mice, rats, and dogs) liver weights in both males and females. In the mouse and rat studies, the minimal increases in mean absolute and relative liver weights were considered non-adverse in the absence of corroborating histopathology. In the case of the dog study, females at 1142 mg/kg bw/day showed a 28% increase in absolute liver weights and a 33% increase in relative liver weights compared to controls. There was also a concomitant increase in slight panlobular hepatocellular hypertrophy. These effects were considered adaptive because the chronic dog study did not show similar effects; therefore, they were considered non-adverse.

The chronic/carcinogenicity study in rats also showed a slight increase in mean absolute and relative liver weights in males and females (4-6% and 9-11%, respectively). There were no supporting histopathological findings; therefore the slight increases were not considered adverse. Although these effects were minor in nature, they can collectively be seen to suggest that the liver is the main target of toxicity for pyroxsulam.

The subchronic studies in mice, rats, and dogs, and the chronic rat and dog studies showed changes in serum cholesterol in at least one sex. In the 90-day mouse study, males in the high-dose group had significantly higher cholesterol levels than the controls. The average cholesterol level in the high-dose males exceeded the historical control range, but it was not statistically different than the average cholesterol level in the concurrent controls. The average serum cholesterol level was increased in the female mice of the high-dose group. The change in female serum cholesterol levels was statistically significant, but within the historical control range. The increase in cholesterol was observed only in the high-dose group; therefore, there was no dose response, and it was not considered adverse.

In the 90-day rat study, high-dose males had an elevated average serum cholesterol level compared to the control, reaching statistical significance and exceeding the historical control range. However, the effect was only seen in males and, within a 28-day recovery period, the cholesterol returned to control levels. In the chronic/carcinogenicity study in rats, the males of the high-dose group had statistically increased levels of cholesterol compared to controls. This increase was not considered adverse because the control animals had cholesterol levels below the historical control range for the majority of time points, and the cholesterol levels of the high-dose males fell within the historical control range for 4/5 time points. The change in cholesterol was a high-dose effect and there was no dose-response.

High-dose females in the subchronic dog study had elevated serum cholesterol levels compared to the control at weeks 7 and 13; however, the control females had cholesterol levels below the historical control range. The cholesterol level at week 13 in females was within the historical control range, and was not considered adverse.

There was no effect on cholesterol in males. In the chronic dog study, the cholesterol response was inconsistent. Serum cholesterol levels appeared higher than the historical control range in the control and mid-dose groups throughout most of the study. The serum cholesterol level in females of the high-dose group was elevated outside the historical control range only at the 12-month time point. Changes in serum cholesterol were not considered to be adverse in the chronic study because there was no clear dose-response, the high-dose serum cholesterol levels fell within the historical control range, and there were no corroborating changes in the male serum cholesterol levels.

Reproduction and Developmental Studies

No treatment-related maternal or offspring effects were observed in the developmental or 2-generation reproduction study in rats at the limit dose (1000 mg/kg bw/day).

There were no maternal or offspring effects up to 300 mg/kg bw/day in the rabbit developmental study. In a range-finding study in rabbits, there was a minimal decrease in maternal body weights (< 5%) and a decrease in food consumption (up to 20%) at 600 mg/kg bw/day. There were no adverse effects on the number of corpora lutea, implantations, resorptions, viable foetuses, foetal body weights, or external foetal morphology at 600 mg/kg bw/day. All rabbits in the 1000 mg/kg bw/day dose group were euthanized on gestation day 16 or 17, prior to scheduled sacrifice, because of severe body weight losses and reduced food intake (> 50%) in two of the six animals. There was no evidence of increased susceptibility in any of the developmental or reproduction studies in rats or rabbits.

Special Studies

No treatment-related effects were observed in the functional observational battery (i.e., motor activity, grip strength, landing foot splay), or histopathology parameters analysed in the chronic neurotoxicity study in rats.

PUBLIC HEALTH STANDARDS

Poisons Scheduling

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

At its 52nd meeting, in February 2008, the NDPSC noted that while pyroxsulam had low acute toxicity, it was a moderate to severe skin sensitiser that warranted inclusion in Schedule 6 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). Based on the toxicity profile of the product, a Schedule 6 poisons schedule classification is appropriate for *CRUSADER*. There are provisions for appropriate warning statements and first-aid directions on the product label.

NOEL/ADI

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

The ADI for pyroxsulam was established at 1 mg/kg bw/day based on a NOEL of 100 mg/kg bw/day in an 18 – month mouse feeding study and using a 100-fold safety factor in recognition of the extensive toxicological database available for pyroxsulam.

Acute Reference Dose (ARfD)

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

Since no effects could be related to a single or a few doses only, an ARfD is not established for pyroxsulam.

RESIDUES ASSESSMENT

Metabolism

Plants

^{14}C-pyroxsulam labelled in either the pyridine ring (Py-label) or the triazolo-pyrimidinyl ring (TP-label) was applied to spring wheat at an application rate equivalent to 37.5 g a.i./ha Plants were harvested from each plot on the day of application (0 days after treatment, DAT) and at stages representing early forage (7 DAT), hay (51 DAT) and straw and grain (92 DAT).

Each sample was homogenised and analysed by oxidative combustion. The total radioactive residues (TRRs) in forage, hay, straw and grain are tabulated below.

TABLE 1. Total Radioactive Residues (TRRs) in Wheat Matrices

Matrix	Application Timing	PHI (days)	Radiolabel position Py	Radiolabel position TP
			mg equiv/kg	mg equiv/kg
0 DAT	BBCH 14-31[a] (4 leaves unfolded – First node at 1 cm)	0	1.960	1.266
Early Forage (7 DAT)		7	0.707	0.203
Hay (51 DAT)		51	0.111	0.081
Straw (92DAT)		92	0.034	0.023
Grain (92DAT)		92	0.001	NQ

Surface radioactivity was removed from the 0 and 7 day forage harvests by brief immersion of each sample in acetonitrile. Sub-samples of homogenised early forage, hay and straw tissues were extracted with aqueous acetonitrile. Further extractions were conducted, as appropriate, with acidified aqueous acetonitrile and 1 N HCl reflux. Where the TRR in samples were >0.01 mg/kg, their extracts were partitioned against ethyl acetate to determine the amount of organo-soluble residues. Plant extracts and surface washes were analysed by high performance liquid chromatography (HPLC) and thin layer chromatography (TLC)

The relatively low levels of unchanged parent in forage samples from day 7, accounting for 5.7-6.5% of the TRR (0.012-0.046 mg equiv/kg) indicate metabolism is rapid. Residues of 5-OH-XDE-742 and its conjugate were the predominant residues in day 7 forage samples, accounting for a total of 60-68% of the TRR (0.118-0.485 mg equiv/kg). The remainder of the extractable radioactivity was comprised of minor metabolites including 7-OH-XDE-742 and 5,7-di-OH-XDE-742, each accounting for <2% TRR in respective samples, as well as a number of minor unidentified metabolites. Low levels of sulfonic acid, XDE-742-sulfonamide, ADTP and a metabolite tentatively identified as 2'-OH-XDE-742 were also detected.

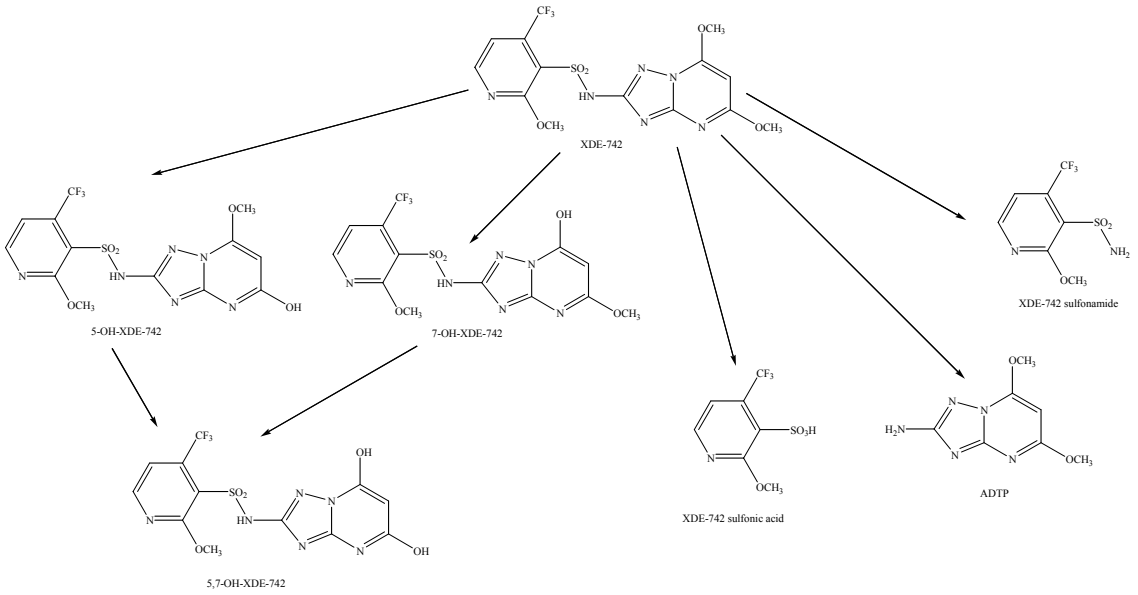
Residues of the 5-OH-XDE-742 and its conjugate were the predominant components in hay sample (51 DAT), accounting for a total of 45- 51% of the TRR (0.039-0.058 mg equiv/kg). Minor metabolites, as identified in the day 7 forage samples, comprised the remainder of the radioactivity. Approximately 11% of the TRR from each sample could not be extracted.

Attempts were made to extract radioactivity from straw samples, the extracts contained insufficient residues for identification. Approximately 40% of the TRR (0.009-0.014 mg equiv/kg) from each sample could not be extracted.

Residues in grain were too low (<LOD-0.001 mg equiv/kg) to attempt characterisation and identification of residues.

Results indicate that the metabolism of pyroxsulam in wheat is via the demethylation of the 5 or 7 ether group of the pyrimidine ring to form 5-OH-XDE-742 or 7-OH-XDE-742. The metabolism of pyroxsulam was relatively rapid, with the majority of the radioactive residue in forage and hay being accounted for as either 5-OH-XDE-742 or its conjugates. Only low levels of parent were detected in samples from forage and hay. Minor metabolites including 7-OH-XDE-742 and 5,7-OH-XDE-742 were also identified. The presence of these minor metabolites (ADTP, 2'-OH-XDE-742, sulfonic acid and XDE-742 sulfonamide) indicates cleavage of XDE-742 across either side of the sulfonamide nitrogen between the pyridine and triazolo-pyrimidinyl heterocyclic rings.

FIGURE 1. Proposed Metabolic Profile of XDE-742 in Wheat Matrices



Poultry

^{14}C-XDE-742 labelled in either the pyridine ring (PY) or the triazolo-pyrimidine ring (TP) was orally administered to laying hens for 7 days at the nominal dose of 10 mg a.i./kg feed/day in the diet (equivalent to 0.839 mg a.i/kg bw).

Eggs and excreta were collected daily. The animals were sacrificed within 24 hours of the final dose and samples of liver, muscle (breast and thigh), fat (abdominal), and skin with subcutaneous fat were collected.

Each sample was homogenised and analysed by oxidative combustion. Only liver and excreta contained sufficient radioactivity to allow further characterisation. Liver and excreta were extracted using acetonitrile:water. Neutral liver extracts were partitioned against hexane. The resulting aqueous phase was acidified and partitioned against ethyl acetate. The post extracted solids were further refluxed with 1.0 N HCl, and the extracts partitioned against ethyl acetate prior to analysis by HPLC.

The dose was almost entirely excreted, with >99% of the administered radioactivity recovered from the excreta. The day 7 excreta extracts contained primarily unchanged parent at 89.5% (5.925 mg equiv/kg) and 92.2% of the TRR (6.874 mg equiv/kg) from the ^{14}C-TP and ^{14}C-PY labelled samples, respectively. Other components, eluting in the regions of the 5-OH-XDE-742, 7-OH-XDE-742 metabolites, polar compounds and unidentified components of the residue were each present ≤4% of the TRR (up to 0.212 mg equiv/kg) for both labels.

Eggs from hens treated with either label each contained less than 0.01% of the administered dose (<0.005 mg equiv/kg).

