Public Release Summary
on

Evaluation of the new active

FLUMIOXAZIN

in the product

Pledge 500 WG Herbicide

Australian Pesticides and Veterinary Medicines Authority

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FOREWORD

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

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Commonwealth Department of Health and Ageing (Office of Chemical Safety [OCS]), the Department of Environment and Heritage [DEH]} (Chemical Assessment Section), the National Occupational Health and Safety Commission [NOHSC] (previously Worksafe Australia) and State departments of agriculture and environment.

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

The information and technical data required by the APVMA to assess the safety of new chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in the APVMA's publications *Ag Manual: The Requirements Manual for Agricultural Chemicals* and the *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, 1st Floor, 22 Brisbane Avenue, Barton, ACT.

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

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LIST OF ABBREVIATIONS AND ACRONYMS

AC	Active Constituent {source for product manufacture} (previously called the Technical Grade Active Constituent [TGAC])
Ac	Active constituent
ADI	Acceptable Daily Intake (for humans)
A/G	Albumin/Globulin ratio
AHMAC	Australian Health Ministers Advisory Council
Ai	Active ingredient
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase (previously SGPT)
AST	Aspartate Aminotransferase (previously SGOT)
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
BD	Bulk Density (soil)
BUN	Blood Urea Nitrogen
Bw	Bodyweight
D	Day
DAT	Days After Treatment
DEH	Department Of Environment and Heritage
DM	Dry Matter
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
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
FW	Fresh Weight
G	Gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
H	Hour
Ha	Hectare
Hct	Heamatocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
Id	Intradermal
Im	Intramuscular
Ip	Intraperitoneal
IPM	Integrated Pest Management
Iv	Intravenous
in vitro	outside the living body and in an artificial environment
in vivo	Inside the living body of a plant or animal

Kg	Kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LAP	Leucocyte Alkaline Phosphatase
LC_{50}	concentration that kills 50% of the test population of organisms
LC-MS/MS	Liquid Chromatography, Mass Spectroscopy
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LDH	Lactate Dehydrogenases
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Corpuscular Volume / Mean Cell Volume (red blood cells)
Mg	Milligram
ML	Millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
Ng	Nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
NOHSC	National Occupational Health and Safety Commission
OC	Organic Carbon
OCS	Office of Chemical Safety [Therapeutic Goods Administration]
OM	Organic Matter
Po	Oral
Ppb	parts per billion
PHI	Pre-Harvest Interval
PPE	Personal Protective Equipment
Ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
S	Second
Sc	Subcutaneous
SC	Suspension Concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration (OCS is part of this)
TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
mg	Microgram
Vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of *PLEDGE® 500 WG HERBICIDE (PLEDGE®)*, which contains the new active constituent flumioxazin.

Responses to this Public Release Summary (PRS) will be taken into account by the Australian Pesticides and Veterinary Medicines Authority (APVMA), in deciding whether the product should be registered, and in determining appropriate conditions of registration and product labelling.

Copies of full technical evaluation reports on flumioxazin, covering toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA upon request (see order form on last page). They can also viewed at the APVMA Library, located at the APVMA's offices, First Floor, 22 Brisbane Avenue, Barton, ACT.

Written comments should be submitted by **16 January 2004**, and addressed to:

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Applicant
Sumitomo Chemical Australia Pty. Ltd.

Product Details
It is proposed to register *PLEDGE®*, containing 500g/kg flumioxazin, as a wettable powder. The active will be imported and the product formulated and packaged in Australia, in 1 kg, 5 kg and 10 kg packs. The rate of product use is 30 g/ha. *PLEDGE ®* is proposed for registration in all states.

Flumioxazin is a member of diphenyl ether group of herbicides, which inhibits protoporphyrinogen oxidase (PPO). The applicant is seeking registration of the product for the knockdown and control of various grass and broadleaved weeds when mixed with glyphosate or paraquat/diquat herbicides prior to sowing wheat, barley, lupins, canola, cotton, oats, faba beans, field peas, chick peas and lentils. For weed resistance management, flumioxazin belongs to Group G herbicides

PLEDGE® is being marketed as a spray mix partner for certain knock-down herbicides to improve weed brownout, prior to sowing certain crops. It has been shown to improve the control of several "difficult to control" species [e.g. bellvine (*Ipomea plebeia)*, capeweed (*Arctotheca calendula)*, marshmallow (*Malva parviflora)*, sow thistle (*Sonchus oleraceus)*, wireweed (*Polygonum aviculare)* etc.].

Farming systems across Australia have become dependent upon glyphosate for fallow and pre-sowing weed control, thus becoming at risk for the development of herbicide resistance. While paraquat/diquat herbicides have been available as an alternative, their efficacy has been variable. Addition of *PLEDGE*® to paraquat/diquat herbicides improves efficacy, to provide a viable alternative to glyphosate.

Hence this product is likely to have a genuine and important role in weed management in Australian agriculture.

Products containing flumioxazin are registered in the USA, Argentina, Brazil, Paraguay, China, France, South Africa, Zimbabwe, Israel and Japan.

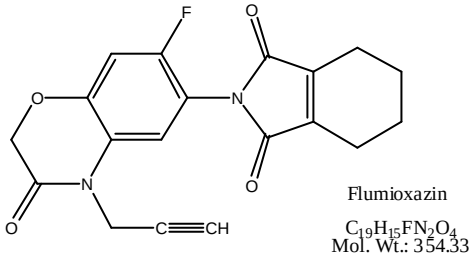
CHEMISTRY AND MANUFACTURE

ACTIVE CONSTITUENT

Flumioxazin is a member of diphenyl ether group of herbicides, which inhibits protoporphyrinogen oxidase (PPO). For weed resistance management, flumioxazin belongs to Group G herbicides

Products containing flumioxazin are registered in the USA, Argentina, Brazil, Paraguay, China, France, South Africa, Zimbabwe, Israel and Japan.

The chemical active constituent has the following properties:

Common Name:	Flumioxazin
Chemical Name (IUPAC):	N-(7-fluoro-3,4-dihydro-3-oxo-4-prop-2-ynyl-2H-1,4-benzoxazin-6-yl) cyclohex-1-ene-1,2-dicarboximide
CAS Registry Number:	103361-09-7
Empirical Formula:	$C_{19}H_{15}FN_2O_4$
Molecular Weight:	354.33 amu
Physical form:	Solid
Colour:	Yellow-brown powder
Odour:	Odourless
Melting Point:	202-204 °C
Density:	1.514 g/mL @ 20 °C
Octanol/water partition coefficient ($K_{o/w}$):	Log $P_{0/W}$ = 2.55 @ 20 °C
Vapour pressure at 25 °C:	N/A
Chemical Structure:	 Flumioxazin $C_{19}H_{15}FN_2O_4$ Mol. Wt.: 354.33
Chemical Family:	N-phenylphthalimide
Chemical Type:	Herbicide
Mode of Action:	Inhibition of protoporphyrinogen oxidase

SUMMARY OF THE APVMA'S EVALUATION OF FLUMIOXAZIN

The Chemistry and Residues Program (CRP) of the APVMA has evaluated the chemistry aspects of flumioxazin (manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable.

Flumioxazin is a new active constituent and there is no compendial specification available for flumioxazin. On the basis of the data provided, the following minimum compositional standard has been established for flumioxazin:

Active constituent	Minimum content
Flumioxazin	Not less than 960 g/kg

Other characteristics of flumioxazin (toxicology, environmental fate etc) are covered in subsequent sections of this Public Release Summary.

FORMULATED PRODUCT

The APVMA's Chemistry and Residue Program (CRP) also assessed submitted data on the formulated product.

Distinguishing name:	Pledge 500 WG Herbicide (*PLEDGE* ®)
Formulation type:	Water Dispersible Granule
Active constituent concentration:	500 g/kg

PHYSICAL AND CHEMICAL PROPERTIES OF THE PRODUCT

Physical state:	Solid (granule)
Colour:	Tan
Odour:	Odourless
Density or specific gravity:	Not applicable
Acidity, alkalinity or pH value:	pH ~6 (1% solution)
Flash point, flammability and auto flammability:	Not applicable
Storage stability:	Stable for at least 2 years when stored under ambient temperature.