Residues in all edible tissues collected at sacrifice were also less than 0.01% of the administered dose for both labels. Residues in ^{14}C-TP-XDE-742 muscle, liver, fat, and skin with fat were less <LOQ, 0.010 mg/kg, <LOQ, and 0.0043 mg/kg, respectively, while residues in ^{14}C-PY-XDE-742 muscle, liver, fat, and skin with fat were <LOQ, 0.019 mg/kg, <LOQ, and <LOQ, respectively.

A very small amount of radioactivity, (<0.01% of the administered dose in each sample, <0.020 mg equiv/kg), was found in the liver. The radioactivity in the liver was characterised as parent (*ca.* 15-30% of the TRR), 742-ADTP (<5% of the TRR), and a range of unidentified polar components (*ca.* 15-45% of the TRR).

Goats
Goats were dosed with [^{14}C]-XDE-742 labelled in either the pyridine-ring (PY) or triazolopyrimidine-ring (TP). The test substances were administered by gavage for 7 consecutive days, corresponding to a dose level of 0.4 mg/kg body weight or the equivalent of 12 ppm in the feed.

Milk, urine and faeces were collected daily. The animals were sacrificed within 24 hours of administration of the final dose.

Each sample was homogenised and analysed by oxidative combustion. Aliquots of urine were mixed with scintillation cocktail and analysed without additional treatment. Faeces were homogenised and suspended in distilled water. These suspensions were freeze dried and solubilized prior to analysis. Proteins in each milk sample were precipitated with acetonitrile. The extracts were combined, concentrated, reconstituted in mobile phase and centrifuged. The final extracts were analysed by radio-HPLC and LSC.

Liver and kidney were the only edible tissues with TRR levels greater than 0.01 mg/kg. Samples of these tissues were extracted with acetonitrile followed by acetonitrile:water. The post extracted solids (PES) were refluxed with 6N HCl. The aqueous extracts were reacted with dimethoxypropane to convert the aqueous fraction to acetone and methanol. The solid material was extracted with acetonitrile and the extracts were combined with the acetone/methanol extracts. The final extracts were analysed by radio-HPLC and LSC.

The majority of the radioactivity was excreted in the urine and faeces. For both labels, the percentages of eliminated radioactivity in urine and faeces were similar, ~37% in the urine for both labels and ~45% and ~54% in faeces for the TP and PY labels, respectively. In urine, unchanged parent accounted for ~95% of the TRR. The remainder of the extracted radioactivity was comprised of 7-OH-XDE-742, 5,7-di-OH-XDE-742 and unidentified metabolites. No single metabolites accounted for more than ~5% of the TRR. In faeces, unchanged parent accounted for ~75-80% of the TRR. The remainder of the extracted radioactivity, which accounted for <10% of the TRR, was comprised entirely of 7-OH-XDE-742.

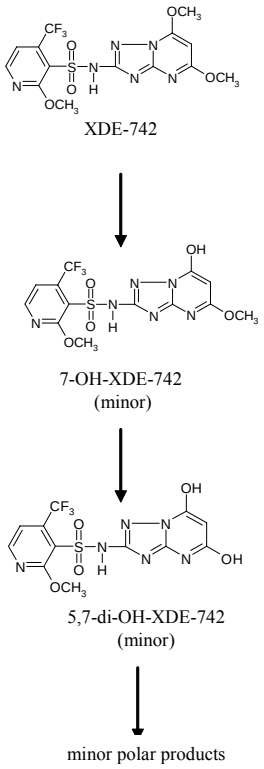
A total of 0.026% and 0.028% of the dose was recovered in milk from the animals dosed with the TP and PY labelled material, respectively, indicating that very little of the administered dose is transferred to the milk. TRRs in milk were low (0.013 mg equiv/kg), and were. comprised entirely of unchanged parent.

The only tissues containing sufficient radioactivity for characterisation and identification were the liver and kidney. Residues in these tissues were comprised largely of unchanged parent which comprised ~42-61% of the TRR (0.008-0.010 mg equiv/kg) in kidney and ~44-64% of the TRR (0.009-0.010 mg equiv/kg) in the liver. Small amounts of 5,7-di-OH-XDE-742 (up to 5% TRR, ≤0.001 mg equiv/kg) were identified in PY labelled liver samples. The remainder of extractable residues in samples from both labels was comprised

of one or more unidentified metabolites, which accounted for up to 15% of the TRR (0.004 mg equiv/kg).

The proportion of pyroxsulam and its metabolites were similar in samples for both labels, indicating that there was no significant cleavage of the molecule across the sulfonamide nitrogen between the pyridine and triazolo-pyrimidinyl ring.

FIGURE 2. Proposed Metabolic Profile of XDE-742 in Lactating Goat



Analytical methods

Analytical methods were provided for the determination of pyroxsulam in plant tissues. Residues of pyroxsulam were extracted from homogenised samples by shaking with an acetonitrile/water (80/20, v/v) solution. An aliquot of the extract was diluted with 0.1 N hydrochloric acid and purified using solid-phase extraction (SPE). The eluate was diluted with stable-isotope labelled internal standard ($^{15}N_3$-XDE-742). The final solution was analysed by liquid chromatography with positive-ion electrospray ionization (ESI) tandem mass spectrometry (LC/MS/MS).

The method was validated with fortification levels of 0.01-1.0 mg/kg for a range of acidic crops, dry crops, oily crops, wet crops and processed products from wheat grain. Individual and average recoveries were within the acceptable ranged of 70-120% and 70-110% respectively, at the LOQ (*0.01 mg/kg) and 100x the LOQ (1 mg/kg). The method was successfully validated by ILV.

Radio-validation of the plant method was undertaken to determine the efficiency of the extraction procedures. Samples of wheat containing aged radio-labelled residues were obtained from a previously conducted ^{14}C-Nature of Residue (NOR) study. LSC of several aliquots of the raw extracts demonstrated 90% of TRR were extracted, indicating that the method is acceptable for the extraction of pyroxsulam in wheat samples. LC/MS/MS-based results demonstrated a recovery of 87% for the method.

Minor modifications of the plant method were made for use on animal matrices. Rather than clean up of the extract by SPE, NaCl and $MgSO_4$ were added. The method was validated in various bovine and poultry tissues as well as eggs and milk. Individual and average recoveries were within the acceptable ranges of 70-120% and 70-110%, respectively, at the LOQ (*0.01 mg/kg) and 10x the LOQ.

An analytical method was also provided for the crop safener cloquintocet-mexyl and its acid metabolite. Residues of cloquintocet-mexyl and cloquintocet-acid were extracted twice from the crop samples by homogenisation with an acetone/citrate (80:20, v/v) buffer solution. The extracts were purified using a polymeric SPE. Samples were analysed by LC/MS/MS.

Validation was conducted using untreated samples of wheat grain, straw, forage and hay that were fortified with both cloquintocet-mexyl and cloquintocet-acid at 0.01, 0.02, 0.05 and 0.1 mg/kg each. Individual and average recoveries for both metabolites were within the acceptable ranged of 70-120% and 70-110%, respectively, at the LOQ (*0.01 mg/kg) and 100x the LOQ. The method was successfully validated by ILV.

Residue definition

In wheat the metabolism of pyroxsulam proceeds via the demethylation of the 5 or 7 ether group of the pyrimidine ring to form 5-OH-XDE-742 or 7-OH-XDE-742. The metabolism of pyroxsulam was relatively rapid, with the majority of the radioactive residue at 7 DAT being accounted for as either 5-OH-XDE-742 or its conjugates. In hay samples at 51 DAT, approximating the proposed WHP, residues of all metabolites in feed commodities were present at <0.1 mg/kg, the most significant metabolite being conjugated 5-OH-XDE-742 accounting for up to 51% of the TRR (0.057 mg equiv/kg). There were no detectable residues of pyroxsulam or its metabolites in either the straw or the grain. The presence of 5-OH-XDE-742 in forage and hay suggest the inclusion of the metabolite in the residue definition would be justified if it were not for the low level of detected. For the purpose of

the current application, a residue definition of parent only in plant commodities is supported.

In both goat and poultry metabolism studies unchanged parent was almost entirely excreted in the urine and faeces as parent. The balance of the excreted radioactivity was comprised of 5-OH or 7-OH metabolites, thus indicating metabolism of pyroxsulam by de-methylation of the 5 or 7 ether groups of the pyrimidine ring. In poultry, radioactivity in the liver was characterised as parent (ca. 15-30% of the TRR), 742-ADTP (<5% of the TRR), and a range of unidentified polar components (ca. 15-45% of the TRR). The 5-OH or 7-OH metabolites of pyroxsulam were not found. Unchanged parent in the liver and kidney of goat were accounted for ~40-60% of the TRR (≤0.01 mg/kg in each sample), with the remainder of the radioactivity comprised of small amounts of 5,7-OH-XDE-742 (up to 5% of the TRR, ≤0.001 mg/kg) and unidentified metabolites (up to 5% of the TRR, ≤0.001 mg/kg). The available animal metabolism data indicate a residue definition of parent only is appropriate.

Validated methods capable of the detection and quantitation of pyroxsulam in plant and animal matrices are available.

The following residue definition is recommended for inclusion in Table 3 of the MRL Standard.

Table 3

Compound	Residue
ADD: pyroxsulam	pyroxsulam.

Freezer storage stability.

Samples of spinach, tomato, potato, soybean, wheat grain, wheat straw, and wheat forage (shoot) were homogenised and fortified with pyroxsulam at a level of 0.10 mg/kg and were stored at approximately -20^{o}C for 24 months. The results indicate that residues of pyroxsulam are stable at -20^{o}C for up to 24 months in spinach, tomato, potato, soybean, and wheat grain, straw, and forage (shoot).

Samples of homogenised spinach, tomato, potato, soybean, wheat grain, wheat straw, and wheat forage were fortified with cloquintocet-mexyl and cloquintocet-acid prepared in methanol, each at a level of 0.10 mg/kg and were stored at ≤ -20^{o}C for a duration of 9 months. The data indicate that residues of cloquintocet-mexyl and cloquintocet-acid are both stable in spinach, tomato, potato, soybean, wheat grain, wheat straw, and wheat forage for up to 9 months when stored at ≤ -20^{o}C.

Residues trials

The applicant has provided 12 Australian residue trials conducted on wheat during 2004 and 2005. A single broadcast application was made to wheat plots between growth stages Z24 (main shoot and 4 tillers) and Z33 (3rd node detectable). The proposed application timing is no later than the 1st node stage of the crops (Z31). The products were applied at rates corresponding to 15 and 45 g ai/ha or 30 and 90 g ai/ha of pyroxsulam and cloquintocet-mexyl respectively (1 to 2× the proposed rate).

Residues of pyroxsulam in wheat grain collected at harvest 58 – 143 DAT at either 15 or 30 g ai/ha were below the LOD (0.003 mg/kg) in all samples (n = 24). It is appropriate to establish an MRL at the LOQ of *0.01 mg/kg for pyroxsulam on wheat. Total residues of cloquintocet-mexyl in wheat grain at harvest 58 – 143 DAT at either 45 or 90 g ai/ha were

<0.02 mg/kg in all samples (n = 24). The current cloquintocet-mexyl wheat MRL of *0.1 mg/kg is appropriate for the proposed use pattern. A harvest withholding period of 'Not required when used as directed' is appropriate for grain.

Residues of pyroxsulam in wheat straw collected at harvest 58 – 143 days after treatment at 15 g ai/ha (1× proposed rate) were <LOD (0.003 mg/kg, fresh wt., n = 10), 0.02 (fresh wt., n=2.). Where samples contained detectable residues on a fresh wt basis, results were corrected for moisture, resulting in residues of 0.02 and 0.03 mg/kg. An MRL of 0.1 mg/kg is appropriate for AS 0654 Wheat straw and fodder, dry. Total residues of cloquintocet-mexyl in wheat straw collected at harvest 58 – 143 DAT at 45 g ai/ha (1× proposed rate) were <0.02 (n = 9), <0.03, <0.04 and <0.05 mg/kg on a fresh weight basis. The maximum residue of <0.05 mg/kg would correspond to <0.07 mg/kg on a dry weight basis. The current MRL of *0.1 mg/kg for cloquintocet-mexyl on the straw and fodder (dry) of cereal grains [except rice] is appropriate.

Residues of pyroxsulam in wheat forage 42 days after application at 15 g ai/ha residues in forage were <LOD (0.003 mg/kg, n = 5) and 0.02 mg/kg on a fresh wt basis. Where samples contained detectable residues on a fresh wt basis, results were corrected for moisture, resulting in residues of 0.04 mg/kg. An MRL of 0.1 mg/kg is recommended for pyroxsulam in wheat forage, dry, in conjunction with a 6 week grazing withholding period. Total residues of cloquintocet-mexyl in wheat straw collected at harvest 58 – 143 DAT at 45 g ai/ha (1× proposed rate) were <0.02 (5) and <0.03 mg/kg on a fresh weight. The current MRL of *0.1 mg/kg for cloquintocet-mexyl on cereal forage (fresh weight) is appropriate.

Animal commodity MRLs.

No animal transfer studies were provided in support of this application as it was demonstrated that residues in feed commodities will not exceed 0.1 mg/kg. Further, it is recognised that pyroxsulam is rapidly absorbed and excreted by livestock, therefore residues would not be readily transferred into milk, eggs or edible tissues; and the estimated dietary burdens for ruminants and poultry were very low in comparison to the feeding levels used in the metabolism studies.

In the goat metabolism study provided, ^{14}C-pyroxsulam was orally administered for 7 days at a dose level corresponding to 0.4 mg/kg bw/day (equivalent to 12 ppm in the feed). Milk, urine and faeces were collected daily. The animals were sacrificed within 24 hours of administration of the final dose and tissues were collected. The dose level in the metabolism study is ~100x the anticipated dietary burden of cattle and sheep, and ~1000x that of pigs. At the feeding level of 0.4 mg/kg bw/day, residues in muscle (and fat) were less then the LOQ (*0.01 mg/kg). Residue in kidney and liver ranged from 0.013-0.25 mg/kg and 0.13-0.22 mg/kg, respectively, while the highest residue in milk was 0.031 mg/kg. At the maximum feeding level, residues in offal and milk are also expected to be <LOQ of 0.01 mg/kg.

In the poultry metabolism study provided ^{14}C-pyroxsulam was orally administered to laying hens for 7 days at the nominal rate of 10 mg a.i./kg feed/day in the diet (equivalent to 0.839 mg a.i/kg bw). Eggs and excreta were collected daily. The animals were sacrificed within 24 hours of the final dose and tissues were collected. The dose level in the metabolism study is ~840x the anticipated dietary burden of poultry. At the feeding level of 0.839 mg/kg bw/day, residues in muscle, skin with fat, fat and eggs were all below the LOQ. Residues in liver ranged from 0.01-0.02 mg/kg. At the maximum feeding level, residues in meat, edible offal and eggs will be <LOQ of 0.01 mg/kg.

Crop rotation

Applications of ^{14}C-XDE-742-TP (triazolo-pyrimidine label) and ^{14}C-XDE-742-PY (pyridine label) were made to confined, outdoor plots of sandy loam soil at rates of 18.11 g a.i./ha (0.0161 lb a.i./A) and ~19 g a.i./ha (0.0169 lb a.i./A), respectively. Soil samples were taken from all plots at the time of application (0 DAT) and immediately prior to planting crops (30 DAT). After ageing the test plots for 30 days, potatoes, lettuce, and wheat were planted into the plots.

In the soil cores collected at planting (30 DAT), an average of 56.7% and 85.8% of the applied TP and PY labeled radioactive test material, respectively, remained in the soil. The majority of the extracted radioactivity was unchanged pyroxsulam.

The TRRs in crops from the ^{14}C-XDE-742-PY treatment ranged from 1 to 12 times as high as TRRs in crops from the ^{14}C-XDE-742-TP treatment. Only potato tops, wheat hay and straw from the ^{14}C-XDE-742-PY treatment contained sufficient radioactivity (TRRs ranged from 0.020-0.036 mg equiv/kg) to allow further analysis. No parent compound was found in any of the plant extracts analysed. No single component of the identified residue was present at ≥0.007 mg/kg in any sample. The majority of the TRR was accounted for as unidentified metabolites.

The presence of radioactivity in rotational crop samples is evidence that pyroxsulam and possibly its metabolites will be taken up from the soil and translocated within the plant. Where uptake of pyroxsulam occurs, initial metabolism is likely to result in the formation of 5-OH-XDE-742 and 7-OH-XDE-742 metabolites. Also, it is possible that the 5-OH-XDE-742 and 7-OH-XDE-742 metabolites, present in the soil at the time of planting, could be taken up from soil into plant tissue. Conversion of the 7-OH-XDE-742 to the 6-Cl-7-OH-XDE-742 metabolite is proposed as an additional transformation.

It is concluded that the metabolites of pyroxsulam may be present at low levels (<0.01 mg/kg) in raw agricultural commodities from rotational crops planted 30 days after direct application of pyroxsulam. Residues of unchanged parent are not anticipated in harvested commodities. No individual metabolites are expected to be present at a level greater than 0.01 mg/kg. As such, plant back intervals are not required from a residues perspective.

Fat solubility and potential for bioaccumulation

The Log(K_{ow})(20^{o}C) of pyroxsulam at pH's 4, 7 and 9 is 1.08, -1.01 and -1.60, respectively, which indicates it is unlikely to partition preferentially into fat. This is supported by the results of the results of the livestock metabolism studies. It is considered pyroxsulam is unlikely to bio-accumulate.

Spray drift

The label includes the standard PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS statement and prohibits aerial application. The label also includes the following boom spray instructions "Apply *CRUSADER* in sufficient water to obtain good coverage. It should be applied by an accurately calibrated ground rig using a water volume of 50–100 L/ha. Sprayers should aim to apply medium quality spray based on BCPC specifications and in accordance with ASAE standard S-572"

The potential for spray drift of *CRUSADER* was determined using AgDRIFT. Based on a target concentration of 0.1 mg/kg in the feed, and a medium-course spray quality and a low

boom hight, the required no spray zone would be <10m. Therefore it is not considered necessary to recommend a no-spray zone from a residues perspective.

Dietary exposure assessment

The chronic dietary exposure to pyroxsulam 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 Pyroxsulam is equivalent to <1% of the ADI. It is concluded that the chronic dietary exposure of pyroxsulam is 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:			
Pyroxsulam	MO 0105	Edible Offal (mammalian)	*0.01
	PE 0112	Eggs	*0.01
	PO 0111	Poultry, edible offal of	*0.01
	PM 0110	Poultry, meat	*0.01
	MM0095	Meat (mammalian)	*0.01
	ML 0106	Milks	*0.01
	GC 0654	Wheat	*0.01

Table 3

Compound	Residue
ADD:	
Pyroxsulam	Pyroxsulam

Table 4

Compound	Animal feed commodity		MRL (mg/kg)
ADD:			
Pyroxsulam	AS 0654	Wheat straw and fodder, dry	0.1
		Wheat forage, dry	0.1

WITHHOLDING PERIODS:

HARVEST: NOT REQUIRED WHEN USED AS DIRECTED

GRAZING: DO NOT GRAZE OR CUT TREATED CROPS FOR STOCKFEED FOR 6 WEEKS AFTER APPLICATION.

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

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

As a commodity group, cereal grains (including wheat, oats, cereal rye, triticale and barley) are a major export commodity. Of these commodities, wheat is by far the most significant to Australia in terms of the value and volume of exports. Livestock and some commodities derived from livestock are also considered to be major export commodities.

Pyroxsulam MRLs are recommended at the limit of quantitation (*0.01 mg/kg) for wheat grains, mammalian meat, offal, milk and poultry meat, offal and eggs. As detectable residues of pyroxsulam are not anticipated in treated commodities, or animal commodities where livestock have consumed treated feeds, residues are expected to comply with the standards of key export markets.

No changes to existing MRLs for cloquintocet-mexyl in wheat or animal commodities are required.

Assessment of pyroxsulam for registration is being undertaken as a trilateral review between the U.S., Canada, and Australia.

Products containing pyroxsulam have recently been registered for use on wheat in the US, and registration is expected in Canada shortly. The following tolerances were established in the US.

Country/status	Residue Definition	Commodity	Tolerance, mg/kg (expiry date)
US	pyroxsulam, N-(5,7-dimethoxy[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)-3-pyridinesulfonamide in or on the raw agricultural commodities:	Wheat, forage	0.06
		Wheat, grain	0.01
		Wheat, hay	0.01
		Wheat, straw	0.03

Whilst one of the objectives of this joint-review with Canada and the US is to harmonise MRLs, due to policies and assumptions of each participant (particularly in relation to the feeding of treated crops to livestock and the need for animal commodity MRLs) not all MRLs are aligned. The notable exception is the recommendation of MRLs (at the LOQ), for animal commodities by the APVMA where the US and Canada do not set MRLs.

Commodities relevant to the current application are exported, but are not expected to contain detectable residues. It is considered unlikely that the proposed registration of *CRUSADER* will unduly prejudice trade. A final determination of undue prejudice to trade or commerce will be made following the completion of this public consultation process.

Formulation, packaging, transport, storage and retailing

CRUSADER will be formulated in the USA, France and New Zealand and imported to Australia. The product will be packaged in 1 or 5 L polyethylene terephthalate (PET) or fluoridated high density polyethylene (FHDPE), or 10, 20 and 200 L FHDPE containers. Formulation workers may be exposed to the active constituents, other ingredients and/or product. In addition, transport and warehouse workers, storepersons, and retailers will handle the packaged product and will be exposed to the product only if packaging is breached.

Use pattern and exposure profile

CRUSADER is intended for post-emergent control of both grass and broadleaf weeds in wheat, excluding durum varieties. *CRUSADER* can be safely used by workers when handled in accordance with the control measures indicated in this assessment.

The maximum application rate is 500 mL product/ha in a minimum spray volume of 50 L/ha. The product is to be diluted with water before being applied to wheat (from three leaf up to first node of the crop) using ground rig (boom sprayer) application equipment at a certain weed stage. The product will be applied once per season as a post-emergent herbicide.

Farmers and contract spray workers will be the main users of the product. These workers may become contaminated with the product/spray during opening of the containers, mixing/loading, application, cleaning up spills, and maintaining equipment. The main routes of exposure to the product/spray will be dermal, inhalation and ocular.

Although tractor/boom applied herbicides rarely require immediate re-entry for inspection purposes, post-application activities e.g., for scouting purposes are possible.

A Pesticide Handlers Exposure Database (PHED) Surrogate Exposure estimation was conducted by the applicant to determine inhalation exposure during mixing, loading and application using XDE-742 oil dispersible formulation in water (containing 30 g/L pyroxsulam) with vehicle mounted ground boom sprayers in cereals. The OCS considered that this estimation was not appropriate to be used in the repeat dose risk assessment because it is cloquintocet-mexyl (the other active constituent in *CRUSADER*) rather than pyroxsulam, that drives the overall toxicity of the formulated product. The OCS also noted that the maximum treated area/day in Australia by ground boom is five times higher than that used in this PHED estimate provided by the applicant. To estimate worker exposure to cloquintocet-mexyl using *CRUSADER* during mixing, loading and applying the product, the OCS used the PHED Surrogate Exposure Guide. The OCS PHED estimates were relied on for risk management.

Risks to workers during use and recommended PPEs

The main risks associated with acute exposure to *CRUSADER* are eye, skin and respiratory irritation, and skin sensitisation. Risks of irritancy and sensitisation are high for mixer/loaders handling the undiluted product. Risks of irritancy and sensitisation are low for applicators due to the low concentration of the product (max 0.1%) in the spray solution.

The main effects associated with repeat dose toxicity of cloquintocet-mexyl in animals are moderate hepatic necrosis and fibrosis in rats. Based on the use pattern of the product, a NOEL of 200 mg/kg bw/day, from a 28-day rat dermal study, was determined as the most appppropriate for use in the calculation of occupational risks. In the absence of measured

dermal absorption data, default absorption factors of 100% (dermal) and 100% (inhalational) were utilised in the calculation of internal doses from PHED data.

The OCS utilised the Margin of Exposure (MOE) approach in the calculation of risks to workers exposed to cloquintocet-mexyl, where estimated exposures from PHED or determined exposures from an operator exposure study were compared to the NOEL. MOE at and above 100 are considered acceptable risks. In the repeat dose risk assessment based on PHED, MOE were unacceptable even when workers wear an additional layer of clothing (overalls). However, in the repeat dose risk assessment based on the worker exposure study, MOE were acceptable when workers wear gloves and overalls together during mixing/loading and application.