SUMMARY OF THE APVMA'S EVALUATION OF PLEDGE 500 WG HERBICIDE

The manufacture and quality control procedures (e.g. compliance to product release specifications) implemented for *PLEDGE* ® are acceptable.

The applicant provided real time and accelerated stability data from one batch of formulated product (packaged in HDPE and metallised polyester bags). Testing was conducted on all of the product specifications. The results are acceptable, demonstrating that the formulated product should be stable for a minimum of 2 years when stored at ambient temperature.

Based on a review of the chemistry and manufacturing details provided by the applicant, APVMA-CRP supports the approval of flumioxazin manufactured by:

Sumitomo Chemical Company Limited
Olta Works
Ooaze Tsurasaki 2200
Oita City, Oita Prefecture 870-0194
JAPAN.

Based on a review of the data provided by the applicant to the APVMA, the APVMA is satisfied that the chemistry and manufacturing details of *PLEDGE* ® are acceptable.

TOXICOLOGICAL, METABOLISM AND TOXICOKINETICS ASSESSMENT

SUMMARY

Flumioxazin is a herbicide, new to the Australian market. It is structurally related to a registered herbicide, carfentrazone-ethyl. Flumioxazin is proposed to reduce the enzyme activity of protoporphyrinogen oxidase (PPO) and hence cause accumulation of porphyrins and which leads to cellular injury in plants. The product, *PLEDGE*®, is a water dispersable granule containing 500 g of flumioxazin per kilogram of product.

Following ingestion, flumioxazin is rapidly absorbed, extensively metabolized and eliminated. Dermal absorption is slow and limited in extent. It has low acute oral, dermal and inhalation toxicity. It is a slight eye irritant, but not a skin irritant or sensitiser. *PLEDGE*® shows similar acute toxicity as the active ingredient except that it is a slight skin irritant.

In repeated dose studies in mice, rats and dogs, flumioxazin caused liver toxicity characterised by alterations in liver function and enzyme activities. Oral and dermal exposure induced anaemia and other haematological disturbances in rats. Flumioxazin was negative in studies designed to detect its potential to damage genetic material (DNA), and it did not induce cancers in life-time exposure studies in animals.

In developmental studies, an increased incidence of foetal death, impaired foetal development and growth retardation was observed in rats, following oral or dermal exposure at levels which were not toxic to the dams. This has necessitated a label warning statement to alert women of child-bearing age to avoid mixing, loading or spraying any product containing flumioxazin.

CONCLUSION: Based on an assessment of the toxicology, it was considered that there should be no adverse effects on human health from the use of *PLEDGE*®, when used in accordance with the label directions.

EVALUATION OF TOXICITY

INTRODUCTORY NOTES

The toxicological database for flumioxazin 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.

Metabolism and Toxicokinetics

In mice given an oral dose of 30 mg/kg bw flumioxazin on gestation day 10, peak levels were reached within 1 h in all tissues and excretion was essentially complete in 24 h, mainly in the faeces. Metabolism was qualitatively similar to that in rats. Peak levels found in amniotic fluid and in foetuses were approximately 50% and 20% respectively of the peak level in maternal plasma.

In rats, absorption after oral dosing was rapid with highest levels in the kidneys and liver. Absorption could not be quantified based on the data available. Following a single or repeated low oral dose (1 mg/kg bw) or a single high oral dose (30 or 100 mg/kg bw) of radio-labelled flumioxazin to rats, excretion was complete within 48 hours, with the majority (57-87%) in faeces and less in urine. Metabolism of absorbed flumioxazin was extensive, and hydroxylation and incorporation of the sulfonic acid group were the main metabolism pathways. A small percentage (≤ 5%) of the parent compound, and 7 to 10 identified and a number of unidentified metabolites, were detected in the faeces and urine.

In pregnant rats on gestation day 12, the kinetics and metabolism of a 30 mg/kg bw oral dose was similar to that in non-pregnant rats. Peak levels found in amniotic fluid and in foetuses were approximately 45% and 30%, respectively, of the peak level in maternal plasma.

Low dermal absorption (≤ 8.3% dose) was observed following a single dermal application of radio-labelled flumioxazin in male rats at a low dose (0.02, 0.2 or 1 mg/rat for 0 - 24 h, equivalent to 0.08, 0.8 or 4.2 mg/kg bw), in female rats at a high dose (200 or 800 mg/kg bw for 0 - 6 h), or in pregnant rats (100 mg/kg bw for 0 - 6 h, on gestation day 13). The majority of radioactivity (≥ 80%) was recovered in the skin surface/washing, and a small portion in the skin of the application site. The absorption was slow, followed by delayed distribution and elimination. Total systemic absorption increased in a time- and dose- dependent manner. The concentration of radioactivity in the foetus was approximately 20% of that in maternal blood of rats on gestation day 13.

In rabbits given an oral dose of 30 mg/kg bw flumioxazin on gestation day 12 a similar distribution to that in rats was seen. In general the peak tissue levels achieved were considerably lower than those achieved in the tissues of rats. Only 30% of the dose was eliminated in a 24 h period with 18% in faeces and 12% in urine. Metabolism was qualitatively similar to that in rats. Peak levels found in amniotic fluid and in foetuses were approximately 40% and 10% respectively of the peak level in maternal plasma.

Acute Studies

Flumioxazin has low oral (LD_{50} > 5000 mg/kg bw with no deaths), dermal (LD_{50} > 2000 mg/kg bw with no deaths) and inhalation toxicity (LC_{50} > 3930 mg/m^3/4h with no deaths) in rats. It is neither a skin irritant in rabbits, nor a skin sensitiser in guinea pigs, but it is a slight eye irritant in rabbits.

PLEDGE® has low oral (LD_{50} > 5000 mg/kg bw with no deaths), dermal (LD_{50} > 2000 mg/kg bw with no deaths) and inhalation toxicity (LC_{50} > 969 mg/m^3/4h, the maximal attainable concentration, with no deaths) in rats. It is a slight irritant to the eyes and skin of rabbits**,** but is not a skin sensitiser in guinea pigs.

Short-term Studies

Mice received flumioxazin at 0, 1000, 3000 or 10000 ppm in the diet for 28 days. No treatment related changes were observed. There were no effects at 10000 ppm, equal to 1366 (males) and 1698 (females) mg/kg bw/day.

Rats received a dermal application of flumioxazin at 0, 100, 300 or 1000 mg/kg bw to the skin for 6 h/day, for 21 days. Lower haemoglobin and haematocrit values, higher reticulocyte counts, and increased splenic extramedullary haematopoiesis were observed in females at 1000 mg/kg bw/day. There were no effects at 300 mg/kg bw/day.

Subchronic Studies

Rats received flumioxazin at 0, 30, 300, 1000 or 3000 ppm in the diet for 5 or 13 weeks. Some females at 3000 ppm showed pale auricles, eyes or limbs, and one rat (of 10) had decreased spontaneous activity and died. Food consumption was lower at 1000 (females) and 3000 ppm in the first week. Rats at 1000 and 3000 ppm showed anaemia, including significant decreases in haemoglobin, haematocrit, MCV, MCH, MCHC, and bone marrow myeloid/erythroid ratio, and increases in reticulocyte counts and erythroblast ratios. Some females at 3000 ppm had increased BUN, ALT, AST, LDH, ALP, γ-GGT, triglycerides, bilirubin and albumin/globulin ratio, and decreased cholinesterase.

Rats at 1000 and 3000 ppm showed increased liver weight, ballooning of centrilobular hepatocytes, necrosis, and brown pigment in the sinusoidal hepatocytes and bile canaliculi. The incidences of dark colour, enlarged size and increased weight of the spleen, and splenic extramedullary hematopoiesis were higher at 3000 ppm, and hypercellularity, myelofibrosis and/or osteosis of the bone marrow were observed in females at 3000 ppm. Brown pigment within the tubular epithelial cells and tubular vacuolization in the kidney, cortical cytoplasmic vacuolization in the adrenal, thyroid cysts, atrophic changes with foam cells in the thymus, and sinus histiocytosis in the lymph node were also seen in some females at 3000 ppm. Some pathological changes in the spleen and bone marrow also occurred in females at 1000 ppm following 5-week dosing. The NOEL was 300 ppm, equal to 19 (males) and 22 (females) mg/kg bw/day.