Based on the risk assessment, cotton overalls buttoned to the neck and wrist (or equivalent clothing) and a washable hat and elbow–length chemical resistant gloves, goggles and disposable mist face mask covering mouse and nose should be worn when opening the container and preparing spray. When using the prepared spray, no particular personal protection equipments are required.

Entry into treated areas

The product remains a potential risk to workers until the oil dispersible liquid dries up particularly via the dermal route. Therefore the following re-entry statement was established:

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

Hazardous classification

Based on available toxicology information, the OCS classified pyroxsulam as a hazardous substance in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following risk phrase:

R43	May cause sensitisation by skin contact

Based on the product toxicology information, the OCS classified *CRUSADER* as a hazardous substance in accordance with ASCC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004) with the following risk phrases:

R20	Harmful by inhalation
R38	Irritating to skin
R41	Risk of serious damage to eyes
R43	May cause sensitisation by skin contact

Pyroxsulam in the product *CRUSADER*

The data package presented in support of the application for the registration of *CRUSADER* addresses the environmental fate and toxicity of pyroxsualm and its relevant metabolites.

Environmental Fate

Hydrolysis

Pyroxsulam did not hydrolyse when held in the dark at 20°C in sterile aqueous buffered solutions at pH 5, pH 7 and pH 9 for 32 days. There was no unidentified radioactivity and sample pH did not change throughout the study. The half-life (lives)/DT50 (50% decline times) of pyroxsulam could not be determined in any of the three buffer systems studied because of this stability to hydrolysis.

Aqueous Photolysis

The aqueous phototransformation of radio labeled pyroxsulam was studied at 20°C in sterile aqueous pH 7 buffered solution. After fifteen days of continuous simulated natural light the two major transformation products were the pyroxsulam-sulfinic acid and pyroxsulam-ADTP, with maximum concentrations of 79.2% and 39.8% of the applied amount, respectively, at 3.8 DAT. Volatiles were found to be 1.2% of the applied radioactivity and total unidentified radioactivity at test termination was 49-69% of the applied radioactivity, respectively. At this time, the major transformation products are made up of multiple, low level components, which could not be separated nor identified in the study. The environmental photolytic half-life is predicted to be 4.5 days at 40°N latitude in summer sunlight. No significant transformations occurred in the dark samples.

Soil Photolysis

The phototransformation of 14C-pyroxsulam was studied on a silt loam soil using a filtered xenon lamp as a light source. Non-sterilised samples were irradiated for up to the equivalent of 30 days of spring sunlight at 50°N latitude. Concentration of the parent pyroxsulam decreased from 98.5% at day 0 to 60.7% of the applied amount at test termination. Since the transformation products formed in the irradiated samples were each less than 6% of applied, they were not conclusively identified. Because the transformation rate of pyroxsulam stored in the dark was greater than the total (phototransformation + non-phototransformation) rate in the irradiated samples, a photolysis half-life could not be calculated and photo degradation of pyroxsulam on soil is assumed not to be an important degradation route in the environment.

Aerobic Soil Metabolism

Three aerobic soil metabolism studies with pyroxsulam and one with the 5,7-dihydroxy metabolite of pyroxsulam were presented in support of the application.

In the first study, the biotransformation of radio labeled pyroxsulam was studied in a French light clay and three German soils, a clay loam, a loamy sand, and a sandy loam for 133 days after treatment (DAT). Pyroxsulam aerobic soil transformation half-lives ranged from 2.1 to 10 days with the concentration of the parent compound decreased from approximately 100% at 0 DAT to less than 5% of the applied radioactivity at the end of study period. Five transformation products reaching concentrations of greater than 5% of the applied radiocarbon were identified. These were 5-hydroxy-pyroxsulam (maximum at 24% of the applied radiocarbon in the clay loam at 3 DAT), 7-hydroxy-pyroxsulam (maximum of 13% of applied radioactivity in the light clay at 7 DAT), 6-chloro-7-hydroxy-pyroxsulam (maximum of 26% of applied radioactivity in the light clay at 7 DAT) and cyanosulfonamide (CSF) and the pyridine sulfonic acid (PSA), with respective maximum concentrations of 8% and 6% of the applied at the 21-DAT and I-month time points. All transformation products were observed at declining concentrations in all soil types at the end of the study period. At the end of the study period, between 5 and 15% of the applied radioactivity was identified as CO_2. Non-extractable residues (NER) accounted for up to 94% of the applied radioactivity, with

60-90% at study termination. The unidentified radioactivity was made up of several small, extractable transformation products in total accounting for less than 5% of the applied radiocarbon.

To investigate the large NER, the same soils were used in the second study, and, after 118 days, samples with more than 10% of the applied radioactivity unextracted after the initial extraction procedure were subjected to additional exhaustive sequential extractions. The concentration of the parent compound decreased from a mean of the four soils of 95% (range of 86.2 to 98.7%) of the applied amount at day 0, to below 5% (range 0.2 to 3.9%) of the applied at the end of study period at all test sites. The DT50 and DT90 of pyroxsulam in aerobic soil for all soil types ranged from 2.1 to 14.6 days and from 6.8 to 48.4 days, respectively. Major degradation products were 5-hydroxy-pyroxsulam (maximum of 24.4% of applied radioactivity at day 4 in the clay loam), 6-chloro-7-hydroxy-pyroxsulam (maximum of 11% of the applied radioactivity in the clay loam on day 7), 7-hydroxy-pyroxsulam (maximum of 7.9% of the applied radioactivity on day 14 in the sandy loam) and pyroxsulam sulphonamide (not seen in the previous study, maximum of 13.2% of applied radioactivity at day 29 in the clay loam and 8.6% at the end of the study). Up to 11 % of the applied radioactivity was recovered in the caustic traps and was assumed to be $C0_2$. Nonextractable residues (NER) accounted for 37.9-82.8% of the applied radioactivity, even after the exhaustive extraction procedures.

The third aerobic soil study examined the degradation of pyroxsulam in sixteen European and North American soils. Samples were incubated in the dark at 20°C under aerobic conditions for up to 1 month after treatment. DT50 values ranged from 1 to 17 days; 12 of the 16 soils had DT50 values of less than 5 days. The aerobic soil degradation rate of pyroxsulam was uniformly rapid, regardless of soil type.

In the final aerobic soil study, the biotransformation of radiolabeled 5,7-di-hydroxy-pyroxsulam was studied in two loamy sands, a light clay and a sandy clay loam. This metabolite was examined because, while not seen in the aerobic soil studies, it was present at greater than 5% of the applied radioactivity in an anaerobic aquatic transformation study. The average concentration of the test compound decreased from 90% of the applied radioactivity at Day 0 to 7% of the applied at the end of the study period (14 days post-application). A geometric mean DT50 of 0.2 days and a DT90 of 8 days were determined. No major or minor transformation products were identified. Averaged non-extractable ^{14}C -residues increased from 9% of the applied amount at Day 0 to 83% of the applied at the end of the incubation period. At study termination, volatile transformation products accounted for up to 15% of the applied radioactivity.

Aerobic Aquatic Metabolism

The aerobic biotransformation of ^{14}C-radiolabeled pyroxsulam was studied in two pond water/sediment systems (one, English and one, French) with the test material applied to the aqueous layer. Over 101 days, material balances for the total systems were 90 to 107% of the applied radioactivity. Pyroxsulam in the water column was initially 90-104% of the applied radioactivity and decreased to less than 15% of the applied radioactivity at experiment's termination. In the sediment, pyroxsulam concentrations were approximately 1 to 13% of the applied radioactivity at day 0 and 10 to 16% at day 75.

The major transformation products detected in the water were pyroxsulam ATSA, (maximum concentration of 10% of the applied radioactivity at Day 54) and 7hydroxy-pyroxsulam, maximum of 33% of the applied radioactivity at Day 17). The major transformation products detected in the sediment were 7-hydroxy-pyroxsulam (26% of the applied radioactivity at Day 17), and an unknown compound (13% of the applied radioactivity at Day 33). No other unidentified transformation products accounted for more than 5% of the applied radioactivity in the total system. Nonextractable residues were 0.1 and 0.2% of the applied radioactivity at Day 0 and ~35 and ~ 70% of the applied radioactivity at the completion of the study. Volatile radioactivity was less than 3% of the applied.

In the water column, the pyroxsulam DT50 values were 10.6 and 20.6 days. In the sediment, the pyroxsulam DT50 values were 14.4 and 20.6 days. The total system DT50 values were 11.9 and 23.6 days. The DT50 values for 7-hydroxy-pyroxsulam were 17.9 and 50.5 days in the water column and 9.7 days and not determinable because the concentration of the metabolite in the sediment was not declining at experimental termination. The ATSA degradate formed had total system DT50s of 22 and 71.4 days.

Anaerobic Aquatic Metabolism

The anaerobic biotransformation of radio labeled pyroxsulam was studied in a flooded soil system using a French silt loam. Pyroxsulam was applied to the soil and water system and retained for 126 days in the dark at 20°C. While anaerobic conditions were maintained in soils, such conditions could not be confirmed in the aqueous phase after day 30 of the exposure. Average material balances over the 126 days were 98.3% of the applied radioactivity. Non-extractable ^{14}C residues (NER) in the soil increased from 0.6% at Day 0 to 25.7% of the applied radioactivity at study termination. At the end of the study 0.1 % of the applied radioactivity was present as $C0_2$. The concentration of pyroxsulam in water decreased from 80.5% at Day 0 to 71.6% at Day 30. The concentration of pyroxsulam in the soil (sediment) increased from 16.7% at Day 0 to 24.9% at Day 30. The major transformation products detected in water were 7hydroxy-pyroxsulam and 5,7-di-hydroxy-pyroxsulam [maxima of 48.6 % (day 58) and 23.5% (day 126) of the applied amount with averages ~23 and 26.5% still in the water column at study's end]. The major transformation products detected in the soil sediment were 7-hydroxy-pyroxsulam and 5,7-di-hydroxy-pyroxsulam, with maximum concentrations of 27.9 % (day 58) and 4.4 % (day 126) of the applied amount respectively. The corresponding concentrations in soil at the end of the study were an average of 12.8 % and 4.1 % of the applied amount, respectively. No minor transformation products were identified in the water or the soil. The unidentified ^{14}C ranged from 0.0 to 3.3 % of the applied amount. Kinetics calculations were not conducted because anaerobic conditions in the aqueous phase were not assured throughout the study but as pyroxsulam was stable through the first 30 days when conditions were indicative of anaerobicity, it is assumed stable in anaerobic aquatic systems.

Soil Adsorption/Desorption

Pyroxsulam

The adsorption/desorption characteristics of radiolabelled pyroxsulam were determined with 10 European soils. For the adsorption phase, the average Kd value for the ten soils was 0.57 mL/g (range 0.19 to 1.76 mL/g); the corresponding average K_{oc} values were 30.0 mL/g (range 7.1 to 54.3 mL/g). Following a single desorption cycle, the average Kd value for the ten soils was 0.42 mL/g (range 0.13 to 1.27 mL/g); the corresponding average $K_{oc\text{-}des}$ value was 22.3 mL/g (range 5.0 to 46.0 mL/g), indicate that pyroxsulam does not bind irreversibly with soil, and can readily desorb. Based on the determined adsorption coefficients in the ten soils, pyroxsulam can be considered very highly mobile according to the classification criteria of McCall et al.. Desorption coefficients, indicate that pyroxsulam does not bind irreversibly with soil, and can readily desorb.