Rats received flumioxazin at 0, 30, 300, 1000 or 3000 ppm in the diet for 13 weeks. At 3000 ppm, body weight was slightly lower. Signs of anaemia, including reduced RBC [red blood cell] count (females), haemoglobin, haematocrit, MCH and MCV values, and bone marrow M/E [myeloid/erythroid] ratio, and increased platelet, reticulocyte and erythroblast counts were observed at 3000 ppm.

Some haematology alterations were also observed at 1000 ppm. Some animals at 3000 and/or 1000 ppm showed decreased levels of AST, ALP and LAP, elevated albumin and A/G ratio. Spleen and liver weights were increased at 3000 ppm. A significantly higher incidence of extramedullary haematopoiesis appeared in the spleen at 3000 ppm, and enlarged spleen or haematopoiesis in the liver and bone marrow was also noticed in a single female of this group. In the liver, lymphocytic accumulation was observed in some rats at 3000 ppm, and fatty metamorphosis, necrosis, hemorrhage or foci of cellular alteration was found in a single rat (of 12) at 3000 ppm. The NOEL was 300 ppm, equal to 21 (males) and 22(females) mg/kg bw/day.

Dogs received an oral capsule dose of flumioxazin at 0, 10, 100 or 1000 mg/kg bw/day for 13 weeks. At 1000 mg/kg bw/day, activated partial thromboplastin time was slightly prolonged in females. Higher cholesterol, phospholipid and alkaline phosphatase levels were noticed at 1000 mg/kg bw/day, and to a lesser extent at 100 mg/kg bw/day.

Bone marrow examination revealed a small but significantly higher proportion of proerythroblasts in females at 1000 mg/kg bw/day. Some dogs at 1000 mg/kg bw/day had higher liver weight, slight proliferation of bile ductules and minimal increased fibrous tissue around hepatic centrilobular veins. Almost all dogs of this group showed proliferation and dilatation of the smooth endoplasmic reticulum in hepatocytes. Lower pituitary weight and higher thyroid weight were also seen in males of this group. The NOEL was 10 mg/kg bw/day.

Chronic Studies

Mice received flumioxazin at 0, 300, 3000 or 7000 ppm in the diet for 52 (satellite group) or 78 (main group) weeks. The RBC count was significantly reduced in males at 7000 ppm. The incidence and severity of centrilobular (males) or diffuse (females) hypertrophy of hepatocytes were higher at 3000 and 7000 ppm. Females at 7000 ppm also showed a higher incidence of plasmacytosis of submandibular lymph node, as well as thickened gastric mucosa which corresponded to adenomatous hyperplasia in the glandular stomach. Slight calcification of the brain was found at higher incidences at 3000 and 7000 ppm. Flumioxazin was not a carcinogen in mice. The NOEL was 300 ppm, equal to 31 (males) and 37 (females) mg/kg bw/day.

Rats received flumioxazin at 0, 50, 500 or 1000 ppm in the diet for 53 or 79 weeks (the satellite group), or 105 weeks (the main group). Decreased haemoglobin, haematocrit, MCV, MCH and MCHC, and/or increased erythroblast and reticulocyte counts were observed at 1000 and 500 ppm, more severe at the early stage of the study, and more severe in females than in males. Myeloid/erythroid ratio (M/E) was reduced in the bone marrow of males at 500 and 1000 ppm. The incidence and/or severity of extramedullary haematopoiesis in the spleen and chronic nephropathy were increased in males at 500 and 1000 ppm. The incidence of tumours was comparable across groups. The NOEL was 50 ppm, equal to 1.8 (males) and 2.2 (females) mg/kg bw/day.

Dogs received oral capsule doses of flumioxazin at 0, 10, 100 or 1000 mg/kg bw/day for one year. A higher incidence of loose/mucosal faeces or diarrhoea was seen at 1000 mg/kg bw/day. Total cholesterol and phospholipid values, and α2-globulin ratio were increased at 1000 mg/kg bw/day. Alkaline phosphatase activity was elevated at 100 and 1000 mg/kg bw/day.

At 1000 mg/kg bw/day, liver weight was increased, with hyperplasia of Glisson's capsule, bile duct proliferation, haemosiderin deposition and inflammation and dilatation of smooth endoplasmic reticulum in some dogs. Increased extramedullary haematopoiesis as well as haemosiderin pigment were observed in the spleen of some males at 100 and 1000 mg/kg bw/day. Prostate weights were reduced in some males at 100 and 1000 mg/kg bw/day. Female pituitary weight at 1000 mg/kg bw/day was also lower. The NOEL was 10 mg/kg bw/day.

Reproduction Studies

Rats received 0, 50, 100, 200 or 300 ppm of flumioxazin in the diet for two generations, with one litter per generation. Mating performance and fertility of the F0 generation were unaffected. During gestation, females at 300 ppm had decreased body weight gain and a red vaginal discharge. A number of those dams had total resorption of implantations and as a consequence, litter size was reduced at 300 ppm.

F1 pup weight at birth was lower at 200 and 300 ppm and pup survival during lactation days 1 - 4 was decreased at 300 ppm. F1 female adult rats given 300 ppm had decreased body weight gain and a number died showing signs of anaemia. Males in this group showed reduced weights of the testes, epididymides and prostate and a number that did not sire offspring had small, flaccid testes with atrophy and hypospermia. The number of F1 male rats that mated was reduced at 200 and 300 ppm but the conception rate in females was unaffected.

The number of F2 live-born pups was decreased at 200 and 300 ppm due either to total loss of some litters or an increase in stillborn pups. Body weight at birth and survival during lactation days 1 to 4 was lower in F2 pups in the 300 ppm group. The NOEL was 100 ppm (approximately 5 mg/kg bw/day).

Developmental Studies

Pregnant rats received 0, 1, 3, 10 or 30 mg/kg bw/day of flumioxazin by oral gavage on days 6 - 15 of pregnancy. Lower gravid uterine weights and lower body weight gains at 30 mg/kg bw/day were associated with decreased live foetal numbers and reduced foetal weight. The incidence of embryo loss in this group was increased and dark reddish fluid/material was found in the uterus at necropsy. The incidence of cardiovascular abnormalities was increased at 10 and 30 mg/kg bw/day, including ventricular septal defect, double aortic arch, persistent left umbilical artery and supernumerary coronary orifice. A slightly higher incidence of absence of renal papilla, and higher incidences of curvature of scapula/ulna and wavy ribs, and lower numbers of ossified sacrococcygeal vertebral bodies were also observed at 30 mg/kg bw/day. The NOEL was 30 mg/kg bw/day for maternal toxicity, and 3 mg/kg bw/day for embryo/foetal developmental toxicity.

Pregnant rats received 0, 30, 100 or 300 mg/kg bw/day of flumioxazin dermally for 6 hours per day, from day-6 to day-15 of pregnancy. Local irritation appeared in some rats with a higher incidence at 300 mg/kg bw/day. Reddish material was observed around the vaginal region of some dams with a higher incidence at 100 and 300 mg/kg bw/day. At 300 mg/kg bw/day, there was lower body weight gain in late gestation, lower gravid uterine weight and dark reddish material in the uterus, which were related to a significantly higher incidence of embryonic deaths.

Hence, the number of live foetuses was lower in this group, and foetal body weights tended to be lower.

The total incidence of cardiovascular abnormalities was higher at 100 and 300 mg/kg bw/day, including ventricular septal defect, persistent right azygous veln and supernumerary coronary orifice. Several cases of curvature of scapula or ulna, a higher incidence of wavy ribs and lower numbers of ossified sacrococcygeal vertebral bodies were also noted at 300 mg/kg bw/day. There were no effects at 30 mg/kg bw/day.

Pregnant rats were given a single oral dose of 400 mg/kg bw flumioxazin on gestation day 11, 12, 13, 14 or 15. The most sensitive developmental stage was day-12 on which the treatment induced higher incidences of embryonic death and ventricular septal defects, and lower foetal body weights.

Artificially-inseminated female rabbits received 0, 300, 1000 or 3000 mg/kg bw/day of flumioxazin by oral gavage from day 7 to day 19 of pregnancy. Reduced body weight gain and food consumption were observed at 3000 mg/kg bw/day during the dosing period, but partially recovered post dosing. The number of implantations, early or late resorptions, gestation index and viable foetuses were comparable among groups.

There were no dose-dependent, significant differences in the litter or foetal incidences for any alteration. The NOEL was 1000 mg/kg bw/day for maternal toxicity, and 3000 mg/kg bw/day for developmental toxicity in rabbits.

Genotoxicity Studies

Flumioxazin was not mutagenic or genotoxic in an Ames test using *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, and *E. coli* WP2uvrA, a chromosomal aberration assay in rat bone marrow cells *in vivo,* and an unscheduled DNA synthesis study in rat hepatocytes *in vivo.*

Other Studies

Mechanism Studies

Female rats received 0, 3000 or 10000 ppm flumioxazin in the diet for up to 5 weeks. The majority of the changes were observed in both treated groups. Anaemia was indicated by significantly reduced RBC, haemoglobin, haematocrit, MCV and MCH, and myeloid/erythroid ratio in the bone marrow. The erythroblast count and the incidence of siderocytes in peripheral blood were increased from day 2. The neutrophil count was initially transiently decreased followed by an increase. Clinical chemistry revealed elevated serum iron levels and lower AST activity. Reduced triglycerides and a slightly increased sodium level were detected at 10,000 ppm only. Spleen and liver weights were increased at necropsy. Elevated urinary coproporphyrin and free erythrocyte protoporphyrin were detected at 3000 ppm.

Pregnant rats were given a single oral dose of 0 or 400 mg/kg bw flumioxazin on gestation day-12 and dams were killed on various gestation days thereafter. For the treated group, embryo death was increased from gestation day-15.

A high incidence of enlarged foetal heart was observed on days 14 and 15,with a lower incidence from day-16, and no increased incidence by days 17 to 20. The incidence of foetal oedema was increased from day-14, and peaked on days 15 - 16, but gradually recovered by day-20. Closure of the interventricular foremen was delayed by treatment. Foetal RBC count and the haemoglobin level were reduced during days 13 - 16, and serum protein level was lower during days 15 - 16, and all recovered by gestation day-20.

Pregnant rats and rabbits were given a single oral dose of 0 or 1000 mg/kg bw flumioxazin on gestation day-12 followed by examination of embryos at various times.

In treated rats, embryo deaths were first observed at 36 h, and reached 93% at 48 h post dosing. Mitochondrial lesions and abnormal iron deposition (from 12 h onwards) were seen in erythroblasts from treated rat embryos. Erythroblastic degeneration (irregular-shaped or pyknotic nuclei, or intracytoplasmic vacuoles of various size) in the circulation and macrophages in erythrophagocytosis in the sinusoidal vessels of the liver were observed from 12 or 24 h post dosing. Peripheral vascular dilatation and dilatation of the sinusoidal vessels in the liver appeared from 24 h onwards. Hepatic necrosis in the peripheral region of the liver as well as a thin anterior thoracic wall, were observed at 48 h. Thin ventricular wall, thin muscular septum and endocardial cushion hypoplasia were noticed from 36 h, but light and electron microscopy failed to identify any primary injury in myocardial cells. The changes in circulating polychromatophilic erythroblasts and hepatocytes of treated rat embryos were confirmed by electron microscopy.

No treatment related changes were found in embryos of rabbits.

Pregnant rats and rabbits were given a single oral dose of 0 or 1000 mg/kg bw flumioxazin on gestation day-12.

In rat embryos, protoporphyrin IX (PPIX) accumulation commenced within 2 h and reached a peak (130 times control) at 12 h post dosing. A lesser increase of PPIX was also seen in rat maternal liver.

PPIX levels in rabbit maternal liver and embryo were very low or undetectable.

Pregnant rats were given a single oral dose of the chemically related compounds, flumioxazin, S-23121 or S-23031 at 0 or 1000 mg/kg bw on pregnant day-12. Flumioxazin and S-23 121 (both of which cause developmental toxicity), but not S-23031 (not toxic to foetal development), induced marked accumulation of PPIX in rat embryos, indicating a correlation between PPIX accumulation in embryos and developmental toxicity.

Pregnant rats and rabbits were given a single oral dose of flumioxazin at 0 or 400, and 0 or 1000 mg/kg bw respectively, on one day of gestation days 10 to 15.

Slightly lower wet weights of rat embryos were observed in rats after a single dose on day 12, 13, 14 or 15. All treated rat embryos showed increased PPIX concentration with the peak after day-12 treatment, which was consistent with the critical period of flumioxazin-induced developmental toxicity. The treatment did not change the PPIX level in rat maternal liver.

No changes were observed in treated rabbits.

Flumioxazin, S-23121 and S-23031 were compared for protoporphyrin oxidase (PPO) inhibition in mitochondria obtained from the liver of non-pregnant rats and rabbits, and from the embryos of rats and rabbits on gestation day 12 or 15. The rank order of inhibitory potency (IC_{50}) was flumioxazin > S-23121 >> S-23031 for PPO from all tissues. Mitochondrial PPO from the liver and embryo of each species behaved similarly *in vitro,* but rabbit PPO was an order of magnitude less sensitive to inhibition by these chemicals than rat PPO.

The interspecies differences in the inhibition of PPO activity by flumioxazin were determined *in vitro* in mitochondria from the liver of rats, rabbits, and adult humans. The relative sensitivity of the species to PPO inhibition in the liver by flumioxazin (IC_{50} nM) was: rat (7.15) > human (17.3) > rabbit (138).

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 to prevent the occurrence of poisoning.

Despite the relatively low acute toxicity of flumioxazin, the NDPSC considered that the potential risks to foetal growth and development warranted inclusion in schedule 7 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP).

This requires a signal heading DANGEROUS POISON, and complements the recommended label warning statement which advises that women of child-bearing age should avoid mixing, loading or spraying any product containing flumioxazin (viz: "This product contains flumioxazin, which causes birth defects in certain laboratory animals. Women of child bearing age are advised not to mix, load or spray his product. They should keep out of areas being sprayed.").

NOEL/ADI

The Acceptable Daily Intake (ADI) is that quantity of an agricultural compound which can safely be consumed on a daily basis for a lifetime and is commonly 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 flumioxazin was established at 0.003 mg/kg bw/day based on a **NOEL** of 3 mg/kg bw/day in an oral developmental study in rats and using a 1,000-fold safety factor in view of the nature and irreversibility of the effect.

Acute Reference Dose (ARfD)

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

The highest acute dose of flumioxazin at which no evidence of toxicity was detected was 3 mg/kg bw in a rat oral developmental study. The **ARfD** was established at 0.03 mg/kg bw on the basis of this NOEL and using a 100-fold safety factor.

RESIDUES ASSESSMENT

SUMMARY

Residues in food

Metabolism studies conducted on peanuts indicate there is limited absorption of flumioxazin from the soil, and that flumioxazin undergoes extensive metabolism in plant tissues. Animal metabolism studies indicate that flumioxazin is extensively metabolised and rapidly excreted with negligible residues in tissues, milk and eggs.

Based upon the knowledge that flumioxazin undergoes extensive metabolism in animals and plants, and that detectable residues are unlikely to be found in treated produce when flumioxazin is used as a pre-sow herbicide, it is appropriate to establish the parent compound as the residue definition.

Validated analytical methods were capable of qualifying flumioxazin residues in harvested grain, seed and straw with a limit of quantification of 0.05 mg/kg for cereals and 0.1 mg/kg for pulses and rapeseed. Similarly, analytical methods are capable of measuring flumioxazin residues in animal tissues, milk and eggs with a limit of quantification of 0.01 mg/kg.

Residue data from trials conducted in Australia support MRLs of *0.05 mg/kg for cereal grains (wheat, barley and oats), *0.1 mg/kg for broad beans, chick-peas, cotton seed, field peas, lupins, lentils and rape seed. As flumioxazin is used early in the growing season, a harvest withholding period will not be required.

Residue analysis of treated animal feed commodities indicate that flumioxazin residues in forage, straw and fodder support the establishment of MRLs at the limit of quantification of 0.05 mg/kg for cereal grain forage, straw and fodder, and rapeseed forage; and 0.1 mg/kg for forage and fodder of lupins, chick-peas, broad beans (faba beans), field peas and lentils, and rape seed straw and fodder. Associated with these MRLs are grazing withholding periods of 6 weeks for forage of cereal grains, rapeseed, lupins, chick-peas, broad beans (faba beans), field peas and lentils.