Pyroxsulam transformation products

The adsorption characteristics of radio labeled pyroxsulam transformation products 5hydroxy-hydroxy-pyroxsulam, 7 -hydroxy-pyroxsulam, 5,7 -di-hydroxy-pyroxsulam, 6-chloro-7-hydroxy-pyroxsulam, pyroxsulam sulfonic acid, and pyroxsulam cyanosulfonamide were studied in a loam, a sandy loam, a loamy sand and a sandy loam. The average 6-chloro-7-hydroxy-pyroxsulam adsorption Kd value was 0.571 mL/g; the average K_{oc} value was 40 mL/g (very high mobility). The average 5hydroxy-pyroxsulam adsorption Kd value was 0.151 mL/g; the average Koc value was 11 mL/g (very high mobility). The average 7-hydroxy-pyroxsulam adsorption Kd value was 0.903 mL/g; the average Koc value was 62 mL/g (high mobility). The average 5,7-di-hydroxy-pyroxsulam adsorption Kd value was 3.556 mL/g; the average

Koc value was 280 mL/g (moderate mobility). The average pyroxsulam cyanosulfonamide adsorption Kd value was 0.073 mL/g; the average Koc value was 7 mL/g (very high mobility). The average pyroxsulam sulfonic acid adsorption Kd and K_{oc} values were <LOD (very high mobility). Based on the average adsorption coefficients ($K_{oc\text{-}ads}$ values) for the four soils used in this study the pyroxsulam transformation products are expected to exhibit moderate to very high mobility in mineral soils according to the classification criteria of McCall *et al.*

Field Dissipation

Field dissipation of an oil dispersion formulation containing 4.7% pyroxsulam (w/w) and cloquintocet safener under Canadian prairie field conditions was conducted in bare ground plots at 4 sites at rates which were 1.7 times those proposed for the Australian use pattern. Soil samples were collected over periods of up to 462 days post-application. Initial pyroxsulam concentrations dissipated generally dissipated steadily from the maximum concentrations with residues primarily in the 15 or 30 cm soil profiles. The major transformation products detected were 7-hydroxypyroxsulam, found at all sites, 6-chloro-7 -hydroxy-pyroxsulam at three sites plus 5-hydroxy-pyroxsulam at one site. These were found primarily in the 15 or 30 cm soil profiles with some detections of the 7-hydroxy metabolite in the 30-45 and 45-60 cm layers.

While the 7-hydroxy-pyroxsulam was present in all the tested soils, the maximum levels (as percentages of the initial pyroxsulam concentrations) were each less than 10% in three of the soils with no metabolite remaining by day 92 in all cases. In the fourth soil, the maximum concentration was 45% of the initial parent concentration 68 days after treatment. At the study's end (162 days after treatment), 12% of the initial parent concentration remained. The maximum 6-chloro-7 -hydroxy-pyroxsulam concentration was 7% (again of the initial pyroxsulam concentration) at day 403 and remaining at 6% at day 462. At the remaining two soils, levels of this metabolite were transient or sporadic and did not exceed 3% of the initial pyroxsulam concentrations. The 5-hydroxy-pyroxsulam occurred on one occasion only, at 2% of the initial pyroxsulam concentration, 7 days after treatment.

Under the tested field conditions, pyroxsulam was found to have a DT50 ranging from 5 to 29 days and a DT90 ranging from 15 to 239 days, calculated using simple first order kinetics. The major transformation product 7-hydroxy-pyroxsulam has a DT50 ranging from 3 to 97 days and a DT90 of 10 to 321 days. A DT50 could only be calculated for 6-chloro-7-hydroxy-pyroxsulam at one site as 84 days with a DT90 of 279 days.

Soil Accumulation

Modelled soil accumulation over a 10 year period indicated no significant yearly carryover of pyroxsulam was expected to occur at the proposed rate and single annual application.

Environmental Effects

Avian

Six avian studies were presented for assessment. Pyroxsulam was practically nontoxic (LD50 > 2000 mg/kg body weight) to the bobwhite quail *(Colinus virginianus)* with a 14 day acute oral LD50 estimated as > 2105 mg pyroxsulam/kg bw and also practically non-toxic to the mallard duck *(Anas platyrhynchos)* with a 14 day LD50 of >2030 mg pyroxsulam/kg bw. There were no compound related toxicity effects (survival or sublethal) in either of these studies. The subacute dietary toxicity of pyroxsulam to bobwhite quail was assessed over 8 days. There were no compoundrelated toxicity effects (survival or sublethal) during this period and the 8 day LC50 was >4883 mg pyroxsulam/kg feed (measured). Subacute dietary exposure of mallard duck to pyroxsulam showed no compound related toxicity effects (survival or sublethal) during a similar 8 day study and the 8 day LC50 was >4840 mg pyroxsulam/kg feed. Pyroxsulam is classified as practically non-toxic to bobwhite quail and mallard ducks on a subacute dietary exposure basis using the nominal concentration (LC50 > 5000 mg/kg feed). A one one-generation reproductive toxicity of pyroxsulam to groups of mallard duck was

assessed over 22 weeks. The reproductive NOEC observed during this study was 500 mg pyroxsulam/kg feed (based on weights of the day 14 ducklings and of the body weights of female ducks at test termination). Although *post-mortem* examinations revealed several birds with regressed or underdeveloped gonads that possibly affected their reproductive activity, the frequency of these observations was low. Also assessed was a one-generation reproductive toxicity of pyroxsulam to bobwhite quail over a period of approximately 26 weeks. No treatment related mortality was observed nor were any significant differences detected in any of the reproductive performance variables when compared to the control. Consequently, the NOEC for effects on reproductive parameters was set at 1142 mg pyroxsulam/kg feed.

Fish

Four acute fish studies were presented for assessment. Two were with pyroxsulam, one with 7-hydroxy-pyroxsulam and one with the ATSA metabolite. An early life stage toxicity study of pyroxsulam to the fathead minnow was also presented.

In a 96-h acute toxicity limit study, juvenile rainbow trout *(Oncorhynchus mykiss)* exposed to pyroxsulam showed no mortality or sublethal effects and the 96 hour LC50 was set a >87 mg pyroxsulam/L. When fathead minnow *(Pimephales promelas)* were exposed to pyroxsulam for 96 hours, no mortality or sub-lethal effects were observed and the 96 h LC50 was set at >94.4 mg pyroxsulam/L. Based on the results of these studies, pyroxsulam would be classified as, at worst, slightly toxic (i.e. 10 < 96 hour LC50 or EC50 ~ 100 mg/L) to fish.

When rainbow trout were exposed to the 7-hydroxy-pyroxsulam metabolite for 96 hours, there were no compound related effects (survival or sub-lethal) observed and the 96 hour LC50 was set at >120 mg 7-hydroxy-pyroxsulam/L with this result showing it would be classified as practically non-toxic to rainbow trout (LC50 or EC50> 100 mglL). In a 96 h acute toxicity limit study, rainbow trout were exposed to A TSA, a pyroxsulam metabolite. There were no compound related effects (survival or sub-lethal) noted and the 96 hour LC50 was set at> 119 mg A TSNL and it is classified as practically non-toxic to rainbow trout (LC50 > 100 mglL).

The 40-day chronic toxicity ofpyroxsulam) to early life stages of the fathead minnow was studied under flow-through conditions. No treatment related effects on the number of embryos hatched, time to hatch, mortality of embryos, larvae, and juveniles and measurement of growth were observed. Small numbers of sub-lethal effects were seen from day 2 through to day 7 of the exposure in both the controls (in 2 of 99 hatched embryos at day 7) and the test concentrations (in 0 of 96 to 5 of 98 hatched at day 7). Based on mortality and sub-lethal effects, the 40 day NOEC was set at 10.1 mg pyroxsulam/L and pyroxsulam is classified as very slightly chronically toxic to fathead minnow (NOEC >1 mg/L).

Aquatic Invertebrates

There were six aquatic invertebrate studies presented for assessment - four with *Daphnia magna* and two with the larvae of the midge, *Chironomus riparius.* These acute and chronic studies addressed the toxicity of pyroxsulam and the pyroxsulam metabolites, 7 -hydroxy-pyroxsulam and ATSA, to aquatic invertebrates.

The 48 h acute static toxicity of pyroxsulam to *Daphnia magna* was tested for effects on daphnid mortality (immobilisation) and other sub-lethal effects. The 48 h EC50 was set at > 100 mg pyroxsulam/L and pyroxsulam is classified as practically nontoxic to *Daphnia magna* (EC50 > 100 mg/L). When daphnia were exposed to 7hydroxy-pyroxsulam for 48 hours, no mortality/immobilization or other sub-lethal effects were observed and the 48 hour EC50 for immobilisation was >99 mg 7-hydroxy metabolite of pyroxsulam/L and the 7-hydroxy metabolite of pyroxsulam is as, at worst, slightly toxic to the daphnid, *D. magna,* (10 < EC50 < 100 mglL). A similar result was observed when daphnia were exposed to the pyroxsulam metabolite, ATSA and the 48 hour EC50 (immobilisation or sub-lethal effects) was set at > 121 mg A TSNL. The A TSA metabolite of pyroxsulam is classified as practically non-toxic to *D. magna* instars (48 hour EC50 >100 mg /L). The 21-daychronic toxicity of pyroxsulam to *Daphnia magna* was studied under static renewal conditions, resulting in a 21 day NOEC

for mortality, growth and reproduction of pyroxsulam as the technical grade material of 10.4 mg pyroxsulam/L, and it is classified as very slightly chronically toxic to *D. magna* (NOEC > 1 mg/L). There was evidence of an effect on daphnid growth at one test concentration but as no dose relationship was present, the effect was deemed biologically insignificant.

The 28 day chronic midge spiked water sediment exposure study of pyroxsulam (98% purity) to first ins tars of the midge, *Chironomus riparius,* was studied under static conditions without renewal with a dose range of 0 to 100 mg pyroxsulam/L of the overlying water column. Emergence in all treatments was greater than 50%, and the 28-day EC50 value for combined male and female midge emergence is > 100 mg pyroxsulam/L (nominal). The NOEC for numbers of males emerged was set at 100 mg pyroxsulam/L and the NOEC for the numbers of females emerged set at 50 mg pyroxsulam/L (both NOECs are nominal concentrations). The 28-day NOECs for both male and female development rates were both set at 100 mg pyroxsulam/L. Pyroxsulam is classified as very slightly chronically toxic to C. *riparius* larvae (NOEC > 1 mg/L). The 28 day chronic midge water sediment study of the 7-hydroxy metabolite of pyroxsulam to *Chironomus riparius* instars, under static conditions without renewal, was also studied. No concentration resulted in >50% reduction in either emergence numbers or development rate and the 28-day EC50 value for emergence and development was empirically set at > 120 mg 7-hydroxy metabolite of pyroxsulam, the highest nominal concentration tested. The 28 day NOEC for combined male and female emergence numbers and the 28' day NOEC for male development rates were each set at 120 mg 7-hydroxy-pyroxsu1am/L with the 28 day NOEC for female development rates set at 30 mg 7-hydroxy-pyroxsulam/L. The 7hydroxy metabolite of pyroxsulam is considered very slightly chronically toxic to the instars of the midge, *Chironomus riparius* (NOEC > 1 mg/L).

Algae

There were eleven algal studies assessed. Four were with pyroxsulam and the remainder, all conducted with the freshwater green alga, *Pseudokirchneriella subcapitata,* with pyroxsulam metabolites. The toxicity of pyroxsulam was also tested to the freshwater green alga, the freshwater bluegreen alga, *Anabaena jlosaquae,* the freshwater diatom, *Navicula pelliculosa,* and the saltwater diatom, *Skeletonema costatum.*

The most sensitive alga was the freshwater green alga where inhibition after 72 hours of mean specific growth rate relative to controls ranged from 3% at 0.0261 mg/L to 90% at 2.04 mg/L. The inhibition of biomass relative to controls ranged from 13% at 0.0261 mg/L to 99% at 2.04 mg/L. After 96 hours, inhibition of cell density relative to controls ranged from 15% at 0.0261 mg/L to 98% at 2.04 mg/L. The 72 hour mean specific growth rate, ErC50, was calculated as 0.695 mg pyroxsulam/L, the 72 hour biomass (area under the curve) EbC50 was 0.111 mg pyroxsulam/L and the 96 hour cell density EC50 was 0.135 mg pyroxsulam/L. Based on the results of this study, pyroxsulam is classified as highly toxic to *Pseudokirchneriella subcapitata* ($0.1 < EC50 \leq 1$ mg/L). While the study with the blue green alga was classified as invalid because of doubts as to whether the aggregates which the alga forms were effectively broken up for counting and whether logarithmic growth was truly achieved, the 0-72 hour mean specific growth rate, biomass and cell density results were, respectively, 41, 22 and 11 mg pyroxsulam/L. Despite the validity issues, such values provide an indication of slight toxicity ($10 < EC50 \leq 100$ mg/L). The study with the freshwater diatom was also classified as invalid because of uncertainties relating to the successful disruption of aggregates/filaments of the *Navicula pelliculosa,* the use of a smaller number of replicates than required by the US EPA, and the lack of inhibitory effects at all but the highest (10 mg/L) exposure concentration and the lack of sustained exponential growth in the solvent control. The reported 0-72 hour ErC50, EbC50 and 96 hour cell density EC50 values were, respectively, 6.9, 5.8 and 7.0 mg pyroxsulam/L. Such values are indicative of moderate toxicity ($1 < EC50 \leq 10$ mg/L). Because of the uncertainty associated with this study and its calculated endpoints, pyroxsulam's toxicity to *Navicula pelliculosa* has not been conclusively demonstrated as

likely to be less than to *Pseudoldrchnerialla subcapitata* and it was recommended that the *Navicula* study be repeated. When the saltwater diatom was exposed to pyroxsulam for 120 hours, inhibition relative to controls ranged from 1 % at 3.4 mg pyroxsulam/L to 58% at 105 mg pyroxsulam/L for mean specific growth rate, from 1 % at 3.40 mg pyroxsulam/L to 93% at 105 mg pyroxsulam/L for biomass, and from 4% at 3.40 mL to 90% at 105 mg pyroxsulam/L for cell density. The 120hour EC50s for mean specific growth rate, biomass and cell density were 84.3, 13.9 and 13.1 mg pyroxsulam/L, respectively. Pyroxsulam is slightly toxic to *Skeletonema costatum* ($10 < EC50 \leq 100$ mg/L).