The likely exposure of livestock from the consumption of treated produce (seeds, grain, forage, straw and fodder) is low and MRLs of *0.01 mg/kg for animal tissues, milk and eggs are recommended.

The registration of *PLEDGE*® does not pose a risk to human health as the NEDI is equivalent to 9% of the ADI and the acute dietary intake is less than 4% of the ARfD . It is noted that there are limited overseas MRLs /tolerances established for flumioxazin in wheat, barley, canola and lupins. However, the residue data shows that flumioxazin residues in treated crops are unlikely to be detected in harvested crops. Animal exposure to treated produce is also unlikely to result in detectable residues in meat or meat products. As residues of flumioxazin are unlikely to occur in harvested grain and seed after pre-sowing treatment with flumioxazin, there is negligible risk to international trade.

Suitable amendments to the *MRL Standard* are recommended, with associated with-holding periods (WHPs).

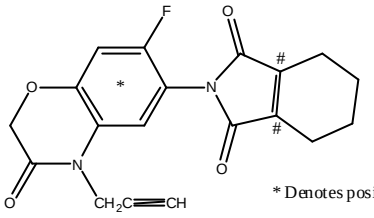
DETAILED REPORT.

The residue evaluation of flumioxazin comprises:

- metabolism studies for peanuts and animals (rats, goats, hens);
- residue data for cereals (wheat and barley) canola and lupins; and
- environmental fate and chemistry.

METABOLISM

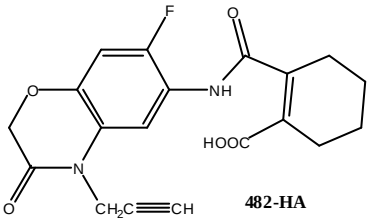
A plant metabolism study using [phenyl-^{14}C]-flumioxazin and [tetrahydrophthaloyl-1,2-^{14}C]-flumioxazin was conducted on peanuts grown on treated soil. Uptake of radioactivity from the soil was low and radioactivity was evenly distributed in the plant tissues (vines, peanut hulls, nutmeal and coats). Characterisation of the radioactive residues showed that the major metabolites were 482-HA (due to imido ring opening of flumioxazin), THPA (hydrolysis of 482-HA) and 1-OH-HPA-1 (hydroxylation of THPA).



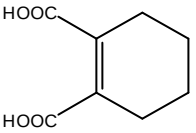
* Denotes position of phenyl-^{14}C label

\# Denotes position of THP-^{14}C label

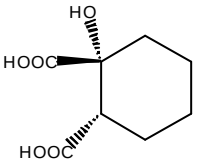
Flumioxazin



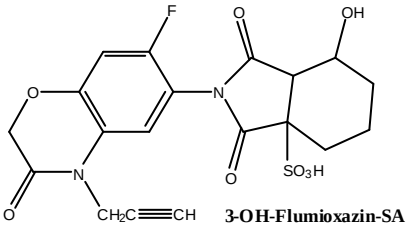
482-HA



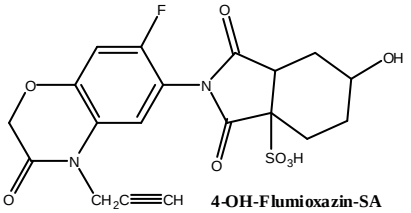
THPA



1-OH-HPA-1



3-OH-Flumioxazin-SA



4-OH-Flumioxazin-SA

Animal metabolism studies were conducted on lactating goats and laying hens using [phenyl-^{14}C]-flumioxazin and [tetrahydrophthaloyl-1,2-^{14}C]-flumioxazin.

Goats were orally dosed with 0.5 mg/kg bw ^{14}C-flumioxazin for five days (equivalent to 12 ppm nominally in the diet). The majority of radioactivity from oral dosing was eliminated in the urine and faeces as metabolites. Negligible residues were transferred into the milk (<0.03 mg/kg equivalents) and into tissues of the animals (<0.19 mg/kg equivalents).

Hens were fed 0.68 mg/kg bw of [phenyl-^{14}C]-flumioxazin for five days (equivalent to ~10 ppm in the diet). The majority of radioactive residue was eliminated in the excreta (93%). Negligible residues were found in tissues (<0.3 mg/kg equivalent) and eggs (<0.4 mg/kg equivalent).

Characterization of the radioactive residues in animal tissues showed that the major metabolic reactions include hydroxylation of the cyclohexane ring; cleavage of the imide linkage; and incorporation of the sulfonic acid group to the 3,4,5,6-tetrahydrophthaloyl moiety forming the metabolites 3-OH-flumioxazin-SA and 4-OH-flumioxazin-SA. There was no discernable difference in the metabolic profile from either labelled starting material, indicating that the metabolic route was independent of the radioactive label used.

In summary, the radioactive residue profiles show that flumioxazin is extensively metabolised in plants and animals. There is very limited uptake of flumioxazin into plants when applied pre-planting to the soil. In animals, there is limited absorption of flumioxazin into tissues, milk and eggs.

Residue definition

Due to the extensive metabolism of flumioxazin in plant and animal tissues, and as finite residues are not likely to be encountered when flumioxazin is used according to Good Agricultural Practice, it is appropriate to set the residue definition as the parent compound only: Flumioxazin **flumioxazin**.

ANALYTICAL METHODS

Determination of flumioxazin residues in plant tissues

Validated analytical methods were used to determine flumioxazin residues in Australian trials conducted on wheat, barley, canola and lupins. The method involves extraction of the residues with aqueous methanol, then partitioning of the residues into dichloromethane. Extracts are cleaned up by column chromatography on florisil. Analysis of flumioxazin residues was performed using gas chromatography with NPD or MS detection, based upon peak area response with respect to a reference standard of known purity.

The methodology is considered adequate for the determination of flumioxazin residues in plant tissues (grain, straw and forage) of wheat, barley, canola and lupins.

The LOQ (Limit of Quantitation, denoted with an asterisk [*]) of the method was determined to be *0.05 mg/kg for cereal grain and forage, and *0.1 mg/kg for cereal straw, lupins (seed and forage), and for canola seed.

Determination of flumioxazin residues in animal tissues

Although animal transfer studies were not provided, a validated analytical method for the determination of flumioxazin residues in meat, eggs, milk and fat was submitted. Samples are extracted with acetone and the residues are partitioned into dichloromethane. In the case of meat and fat samples, further partitioning is conducted with acetonitrile and hexane. The extracts are cleaned up using florisil column chromatography. Quantitation is performed using gas chromatography with nitrogen-phosphorous detection, based upon the response of a reference standard of known purity.

The LOQ of the method in all tissue matrices was *0.01 mg/kg.

Storage stability

Storage stability studies conducted on wheat grain and straw indicates that residues of flumioxazin do not degrade significantly after 9.5 months of frozen storage (-18 °C). Frozen tissue samples from metabolism studies showed minimal deterioration of the radioactivity profile after 4-14 months of frozen storage.

RESIDUE TRIALS

Wheat

Eight Australian residue trials were conducted on wheat crops, where flumioxazin was applied as a pre-plant herbicide at rates of 15-180 g ai/ha (1-12 ×), in accordance with label instructions for *PLEDGE*®. The data show that flumioxazin residue levels in harvested grain are below the limit of quantification of 0.05 mg/kg when flumioxazin was applied up to 12 × the maximum recommended rate. In addition, residues in forage samples collected ~42 days after application (when scaled to the proposed application rate of 15 g ai/ha), straw and fodder are below the LOQ of *0.05 mg/kg.

Barley

Six Australian residue trials were conducted on barley crops, where flumioxazin was applied as a pre-plant herbicide at rates of 15 - 180 g ai/ha (1 - 12 ×), in accordance with label instructions for *PLEDGE*®. The data show that flumioxazin residue levels in harvested grain are below the limit of quantification of *0.05 mg/kg when flumioxazin was applied up to 12 × the maximum recommended rate.

Cereals

Overall, the residue data for wheat and barley are acceptable to extrapolate to other cereals, in particular oats. These data support the establishment of an MRL of *0.05 mg/kg for cereal grains (wheat, barley and oats), forage, straw and fodder. A six (6) week grazing withholding period is recommended to ensure that residues in forage are below detection levels before animals are allowed to graze on failed crops.