Toxicity of the 5-hydroxy-, 7-hydroxy-, 5,7-di-hydroxy-, and 6-chloro-7-hydroxypyroxsulains, ATSA, ADTP and the sulfinic acid metabolite to the freshwater green alga were tested. 0-72 hour ErC50 and EbC50 and 96 hour cell density EC50 values were, respectively, ~36, ~14.4 and ~17.1 mg pyroxsulam/L. These results show the metabolites to be, at worst, slightly toxic to pyroxsulam ($10 < EC50 \leq 100$ mg/L).

Duckweed

Nine studies on the toxicity of pyroxsulam and its metabolites to duckweed *(Lemna gibba)* were presented. Two of these were for pyroxsulam exposures (7 days and for 1 and 3 days) with the remainder for the 5-hydroxy-, 7-hydroxy-, 5,7-di-hydroxy- and 6-chloro- 7 -hydroxy-pyroxsulams and the ATSA, ADTP and sulfinic acid metabolites. Three duckweed growth parameters were determined, frond number (over seven days except for the 1 and 3 day exposure study), mean specific growth rates and biomass (as day 7 dried frond weight) using a dilution or medium control and a solvent (dimethylformamide) control.

When exposed for 7 days, the data generated indicated that, for all three growth parameters, the means of concentrations ~1.34 µg pyroxsulam/L were statistically significantly different from the control means and dose effects were apparent. The EC50 values determined for mean specific growth rate, biomass and frond number were, respectively, 3.88, 3.82 and 2.57 µg pyroxsulam/L, and pyroxsulam is classified as very highly toxic to the duckweed, *Lemna gibba.* In the one and three days' exposure, the EC50 values for mean specific growth rate, biomass and frond number were for the one day's exposure, respectively, >31.3, >31.3 and 37.3 µg pyroxsulam/L. For the three days' exposure, the respective values were, 15.7, 7.3 and 3.7 µg pyroxsulam/L. These results, from non-guideline exposure times and therefore not usable in the risk assessment, confirm the very high toxicity of pyroxsulam to duckweed.

The 7 day ErC50, EbC50 and frond count EC50 results for the metabolites were all approximately a thousand fold higher, being respectively, ≥ 4.0, ≥ 2.1 and ≥ 1.8 mg/L, with such results indicative of the metabolites being at worst, moderately toxic to duckweed.

Terrestrial Invertebrates

There was one combined honeybee oral and contact toxicity study presented together with five earthworm studies. These latter were made up of four acute toxicity studies (pyroxsulam, 5-hydroxy-pyroxsulam, 7 -hydroxy-pyroxsulam and 6-chloro-7hydroxy-pyroxsulam) and one reproduction study with the 6-chloro-7-hydroxypyroxsulam metabolite.

Pyroxsulam, via the oral or contact routes of exposure, was classified as very slightly toxic (LC50 and LD50 > 100 /µg/bee) to the honey bee *(Apis mellifera)* with acute 48 hour LD50 values for acute oral and contact toxicity being, respectively, >107.4 and > 100 µg pyroxsulam/bee. In the oral toxicity study, no mortality or sublethal effects were observed in any of the control or treatment groups over 48 hours while in the contact toxicity study percentage mortalities in the negative control, solvent control and 100 µg pyroxsulam/bee treatment groups were 2, 0 and 0, respectively, after 48 hours. No sublethal effects were observed.

In a 14 day acute toxicity study, earthworms *(Eisenia foetida)* were exposed to pyroxsulam at 0 and 10,000 mg pyroxsulam/kg dry weight of artificial soil. Mortalities and sublethal effects apart from weight change were not observed in the either the control or pyroxsulam-exposed earthworms over the 14 day exposure period. The 14 day LC50 was >10,000 (nominal) mg

pyroxsulam/kg dry weight (dw) artificial soil, which results in pyroxsulam being rated as very slightly toxic (LC50 > 1000 mglkg soil dry weight) to earthworm survival. When earthworms were exposed to the 5-hydroxy metabolite ofpyroxsulam for 14 days at 0 to 1000 (nominal) mg 5-hydroxy metabolite of pyroxsulam/kg dry weight of artificial soil substrate, mortalities and sublethal effects were not observed in the exposed earthworms and 14 day LC50 and EC50 were both set as > 1000 mg 5-hydroxy-pyroxsulamlkg soil (dw). The 5-hydroxy metabolite is classified as very slightly toxic to earthworms (LC50 > 1000 mg/kg dry soil). For the acute studies with the 7-hydroxy and 6-chloro-7hydroxy metabolites, similar results as for the 5-hydroxy-pyroxsulam study were obtained. Both metabolites had 14 day LC50 values of > 1000 mg metabolite/kg dry soil and, consequently, both are rated as very slightly toxic to earthworms. In a 56 day reproduction study, earthworms were exposed to the 6-chloro-7-hydroxy metabolite of pyroxsulam at concentrations of 0 to 130 µg/kg dry weight of artificial soil substrate. Adult earthworm mortality and signs of toxicity were determined after 28 days and the numbers of juveniles produced after a further 28 days determined. There were several mortalities in the control group and most treatment groups during the 28-day adult exposure period, but there was not a dose-response pattern and the mortalities were considered to be incidental and not treatment related. No abnormalities were observed among juveniles collected from the control and treatment groups and the mean numbers of juveniles produced were not significantly reduced relative to the control mean at any test concentration. The 56 day NOEC was set as 65 µg 6-chloro-7-hydroxy-pyroxsulam/kg dry soil, based on the numbers of juveniles produced. This was on the basis of the 130 µg 6-chloro-7 -hydroxy-pyroxsulam/kg dry soil value appearing a rather large difference compared to control: on the order of 30% reduction in juveniles. Although not statistically significant, such a reduction is likely biologically significant.

Terrestrial Plants

There were three terrestrial plant studies presented for assessment. The first of these considered the herbicidal activity of pyroxsulam and a number of its soil metabolites in a post-emergence screening study. Pyroxsulam showed the highest level of herbicidal activity with the metabolites, demonstrating no significant herbicidal activity. The effect of pyroxsulam, as formulated product, on the vegetative vigour of 4 monocotyledon and 6 dicotyledon crops was studied under greenhouse conditions. In some instances, NOECs were greater than ER25 values, possibly attributable to large variability amon,gst replicates. This has resulted in the most sensitive endpoint being taken as the NOEC/ER05 of 0.035 g pyroxsulam/ha for oilseed rape shoot height. The effect of pyroxsulam, again as a formulated material, on seedling emergence was also examined with the same plant species. The NOEC values were again, on occasion, reported as greater than the ER25 values and the sugarbeet NOEC/ER05 value of 0.032 g pyroxsulam/ha has been identified as the most sensitive endpoint (shoot height).

Environmental risk summary

Birds

Exposure at the time of application could occur by birds and mammals eating contaminated insects or by direct contact with the spray or indirect contact with treated vegetation. Estimated concentrations resulting in a diet exclusively based on such exposure ranged between 0.2 and 3.2 mg pyroxsulam/kg feed. These worst case concentrations are well below the 5-day dietary LC50 values for two bird species. Consequently, the proposed use is not likely to present an acute or dietary risk to birds .

Aquatic organisms

Contamination of a shallow (15 cm deep), static waterbody with direct overspray at the maximum application rate of 15 g pyroxsulam/ha is calculated to give a notional concentration in the water of 10 µg pyroxsulam/L and 30 µg cloquintocet-mexyl/L. Based on the relevant ecotoxicity endpoints, acute risk to fish, the water flea, the algae species tested, acute risk is acceptable. Only for duckweed (aquatic plants) is unacceptable risk indicated. With a 10% overspray, the risk to duckweed is mitigable. A further refinement of risk to duckweed from

spray drift of pyroxsulame is possible from use of the more realistic Ganzelmeier spray drift values from ground application. The results of this modelling, plus addition of the standard label statement not to apply under conditions which could be expected to result in spraydrift onto waterbodies, indicate that there is expected to acceptable, acute aquatic risk to aquatic plants from spray drift when the draft label's proposed 5 metre buffer zone is complied with. Based on the chronic aquatic toxicity endpoints available for pyroxsulam, chronic risk is shown to be acceptable provided the proposed label requirements are adhered to.

Because pyroxsulam can be expected to show some mobility and persistence in the environment, there is a potential for both active constituents to enter aquatic habitats in runoff water as a result of their presence in the runoff from treated land. A simple modelling of such runoff indicates unacceptable risk to fish and daphnia. Mitigation of this risk based on a more realistic runoff scenario, one cycle of adsorption of pyroxsulam to the soil and crop interception shows that aquatic risk from runoff from the proposed use pattern is expected to be acceptable. Risk to groundwater is not anticipated from the proposed use pattern.

Non-target invertebrates

The proposed registration of *CRUSADER* at a maximum use rate of 15 g pyroxsulam/ha use is not expected to present unacceptable risks to bees or earthworms. This is based on studies showing that relevant toxicity endpoints were well below the concentrations tested which showed no adverse effects.

Native vegetation

Pyroxsulam could be expected to present a risk to native plants when used as proposed, consistent with its herbicidal properties as a result of off-target spraydrift. While modelling using the Ganzelmeier drift tables indicated that a 15 metre spraydrift buffer would be desirable for protection of native plants, the conservative assumptions used in reaching this decision lead to the conclusion that with adherence to the modified label's "Protection of Crops, Native and Other Non-target Plants" statement that application not take place under conditions which could allow spray to drift onto nearby native plants, risk would be acceptable.

Recommendation on spray quality

Because the conclusions relating to acceptability of aquatic and terrestrial risk are based on use of application of *CRUSADER* as a medium quality spray, the recommendation has been made that the product label should refer to the use of a medium quality spray.

Conclusion

The proposed use of the *CRUSADER* is not likely to present either an acute or dietary risk to birds ingesting residues on plants or insects. Risk to aquatic plants is expected to be acceptable provided a medium quality spray is applied and there are appropriate amendments made to the Protection of Wildlife, Fish, Crustaceans and Environment statement. Similarly, risk to native and non-target terrestrial plants is expected to be acceptable with the use of the medium quality spray and adherence to the Protection of Crops, Native and Other Non-target Plants as amended.

In order to be satisfied that the proposed use of *CRUSADER* will not lead to an unintended effect that is harmful to animals, plants or the environment at the proposed rate and following good agricultural practice, DEWHA recommends that the draft label's Protection of Crops, Native and Other Non-target Plants statement be amended to refer specifically to native and other non-target plants, that the draft label's "Application" statement be amended to state that

medium quality spray should be used; and that the draft label's Protection of Wildlife, Fish, Crustaceans and Environment statements be amended to remove endorsements, ambiguities and omissions currently present.

Acceptance of these recommendations allows DEWHA to recommend that the APVMA be satisfied that the proposed use of *CRUSADER* would not be likely to have an unintended effect that is harmful to animals, plants, things or the environment.

A comprehensive evaluation program was conducted in all Australian States where wheat is a major crop (192 trials) and Canadian provinces (57 trials), to establish the efficacy of *CRUSADER*, alone and in combination with a range of tank mix partners, for the control/suppression of important grass and broadleaf weeds. The objectives of the program were to determine the efficacy of *CRUSADER* on target weeds, to evaluate the effects of *CRUSADER* on the target crop (wheat), and to determine the plant-back safety of rotation crops and pasture species. The replicated trials were conducted and reported according to an appropriately high standard of scientific investigation, including the use of statistical designs and analyses that were sufficiently robust to determine meaningful treatment effects.