Canola [rapeseed]

Five Australian residue trials were conducted on canola crops, where flumioxazin was applied as a pre-plant herbicide at rates of 15 - 90 g ai/ha (1 - 6 ×), in accordance with label instructions for *PLEDGE®*. The data show that flumioxazin residue levels in harvested seed are below the limit of quantification of 0.05-0.1 mg/kg when flumioxazin was applied up to 6 × the recommended rate. Residues found in forage (sampling ~42 -60 days after treatment) were below the LOQ of *0.05 mg/kg. Residues in straw and fodder collected at harvest were also below the LOQ of *0.1 mg/kg. These data support MRLs of *0.1 mg/kg for rapeseed, rapeseed straw and fodder, and *0.05 mg/kg for rapeseed forage. A six (6) week grazing withholding period is recommended to ensure that residues in forage are below detection levels before animals are allowed to graze on failed crops.

Oilseeds

The canola residue data are acceptable to extrapolate to other oilseed crops such as cotton, as requested by the Applicant. Accordingly, the residue data support an MRL of *0.1 mg/kg for cotton seed. The grazing of cotton forage or use of cotton trash will be prohibited.

Lupins

Eight Australian residue trials were conducted on lupin crops, where flumioxazin was applied as a pre-plant herbicide at rates of 15 - 180 g ai/ha (1 - 12 ×), in accordance with label instructions for *PLEDGE®*. The data show that flumioxazin residue levels in harvested seed are below the limit of quantification of *0.05 - *0.1 mg/kg when flumioxazin was applied up to 12 × the recommended rate. Residues found in forage (sampling ~42 - 74 days after treatment) were below the LOQ of *0.05 - *0.1 mg/kg. Residues in straw collected at harvest were also below the LOQ of 0.05-0.1 mg/kg. These data support MRLs of *0.1 mg/kg for lupins (dry), lupin forage and fodder. A six (6) week grazing withholding period is recommended to ensure that residues in forage are below detection levels before animals are allowed to graze on failed crops.

Chick-peas, faba beans, field peas and lentils

The lupin residue data are acceptable to extrapolate to other pulses, such as chick-peas, faba beans, field peas and lentils, as requested by the applicant. Accordingly, the residue data support an MRL of *0.1 mg/kg for chick-peas, faba beans, field peas and lentils; and forage and fodder of chick-peas, faba beans, field peas and lentils. A six (6) week grazing withholding period is recommended to ensure that residues in forage are below detection levels before animals are allowed to graze on failed crops.

Conclusion

When flumioxazin is applied as a pre-sow herbicide for cereals, oilseeds and pulses, finite residues are unlikely to be encountered in harvested grain and seed. Accordingly, MRLs for these commodities will be established 'at or about' the limit of quantification. A harvest withholding period is not required when *PLEDGE®* is used as directed.

Processing studies

No processing studies were required or submitted in the current application. Residues in harvested grain and seed are below the limit of quantification and processing is unlikely to result in finite levels in grain and seed fractions.

Animal commodity MRLs

Animal feeding studies have not been conducted on flumioxazin. The metabolism data show that flumioxazin is rapidly and extensively metabolised in goats and hens, and the residues (parent and metabolites) in animal tissues, milk and eggs are likely to be below the LOQ of 0.01 mg/kg following exposure to treated crops and crop parts. Based upon these data, the following animal commodity MRLs are recommended:

Meat (mammalian)	*0.01 mg/kg
Edible offal (mammalian)	*0.01 mg/kg
Milks	*0.01 mg/kg
Poultry meat	*0.01 mg/kg
Poultry, edible offal of	*0.01 mg/kg
Eggs	*0.01 mg/kg

*: the LOQ of the active in this commodity.

Estimated dietary intake

The chronic and acute dietary intake risk for flumioxazin has been assessed. The ADI for flumioxazin is 0.003 mg/kg bw/day, based upon a NOEL of 3 mg/kg bw/day and a 1,000 fold safety factor.

The NEDI of flumioxazin is equivalent to 9 % of the ADI. With respect to acute dietary intake, an acute reference dose (ARfD) of 0.03 mg/kg bw/day has been set for flumioxazin. The highest acute dietary intake was estimated at less than 4%. It is concluded that chronic and acute dietary exposure to flumioxazin is low and the risk from residues in food is acceptable.

Bioaccumulation potential

The residue data indicate that flumioxazin and metabolites do not accumulate in fat or other animal tissues. Environmental fate data indicate that flumioxazin degrades rapidly in soil ($t_{1/2}$ =11.9-17.5 days under aerobic conditions). Accordingly, it is unlikely that significant residues will be remaining in the soil to pose a residue risk for subsequent crops grown in treated fields. Crop rotation advice on the product label is therefore not required.

Recommendations

The registration of *PLEDGE*® is supported from a residues perspective, and the following amendments to the *MRL Standard* are recommended in relation to the proposed use of *PLEDGE*® :

Table 1

Compound	Food			MRL (mg/kg)
ADD: **Flumioxazin**				
	VD	0523	Broad bean (dry)	*0.1
	GC	0080	Cereal grains (wheat, barley and oats)	*0.05
	VD	0524	Chick-pea (dry)	*0.1
	SO	0691	Cotton seed	*0.1
	MO	0105	Edible offal (mammalian)	*0.01
	PE	0112	Eggs	*0.01
	VD	0561	Field pea (dry)	*0.1
	VD	0533	Lentils (dry)	*0.1
	VD	0545	Lupins (dry)	*0.1
	MM	0095	Meat [mammalian]	*0.01
	ML	0106	Milks	*0.01
	PM	0110	Poultry meat	*0.01
	PO	0111	Poultry, Edible offal of	*0.01
	SO	0495	Rape seed	*0.1

*****: the LOQ for the particular commodity

Table 3

Compound	Residue
ADD: **Flumioxazin**	Flumioxazin

Table 4

Compound	Animal feed commodity			MRL (mg/kg)
ADD: **Flumioxazin**				
			Forage of cereal grains (wheat, barley and oats) [fresh weight]	*0.05
			Forage of rapeseed [fresh weight]	*0.05
			Forage and fodder [fresh weight] of lupins, chick-peas, broad beans (faba beans), field peas and lentils	*0.1
	AS	0081	Straw and fodder (dry) of cereal grains (wheat, barley and oats)	*0.05
			Rape seed straw and fodder	*0.1

*****: the LOQ for the particular commodity

The following withholding periods are required in conjunction with the above MRL:

Cereal grains (wheat, barley and oats):
Pulses (lupins, chick-peas, broad (faba) beans, field peas, and lentils):
Rape seed (canola seed):

Grazing: Do not graze or cut for stock food for 6 weeks after application.
Harvest: Not required when used as directed.

Cotton:

Grazing: Do not graze or cut for stock food.
Harvest: Not required when used as directed.

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Potential risk to Australian export trade

Plant/crop residues

The use of flumioxazin as a pre-sowing herbicide on cereal grains (wheat, barley and oats), oilseeds (cotton and rapeseed) and pulses (lupins, faba beans, field peas, chick-peas and lentils) is unlikely to unduly prejudice Australian trade, when *PLEDGE*® is used in accordance with the label directions and Good Agricultural Practice.

Codex MRLs have not been determined for flumioxazin. There are MRLs/tolerances at the limit of quantification of *0.02 or *0.05 mg/kg for soybean (USA, Brazil, Paraquay), peanut (USA), grape vine (France) and groundnuts (South Africa). There are also proposed tolerances for grapes, cottonseed, cotton gin by-products, and almonds in the USA. It is noted that there are no overseas MRLs /tolerances established for flumioxazin in wheat, barley, canola and lupins.

However, the residue data show that flumioxazin residues in treated crops are unlikely to be above detectable limits in harvested grain and seed. Accordingly, export of cereal grains, oilseeds and pulses from treated crops is not expected to unduly prejudice Australian trade.

Animal-commodity residues

A grazing/stock food interval will apply to forage of cereals, rapeseed, lupins, faba beans, field peas, chick-peas and lentils. The grazing of cotton forage is prohibited.

The likelihood of finite tissue residues occurring in grazing animals, pigs and poultry, as a result of feeding on forage, straw and fodder from treated produce is considered small. Hence the risk arising from animal exposure to treated produce is low and is also unlikely to result in detectable residues in meat or meat products.

SUMMARY

In summary, based upon the proposed use-pattern and the residue data submitted, the proposed use of *PLEDGE*® is unlikely to unduly prejudice trade.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

NOHSC has conducted an assessment on the water dispersible granule formulation of flumioxazin, called *PLEDGE*®.

Health hazards

Flumioxazin has been classified as a hazardous substance for reproductive toxicity, with the risk phrase R61 (May cause harm to the unborn child).

PLEDGE® has been classified as a hazardous substance, according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999b), also with the risk phrase R61. A suitable warning statement has been added to the product-label, to mitigate this risk ("This product contains flumioxazin, which causes birth defects in certain laboratory animals. Women of child bearing age are advised not to mix, load or spray his product. They should keep out of areas being sprayed.").

Flumioxazin will be manufactured overseas. It has low oral, dermal and inhalation toxicity in rats. It is neither a skin irritant in rabbits, nor a skin sensitiser in guinea pigs, but is a slight eye irritant in rabbits. Developmental effects are the main hazards associated with repeated exposure to flumioxazin.

PLEDGE® has low oral, dermal, and inhalation toxicity in rats. It is a slight irritant to the eyes and skin of rabbits, but is not a skin sensitiser in guinea pigs.

Formulation, packaging, transport, storage and retailing

PLEDGE® will be formulated in Australia from imported flumioxazin. The product will be available in 1 kg (45 mm neck size) and 5 and 10 kg (52 mm neck size) high density polyethylene (HDPE) containers.

Transport workers, store persons and retailers will handle the packaged product and could become contaminated if the packaging were breached.

Use and exposure

PLEDGE® is indicated for rapid brown-out and control of various grass and broadleaved weeds when mixed with certain knock-down herbicides prior to sowing wheat, barley, lupins, canola, cotton, oats, faba beans, field peas, chick peas and lentils.

PLEDGE® will be applied at a maximum application rate of 30 g/ha, in a minimum spray volume of 40 L/ha water, by tractor mounted boom spray with hydraulic nozzles, prior to sowing the crops mentioned above. A maximum of 2 applications will be made per year from December to July.

Workers may be contaminated with the product during mixing/loading and application, cleaning up spills, cleaning and maintaining equipment, and at re-entry. The main routes of exposure to the product are dermal, ocular and inhalation.

There are no available worker exposure data on *PLEDGE*®. NOHSC used the UK Predictive Operator Exposure Model (POEM) and Pesticide Handlers Exposure Database (PHED) Surrogate Exposure Guide (1998) to estimate applicator exposure to *PLEDGE*®.

These estimates, in conjunction with toxicology data, demonstrated that the use of clothing, gloves and face shield or goggles during mixing/loading is required to protect workers during acute and repeated exposure.

Entry into treated areas

Workers entering treated areas can be exposed to product residues and degradation products during crop management activities.

Using the US Occupational Post-Application Risk Assessment Calculator (US Policy 003.1) and based on the toxicity profile and use pattern of *PLEDGE*®, NOHSC concluded that workers re-entering treated areas will not be at risk. Therefore, NOHSC does not recommend a re-entry statement. However, any re-entry statements for the partner herbicide used with *PLEDGE*®, would need to be complied with.

Recommendations for safe use

Users should follow the instructions and Safety Directions on the product label. Safety Directions include the use of cotton overalls buttoned to the neck and wrist and a washable hat, elbow-length PVC gloves and face shield or goggles when opening the container and preparing the spray.

The personal protective equipment recommended should meet the relevant Standards -Australia standard.

Conclusion

NOHSC supports the registration of flumioxazin in *PLEDGE*® at 500 g/kg as a water dispersible granule formulation, for use with certain knock-down herbicides, prior to sowing wheat, barley, lupins, canola, cotton, oats, faba beans, field peas, chick peas and lentils.

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

ENVIRONMENTAL ASSESSMENT

SUMMARY

Flumioxazin was readily hydrolyzed at pH 5 and very rapidly degraded at pHs 7 and 9. It was photo-degraded in the aqueous photolysis and soil photolysis studies.

Soil metabolism under aerobic conditions was rapid with a first half-life of between 12 - 17.5 days but slowed down thereafter. Under anaerobic conditions there was rapid depletion from the water column to < 4% after 3 days, with corresponding increase in soil concentrations; half lives in solid phase were 73 and 117 day for the two anaerobic studies.

Mobility was rated as low (clay-rich soils) to high (sandy soils) in column leaching studies. While there was indication of leaching in sand soils, there was no significant leaching in aged soil residues.

The field study showed that dissipation occurs in two stages, with a fast initial half life of 12 days which then slowed down to give an overall half life of 75 days. There was no significant leaching in a field lysimeter study, with no detectable residues of flumioxazin below 7.5 cm. Bioaccumulation of flumioxazin is not expected.

Flumioxazin was practically non-toxic to birds (bobwhite quail and mallard ducks) in acute, short-term and generational studies. It was moderately to slightly toxic to fish (rainbow trout and bluegill sunfish) and moderately to highly toxic to aquatic invertebrates in acute studies. As expected, flumioxazin was very highly toxic to a range of algae species and duckweed.

Terrestrial invertebrates (earthworms, and honeybees) were generally unaffected by it. Soil microbial respiration, tested at rates significantly above those proposed for Australia, was not affected by flumioxazin; however, nitrogen mineralisation was initially affected (14 days) but there was no significant effect after 28 days.

The proposed use of *PLEDGE*® is not expected to pose an unacceptable hazard to birds, earthworms, honeybees, predatory mites, parasitic wasps, soil microbial respiration, fish or aquatic invertebrates.

However, to protect algae and aquatic plants (duckweed), a spray-drift buffer of 10 metres is justified. Similarly, a suitable spray-drift buffer of 10 m would mitigate the risk to non-target terrestrial plants.

The hazard from run-off is expected to be low.

DETAILED REPORT

ENVIRONMENTAL EXPOSURE

PLEDGE® contains the new technical active flumioxazin at 500 g-ai/kg. It will be applied at 30 g/ha (15 g-ai/ha), tank mixed with glyphosate or paraquat/diquat, for rapid brown-out of a range of broad leaf and grass weeds, prior to sowing wheat, barley, lupins, canola, cotton, oats, faba beans, field peas, chick peas and lentils. A maximum of 2 applications would be made per annum, between December and July.

ENVIRONMENTAL CHEMISTRY AND FATE

Hydrolysis

In 2 hydrolysis studies, conducted according to US EPA Guidelines, hydrolysis was quick with a half-lives of 3.4 and 5.1 days at pH 5, and 14 and 22 minutes at pH 9. The degradation curves at pH 7 showed a break between 2-4 days, with half-lives of 20 h and 1.4 days for the first 3 days, and 14 days for the last 3-30 days. Flumioxazin was hydrolysed to the amide 482-HA at all pHs tested but cleavage of the amide linkage to give the amine and the dicarboxylic acid only occurred at pH 7 and 5.

In the second hydrolysis study with flumioxazin labelled in the tetrahydrophthalimido (THP) moiety, again conducted according to US EPA Guidelines**,** the half lives were 3.43 days and 14.5 minutes at pHs 5.0 and 9.0, respectively, following the first-order kinetics. Under the neutral conditions at pH 7.0, hydrolysis was again biphasic as previously, with the initial half-life of 20.2 h within 2 days and thereafter slower, with a half-life of 10.9 days.

Although the rates were greatly dependent on pH, flumioxazin was susceptible to hydrolysis at any pH tested. Based on the initial half-lives, it is rated as readily degradable at pH 5, and very rapidly degradable at pH 9 and 7.

Photolysis

In aquatic photolysis studies, conducted to US EPA Guidelines, the calculated solution photolysis half-life of flumioxazin (phenyl label) at pH 5 was 20.9 hours over the first 48 hours but the rate of degradation decreased thereafter. From 48 hours to 720 hour the half-life was calculated by Environment Australia as 462 hours and it was noted that this is significantly longer than that in the dark controls. The calculated degradation half-life under dark control conditions was 118.5 hours and was first order over the entire time, consistent with the hydrolysis study. For the compound labelled in the other ring (THP label), the half-life was 26.3 hours for the first 48 hours but over the last 28 days there was no consistent degradation and it would appear that degradation of parent stopped. The calculated degradation half-life under dark control conditions was 96 hours.

The principal photo-degradate in both cases was identified as a ring-contracted product, formed by hydroxylation and subsequent molecular rearrangement.