Overall, the performance of *CRUSADER*, which was always applied to wheat from the 3-leaf stage on, was consistent in terms of both efficacy and crop selectivity (safety) across the experimental sites and years. At the rate recommended (15 g a.i./ha or 500 mL of product per ha), this herbicide provided good (80-90%) to excellent control (> 90%) of wild oats, phalaris and bromegrass, and strong suppression (generally 75-80% control) of rye grass and silvergrass. When *CRUSADER* was applied to broadleaf weeds, control was excellent for bedstraw, volunteer crops (field pea, chickpea and canola), Indian hedge mustard, buckwheat and turnip weed, while it achieved good (80-90%) control with several other common broadleaf weeds. Many troublesome weed populations, such as capeweed, sowthistle, prickly lettuce and deadnettle, were controlled effectively with *CRUSADER* tank mixed with MCPA, Lontrel or other herbicide combinations. The effect of *CRUSADER* on grass weeds was not diminished by tank mixing with broad1eaf partner herbicides. The trials and treatments covered adequately the range of weeds that are mentioned in the draft label.

Likewise, the comprehensive program that was conducted to determine the selectivity of *CRUSADER*, when used as a post-emergence spray applied to wheat, produced consistent results. In most trials, at the recommended rate of *CRUSADER* or its analogues to bread wheat varieties, there was an acceptable level of early setback (i.e., mild symptoms of early injury, insufficient to reduce grain yields in a weed-free situation). The data justified the recommendation not to use *CRUSADER* on durum wheat varieties due to unacceptable levels of early injury.

With 2 exceptions (maize and soybean), the Australian plant-back crop safety trials covered all of the plant-back crops listed on the draft label.

The data presented demonstrate that *CRUSADER* will be effective in controlling/suppressing the weed species claimed and will be safe to use over the target crop wheat (excluding durum varieties) when used according to the proposed label instructions.

Summary of supporting information

The applicant, Dow Agrosciences Australia Limited, has applied to the APVMA to register the product, *CRUSADER*, for the post-emergence control of certain grass and broadleaf weeds in wheat. The product is an oil dispersible formulation containing 30 g/L of a new active ingredient (pyroxsulam) + 90 g/L of cloquintocet-mexyl, a herbicidal safener that is already contained in other herbicide products registered by APVMA. Pyroxsulam is a Group B (ALS inhibitor) herbicide.

Overall, the quality of the information package was excellent. In the summary, tables and

appendices, the information was presented in a manner that was uniformly accurate, comprehensive and clear. In the appendices, each of the trials was comprehensively described and the overall results from each set of trials were summarised, adequately and accurately.

Trial data assessment

Experimental program

The evaluation program submitted by the applicant, Dow AgroSciences, comprised descriptions and summaries from ~250 trials conducted by Dow AgroSciences or their contracted agent. With the exception of a group of 57 trials from the cropping areas of Canada, all of the reported trials were conducted in Australia. The trials were sited in commercial wheat fields throughout Queensland, NSW, Victoria, South Australia and Western Australia.

The main purposes of the program were to determine:

- The efficacy of *CRUSADER* (and/or earlier formulations of pyroxsulam) in controlling weeds, both grass and broadleaf types, when the product was applied at a range of rates, alone or in combination with various tank-mix partners. The trials covered a range of pyroxsulam formulations, which produced similar results at equivalent rates of the active ingredient. Either the recommended rate of pyroxsulam (*CRUSADER* @ 15 g active ingredient (a.i.) per ha) or a slightly higher rate (*CRUSADER* @ 18.75 g a.i./ha) was always included. All of the trials contained an untreated control (nil herbicide) and most included commercial standard herbicides (notably iodosulfuron; mesosulfuron) at their recommended label rates .
- The level of safety (or selectivity) to the target crop (wheat). Several weed-free trials were undertaken to assess the phytotoxicity effects, if any, of pyroxsulam on the target crop. An untreated control (nil herbicide) and commercial standard herbicides were included in the range of treatments.
- Plant-back safety of pyroxsulam to rotation crops, sown at various times after the initial application of the herbicide to wheat. The rotation crops included cereals (oats, barley, sorghum), legume crops (chickpea, lentil, lupin, faba bean, vetch), oilseeds (cotton, sunflower, canola) and pasture species (lucerne, serradella, subterranean clover, annual medic).

In addition, a replicated greenhouse experiment was undertaken to determine the rain-fastness of *CRUSADER*. A Technical Profile document was included in the submission to provide technical information on the chemistry and behaviour of pyroxsulam.

In each of the trials, the design of the experiment (generally a randomised complete block - RCB), the selection of the treatments and rates of the herbicides (including a nil treatment), the choice of pyroxsulam/standard herbicides and tank mixes, the level of replication (4 replications), the parameters measured (visual assessment and counts for the control of weeds, visual ratings for wheat crop injury, wheat grain yields) and the statistical analyses conducted, were all adequate and appropriate in terms of evaluating the efficacy and safety of *CRUSADER* and its pyroxsulam analogues. Tables of means were shown for observations on the treatments in each experiment, and mean separation was achieved by the use of letters to define similar/dissimilar means using a test at the appropriate probability level (P=0.05).

Analysis of data and interpretation

Overall, the performance of *CRUSADER*, which was always applied to wheat from the 3-leaf stage on, was consistent in terms of both efficacy and crop selectivity (safety) across the experimental sites and years. At the rate recommended (15g a.i./ha or 500mL of

product per ha), this herbicide provided good (80-90%) to excellent control (> 90%) of wild oats, phalaris and bromegrass, and strong suppression (generally 75-80% control) of rye grass and silvergrass. When *CRUSADER* was applied to broadleaf weeds, control was excellent for bedstraw, volunteer crops (field pea, chickpea and canola), Indian hedge mustard, buckwheat and turnip weed, while it achieved good (80-90%) control with several other common broadleaf weeds. Many troublesome weed populations, such as capeweed, sowthistle, prickly lettuce and deadnettle, were controlled effectively with *CRUSADER* tank mixed with MCPA, Lontrel or other herbicide combinations. The effect of *CRUSADER* on grass weeds was not diminished by tank mixing with broadleaf partner herbicides. The trials and treatments covered adequately the range of weeds that are mentioned in the draft label.

Likewise, the comprehensive program that was conducted to determine the selectivity of *CRUSADER*, when used as a post-emergent spray applied to wheat, produced consistent results. In most trials, at the recommended rate of *CRUSADER* or its analogues, there was an acceptable level of early setback to wheat, generally rated at 0-15% injury on the linear scale that was used to rate the extent (frequency and severity) of injury to the wheat seedlings. By the time of harvest, this level of injury was acceptable in that wheat yields from the treated plots were the statistical and absolute equivalent of the yields recorded from untreated, weed-free plots; yields from weedy plots were 15-20% lower, thereby justifying the use of herbicide. Tank mixes of *CRUSADER* with partner broadleaf herbicides had no effect on the safety of use of the herbicide on wheat.

There were 2 anomalies to this general pattern of selectivity results. First, in a trial conducted at Toowoomba, some wheat varieties including 4 durum varieties were sensitive at an early stage to the recommended rate (15g a.i./ha) of pyroxsulam and especially so to the 30g a.i/ha rate; however, at these rates there were no statistical yield penalties on the herbicide treated plots, even in the case of the durum varieties. Second, in an AC&RS trial conducted at York (W A), early injury levels were about 25% as they were with iodosulfuron (Hussar, the commercial standard); the high level was attributed to heavy rain and leaching changing the normal uptake of herbicide by wheat roots. These examples illustrate that, under certain conditions, adverse experiences can occur with these persistent Group B herbicides. However, the incidence of a greater than acceptable level of wheat damage was low and in line with the level occurring with iodosulfuron, the commercial standard. In addition, as a result of these experiences, the applicant has guarded against their commercial occurrence with warnings on the draft label for *CRUSADER* about spray overlap and the application of the herbicide to durum varieties (not recommended).

In several trials, the adjuvants Uptake (oil) and BS-I000 (surfactant) were compared. Generally there was no great difference in herbicide performance between these two materials but the latter is the preferred adjuvant in tank mixes.

The Australian plant-back crop safety trials covered all of the plant-back crops listed on the draft label except maize. In this set of trials, there was only one where an annual medic (snail medic) occurred but lucerne *(Medicago sativa)* occurred in several trials. The applicant has requested that soybean be added to the list of plant-back crops on the label, since there is sufficient information available from Canadian trials to warrant this inclusion. One trial conducted at Halbury in South Australia pyroxsulam @ 18.75 g a.i./ha produced injury levels to rotational crops that was rated of borderline acceptability (15-30%) - the trial notes indicated that herbicide decomposition may have been slower than normal due to soil (sand over alkaline clay) and climatic conditions (heavy rain promoting leaching of the herbicide to the clay zone followed by drought slowing microbial decomposition).

Specific label claims

The draft label for the use of *CRUSADER* claims that the product is capable of providing adequate control of a specified list of weeds (including wild oats, brome grass, annual phalaris, bedstraw, turnip weed, and volunteer crops) and suppressing a number of additional weeds (annual ryegrass, silvergrass, legume crop and pasture seedlings in cereal crops). The Directions for Use table goes on to specify recommendations for tank mixing with specific broadleaf herbicides to improve the control of weeds such as capeweed, wild radish, climbing buckwheat and milk thistle. For application alone or in combination with herbicide partners, the rate of pyroxsulam recommended is 15g a.i/ha (500 mL of *CRUSADER* per ha).

All of these claims are supported by the results from the Australian efficacy trials. Likewise, the data from the Australian trials supported the use of Uptake Spraying Oil at 0.5% v/v when *CRUSADER* was used alone and BS-1000 at 0.25% when *CRUSADER* was used with tank mixes.

Crop safety

Considerable care was taken in the experimentation phase to determine the safety of *CRUSADER* when used on the target crop, wheat, and to determine the appropriate plant-back intervals for rotation crops. Such care is warranted for persistent Group B herbicides. From the results of the trials, *CRUSADER* does cause some injury to wheat at an early stage after application. However, the trials demonstrated that the level of injury was, with rare exceptions, within the acceptable range and insufficient to depress grain yield. This was only slightly more than the commercial standard iodosulfuron. Sufficient data were presented to justify the safe use of *CRUSADER* generally on bread wheat varieties, subject to the use of a recommended non-ionic adjuvant when tank mixed and to the restraints that apply to stressed wheat, which are mentioned on the draft label.

The recommendation that the product not be applied to durum wheat varieties (those derived from crosses with *Triticum durum)* is conservative but justified by the trial results.

Sufficient data were presented to justify the recommended plant-back periods that apply to rotation crops and pastures.

POISON

KEEP OUT OF REACH OF CHILDREN

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Crusader*

Herbicide

ACTIVE CONSTITUENTS: **3**0 g/L PYROXSULAM
90 g/L CLOQUINTOCET-MEXYL

SOLVENT: 750 g/L LIQUID HYDROCARBON

GROUP B HERBICIDE

An oil dispersible liquid formulation for post-emergence control of grass and broadleaf weeds in wheat, excluding durum varieties, as specified in the Directions for Use.

IMPORTANT: READ THIS BOOKLET BEFORE USE.

Dow AgroSciences Australia Limited
A.B.N. 24 003 771 659
20 Rodborough Road
FRENCHS FOREST NSW 2086
www.dowagrosciences.com.au
CUSTOMER SERVICE TOLL FREE: **1-800 700 096**

* Trademark of Dow AgroSciences

GMID:

DIRECTIONS FOR USE: ***For application to wheat only (excluding durum varieties); from 3 leaf up to 1st node of the crop*****.**

RESTRAINTS

DO NOT apply to crops or weeds which may be stressed due to prolonged periods of extreme cold, moisture stress (water-logging or drought) or previous herbicide treatment, as crop damage or reduced levels of control may result (see crop safety warning below).
DO NOT spray if rain is likely to occur within 6 hours.
DO NOT apply later than the 1st node stage of the crops.
DO NOT apply by air.
DO NOT apply to durum varieties of wheat.
DO NOT double overlap or double spray wheat.

Table 1. Grass weed control

Weeds	Weed stage	Rate/ha	Critical Comments
Wild oats (*Avena* spp.), Brome grass (*Bromus diandrus*), Phalaris spp., Annual ryegrass (*Lolium rigidum*)- suppression	1-3 leaf (pre-tillering)	**500 mL**	**Always use BS-1000 at 250 mL/100 L.** Weeds may only be suppressed where densities of > 150 plants/m^2 are treated. **Ryegrass suppression**: Weeds may survive treatment, but will usually show reduced growth and seed set.

Table 2. Broadleaf weed control

Weed	Weed stage & size	Rate/ha	Critical Comments
Bedstraw (*Galium tricornutum*)	**Cotyledon - 6 whorl Up to 10 cm**	**500 mL**	**Always use BS-1000 at 250 mL/100 L.** For heavy weed populations (> 50/m^2) use tank-mixes and highest rate of partner herbicide where a range is stated.
Turnip weed (*Rapistrum rugosum*)	**Cotyledon - 4 leaf Up to 10 cm**		
Volunteer crops:			
Canola (*Brassica napus*)	**Cotyledon - 4 leaf Up to 10 cm**		
Chickpea (*Cicer arietinum*)	**Cotyledon - 6 leaf Up to 15 cm**		
Faba bean (*Vicia faba*)	**Cotyledon - 4 leaf Up to 10 cm**		
Field pea (*Pisum sativum*)	**Cotyledon - 6 node Up to 12 cm**		
Lentil (*Lens esculentum*) – suppression	**Cotyledon - 6 leaf Up to 8 cm**		
Lupins (*Lupinus albus*)- suppression	**Cotyledon - 4 leaf Up to 6 cm**		
Medic spp.	**Cotyledon - 4 leaf Up to 8 cm**		
Subclover (*Trifolium subterraneum*) – suppression	**Cotyledon - 4 leaf Up to 5 cm**		
Vetch (*Vicia sativa*) - suppression	**Cotyledon - 4 leaf Up to 10 cm**		

Capeweed (*Arctotheca calendula*)	**Cotyledon - 6 leaf Up to 12 cm**	**500 mL** + 60-120 g of Lontrel* 750 SG + 350 mL MCPA LVE (500 g/L) **or** + 500 mL Bromoxynil/MCPA (200 + 200 g/L) **or** + 500 mL Bromoxynil/MCPA + 40 g Lontrel 750 SG	Where tank-mixes are applied, treat wheat at the labelled growth stage for the partner herbicide. Tankmixes with MCPA LVE at 500 mL/ha must be applied from 5 leaf stage wheat onwards.
Wild radish (*Raphanus raphanistrum*)	**Cotyledon - 4 leaf Up to 15 cm**	**500 mL** + 350 - 500 mL MCPA LVE	
Indian hedge mustard (*Sisymbrium orientale*)	**Cotyledon - 6 leaf Up to 10 cm**		
Climbing buckwheat (*Fallopia convolvulus*)	**Cotyledon - 4 leaf Up to 10 cm**	**500 mL** + 500 mL Hotshot* Herbicide	
Milk thistle (Common Sowthistle) (*Sonchus oleraceus*)		**500mL** + 500 mL Hotshot Herbicide + 500 mL MCPA LVE	

*Trademarks of Dow AgroSciences

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

HARVEST WITHHOLDING PERIOD

WHEAT: Not required when used as directed.
When using *CRUSADER* Herbicide in a tank mix with another product, observe the Harvest Withholding Period of the other product.

STOCKFOOD WITHHOLDING PERIOD

DO NOT GRAZE OR CUT TREATED CROPS FOR STOCK FEED FOR 6 WEEKS AFTER APPLICATION of *CRUSADER* Herbicide. When using *CRUSADER* Herbicide in a tank mix with another product, observe whichever Stockfood Withholding Period is the longer.

CROP SAFETY

Yield is normally unaffected by treatment with *CRUSADER* Herbicide or tankmixes. However, transient stem shortening and crop yellowing may occur. Symptoms may be worse where wheat is stressed, heavy rain/irrigation follows application, crops are grown in alkaline soil conditions, crop has poor root growth, double overlap of spray has occurred or a combination of any or all the above. Where crop stress occurs, a longer period may be required for recovery, especially if the crop is stressed by root or foliar disease, poor nutrition, water logging, drought or cold stress. In severe cases and seasons where a hot, dry spring occurs, flowering may be delayed and yield may be reduced. *CRUSADER* Herbicide has been tested over major commercially grown wheat varieties, but not all of those that may be grown. For information on wheat variety selectivity consult your local reseller or Dow AgroSciences.

GENERAL INSTRUCTIONS

MIXING: *CRUSADER* Herbicide is an oil-based concentrate which may show some separation on storage. Roll, shake or invert the container several times to ensure that *CRUSADER* Herbicide has completely redispersed before measuring to mix. *CRUSADER* Herbicide should be added to the spray tank with simultaneous agitation. If agitation is limited, premix the *CRUSADER* Herbicide in a bucket before adding to the main tank. Once diluted correctly, *CRUSADER* Herbicide remains in suspension. **If tank mixing with other products, the following order should be followed:**

1. Quarter fill the spray tank, maintaining agitation, then:
2. Add *CRUSADER* Herbicide (as described above)
3. Add water to half fill the spray tank
4. Add wettable powders, water dispersible granules or suspension concentrates.
5. Add emulsifiable concentrates.
6. Add BS-1000 when spray tank is half-full.
7. Add water to bring to the final spray volume.

CRUSADER Herbicide should be mixed and sprayed out within 8 hours.

COMPATIBILITY

CRUSADER Herbicide is compatible with the following:
***Broadleaf Herbicides*:** Bromoxynil, bromoxynil-MCPA, MCPA LVE, MCPA amine, Hotshot Herbicide and Lontrel 750 SG Herbicide.
***Adjuvants*:** Always use BS-1000 at 250 mL/100 L spray volume.

APPLICATION

Boom Spraying: Apply *CRUSADER* Herbicide in sufficient water to obtain good coverage and by an accurately calibrated ground rig using a water volume of 50– 100 L/ha. Sprayers should aim to apply a medium quality spray based on BCPC specifications and in accordance with ASAE standard S-572.

CLEANING SPRAY EQUIPMENT

After using *CRUSADER* Herbicide, empty the tank completely and drain the whole system. Thoroughly wash inside the tank using a pressure hose, drain the tank and clean any tank, pump, line and nozzle filters.
Partial Cleaning **(Rinse only -**before using rig to spray barley, triticale and wheat): After cleaning the tank as above, quarter fill the tank with clean water and circulate through the pump, line, hoses and nozzles. Drain and repeat procedure twice.
Complete Cleaning (**Decontamination** -before using rig to spray crops that are susceptible to *CRUSADER* Herbicide. After cleaning the tank as above, quarter fill the tank with clean water and add a liquid alkali detergent (e.g. Surf®, Omo®, Drive®) at 500 mL/100 L water and circulate throughout the system for at least fifteen minutes. Drain the whole system. Then remove filters and nozzles and clean separately. Finaly rinse inside the tank thoroughly using a pressure hose and flush system with clean water and allow to drain. Note: Chlorine-based cleaners are NOT recommended.

Rinse water should be discharged onto a designated disposal area or, if this is unavailable, onto unused land away from desirable plants and their roots and watercourses.

RESISTANT WEEDS WARNING

GROUP	B	HERBICIDE

CRUSADER Herbicide contains a member of the triazolopyrimidine sulfonanilide group of herbicides. The product has the acetolactate synthase (ALS) inhibitor mode of action. For weed resistance management, the product is a Group B herbicide. Some naturally occurring weed biotypes resistant to the product and other Group B 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 will not be controlled by this product or other Group B herbicides. Since the occurrence of resistant weeds is difficult to detect prior to use, Dow AgroSciences accepts no liability for any losses that may result from the

failure of the product to control resistant weeds. Strategies to minimise the risk of herbicide resistance are available. Contact your farm chemical supplier, consultant or local Department of Agriculture.

PRECAUTIONS

RE-ENTRY STATEMENT

Do not allow entry into treated areas until the spray has dried, unless wearing 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 CROPS, NATIVE AND OTHER NON-TARGET PLANTS

Do not apply under weather conditions or from spraying equipment that may cause spray to drift onto nearby native and other non-target plants or susceptible plants/crops, cropping lands or pastures.

Planting Crops Following Use of CRUSADER in Previous Wheat Crop

Planting crops 'dry' without the minimum rainfall (as stated in the table below) increases the risk of injury to susceptible crops. Susceptible crops include but are not limited to those listed in the table below.

Plant-back Periods

Area/State	**Rain or irrigation needed***	**Plant-back Interval**	**Crops to be planted**
SA, Sth NSW, Tas, Vic, and WA (**Winter dominant rainfall areas**) All soils	25 mm rain or more	9 months	Barley, canola, chickpeas, cotton, faba beans, field peas, lentils, lupins, lucerne, maize, medics, oats, ryegrass, sub-clover, sorghum, soybeans, sunflower, vetches, and white clover Note: For all other crops, consult your reseller or local Dow AgroSciences' representative.
Nth NSW and Qld (**Summer dominant rainfall areas**) Vertosol soils	50 mm or more rain or irrigation	6 months	
For all situations, sufficient rainfall to enable soil wetting for at least one week is essential to enable residue breakdown before planting following crops other than wheat.			

*on shallow, duplex or low organic matter soils and/or where rain or irrigation in one fall or over subsequent days is insufficient to thoroughly wet soil to 10 cm for one week or more in the summer to autumn period, extended plant-back times will apply and susceptible crops should not be planted for at least 12 months after application of *CRUSADER* Herbicide. Contact Dow AgroSciences, your farm chemical supplier, consultant or local Department of Agriculture for advice.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

CRUSADER Herbicide is highly toxic to algae and aquatic plants. **DO NOT** contaminate streams, rivers or waterways with chemical or used containers.

DO NOT apply under meteorological conditions or from spraying equipment that could be expected to cause spray drift onto wetlands, natural surface waters, neighbouring properties or other sensitive areas. For ground application, a buffer zone of 5 metres is required between the downwind edge of the boom and the closest edge of waterbodies.

STORAGE AND DISPOSAL

Store in the tightly closed original container in a securely locked place, out of direct sunlight.
DO NOT store near food, feedstuffs, fertilisers or seed.

This container can be recycled if it is clean, dry, free or visible residues and has the ***drum****MUSTER* logo visible. Triple or pressure rinse containers for disposal. Dispose of rinsate by adding it to the spray tank. Do not dispose of undiluted chemicals on site. Wash outside of the container and the cap. Store cleaned container in a sheltered place

with the cap removed. It will then be acceptable for recycling at any ***drum****MUSTER* collection or similar container management program site. The cap should not be replaced but may be taken separately.
If not recycling break, crush or puncture and bury empty packaging in a local authority landfill. If no landfill is available, bury the packaging below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty packaging and product should not be burnt.

SMALL SPILL MANAGEMENT
Wear appropriate clothing whilst cleaning up small spills (see SAFETY DIRECTIONS). Apply absorbent material such as earth, sand, clay granules or cat litter to the spill. Sweep up material and contain in a refuse vessel for disposal. Disposal of the contaminated material must be done in accordance with STATE and/or LOCAL regulations.

SAFETY DIRECTIONS
Harmful if inhaled. May irritant nose and throat. Will irritate the skin. Will damage the eyes. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin.

When opening the container and preparing the spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and a washable hat, elbow length chemical resistant gloves, goggles and disposable mist face mask covering mouth and nose.

If product on skin, immediately wash area with soap and water. If product in eyes, wash it out immediately with water

After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each day's use, wash gloves and contaminated clothing.

FIRST AID
If poisoning occurs contact a doctor or Poisons Information Centre. Phone: *Australia* 13 11 26, New Zealand 0800 764 766

If swallowed do NOT induce vomiting, give a glass of water.

MATERIAL SAFETY DATA SHEET
Additional information is listed in the Material Safety Data Sheet for **CRUSADER HERBICIDE** which is available from Dow AgroSciences on request. Call Customer Service Toll Free on 1-800 700 096 or visit www.dowagrosciences.com.au
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NOTICE
Seller warrants that the product conforms to its chemical description and is reasonably fit for the purposes stated on the label when used in accordance with directions under normal conditions of use. No warranty of merchantability or fitness for a particular purpose, express or implied, extends to the use of the product contrary to label instructions, or under off-label permits not endorsed by Dow AgroSciences, or under abnormal conditions.

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

Barcode for stock identification

*Trademark of Dow AgroSciences, ®Registered Trademark

APVMA Approval No. 61277/xxxx

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.

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