The soil photolysis was conducted according to US EPA Guidelines using a microbially active soil. Flumioxazin degraded more rapidly on irradiated soil than on dark soil.

The calculated soil degradation half-life using the phenyl label was 3.2 days and with the THP label the half-life was 8.4 days. The half-lives for dark controls were 11.8 and 15.7 days, consistent with the aerobic soil metabolism study (half-life 11.9 - 17.5 days).

Aerobic soil metabolism

The soil metabolism of ^{14}C-flumioxazin, uniformly labelled in either the phenyl or in the THP moieties, was studied under aerobic conditions using a sandy loam soil in accordance with US EPA Guidelines. Flumioxazin degraded under the study conditions with a half-life for the first 28 days of 11.9 and 17.5 days for the phenyl and THP labels respectively. Over the first 90 days the half-life was 18 for the phenyl label and 28 days for the THP label, the duration of the THP study. The primarily degradates were CO_2 (11% for phenyl and 55% for THP), and soil-bound residues, with several minor components.

The half-life of flumioxazin was studied under aerobic conditions using 4 soils, typical for soybean and peanut growing regions of US, in accordance with the EPA Pesticide Assessment Guidelines. This was not conducted as a metabolism study but rather to determine the half-life of parent in the selected soils. The first half-lives ranged from 5 days to 19 days and are comparable to those in the previous studies using radio-labelled flumioxazin.

Anaerobic soil metabolism

The soil metabolism of flumioxazin was studied in accordance with US EPA Guidelines under anaerobic conditions using a sandy loam soil. Flumioxazin was uniformly labelled in either the phenyl or in the THP moieties. Flumioxazin rapidly degraded/dissipated from the water column to the sediment with the half-life/dissipation rate or of 3.1 and 4.1 hours for phenyl and THP label, respectively. The half-life in the soil phases was approximately 117 days and 73 days for phenyl and THP, respectively.

The proposed degradation pathway involved hydrolysis to the amide (~50% after 1day) as the major metabolite, which was then reduced. At Day 182, there was 16.2% and 14.7% of the applied ^{14}C as the reduced amide, in [^{14}C -phenyl] and [^{14}C -THP] flumioxazin treated waters samples, respectively. Analysis of the soil extracts recovered some parent, ~11 % for both labels, together with smaller amounts of the two principal degradates, the amine and later on the reduced amine.

Mobility

No batch adsorption/desorption studies for flumioxazin were presented. However, adsorption studies on 3 of the metabolises in a range of agricultural soils, conducted to US EPA Guidelines, were presented. The metabolites were: the amine formed from hydrolysis/degradation, the diacid and a minor metabolite. The amine was rated as having low to medium mobility (K_{oc} from 336 - 620), the diacid as medium to very high mobility (K_{oc} 13 - 339) and the minor metabolite as low to high (K_{oc} 65 - 1052). As these metabolites further degraded in the degradation studies, significant leaching is not expected despite the adsorption/desorption studies showing high mobility.

In column leaching studies using 4 agricultural soils and radio-labelled flumioxazin (phenyl and THP label), conducted to US EPA Guidelines, the mobility of flumioxazin was low to high. There was significant leaching in the sand (64 - 67% of applied) and sandy loam soils (51 - 54%) but less in the silt loam (7 - 15%) and clay loam (3 - 4.9%) soils.

The K_{oc}s calculated from the column leaching were (average from both labels) 111, 270, 1190, and 655 for the sandy loam, sand, silt loam and clay loam soils respectively.

Based on the results of this study and the short aerobic degradation half-life of the test material in a soil metabolism study (11.9 days), the company concludes the potential for flumioxazin to leach in soil is low. While significant leaching in the sandy soil columns occurred, this was not encountered in the field dissipation study or the lysimeter study.

The leaching characteristic of aged [phenyl- ^{14}C]-flumioxazin was conducted in accordance with US EPA Guidelines using soil column leaching methods on 4 representative agricultural soils. After aging for 30 days under aerobic conditions the aged soil samples were applied to leaching columns then leached continually over 20 days. Most of the applied radioactivity remained in the uppermost part of the soil columns. The amount of applied radioactivity found in the leachate ranged from 28.0% for the sandy loam to 3.6% for the clay loam. The radioactivity in leachate was distributed primarily among unchanged parent, a number of metabolites and unextracted residues.

Field Dissipation

Flumioxazin was applied at 107 g ai/ha to no-till ground (ie no crop but dead vegetation present). The application, site preparation and test site location were based on the proposed use pattern for soybeans. The soil was classified as silt loam.

The results show that dissipation of flumioxazin at this test site occurred in two stages. First order regression analysis of the 0 - 28 day data (linear phase of the study) resulted in an estimated half-life of 12.5 days for flumioxazin. Using all the data points gave a half life of 75 days and a DT_{90} of 246 days but the fit was relatively poor; however, when compared to the raw data, the DT_{90} was consider reasonable.

No significant vertical movement of the flurnioxazin residues in the soil profile was observed.

Field Lysimeter Study

A radio-labeled field dissipation study was conducted following US EPA Guidelines using outdoor lysimeters. The lysimeters were pressed into the soil (a loamy sand) to a depth of approximately 90 cm (36 inches) equipped for the collection of leachate and surface runoff water.

Flumioxazin, uniformly radio-labelled with ^{14}C, was applied to the top of the lysimeters at 107 g ai/ha. Then the lysimeters were subjected to natural environmental conditions and supplemental irrigation water was added as necessary so that the lysimeters received equivalent to about 110% of the cumulative 10-year average rainfall on a weekly basis.

The majority of the radioactivity was confined to the surface 0 - 7.5 cm soil layer. No significant radioactivity was detected in soil layers below the surface layer and analysis of these soil sections showed that there was no detectable flumioxazin.

In no case was the amount of radioactivity present in the leachate or runoff water greater than or equal to 1% of applied and therefore no attempt was made to characterise leachate or runoff water radioactivity.

Using first-order kinetics, the calculated field half-life for flumioxazin over the first 111 days was approximately 27 days and 38 days over the whole 177 days

Bio-accumulation

It was argued by the applicant that flumioxazin is likely to hydrolyse in any bioaccumulation test and only the hydrolysis degradates are likely to be available for possible bioaccumulation.

Given that these are quite polar (log P_{ow} < 1), significant bioaccumulation of these compounds is unlikely. Further, as the metabolites formed by soil micro-organisms are tightly bound to soil, and thus do not desorb into the surrounding water, they are unlikely to bio-accumulate in the environment. The lack of a bioaccumulation study was considered acceptable.

Accumulation in soils

Based on a worst-case aerobic soil biodegradation DT_{50} of 28 d, Environment Australia calculated an annual carryover of about 0.01% or 3.9% using the field half-life of 78 days. If annual applications were to be made to the same plot of land, accumulation of flumioxazin in soils would negligible.

ENVIRONMENTAL TOXICOLOGY

All studies on environmental toxicology were conducted to US EPA Guidelines, unless otherwise stated.

Birds

Flumioxazin was practically non-toxic to both bobwhite quail and mallard duck adults in single oral dose tests with the LD_{50} > 2,250 mg-ai/kg-bw. This was also true with quail chicks and ducklings in 5-d dietary exposures with the LC_{50} > 5,620 mg-ai/kg food.

In the one-generation studies for both species, the NOEC was the highest dose tested of 466 mg-ai/kg food.

Fish

In flow-through conditions flumioxazin is rated at worst as slightly toxic to bluegill, with a 96-hour LC_{50} of > 21 mg/L and NOEC of 3.9 mg/L, and moderately toxic to rainbow trout with a 96-hour LC_{50} of 2.3 (1.8 - 2.8). For sheeps-head minnow there was no effects at 4.7 mg-ai/L, the highest concentration achieved in the study, which was the NOEC and flumioxazin is rated at worst as moderately toxic to this species.

In a 21-day toxicity test to rainbow trout, again under flow-through conditions, the LC_{50} was estimated at 2.1 mg/L but was not considered reliable. The 21 -day no-observed effect concentration was 0.37 mg/L.

An early life stage test (87-days) using rainbow trout was conducted in accordance with US EPA Guidelines with a NOEC of 7.7 µg/L and LOEC of 16µg/L, from the adverse effects on fish growth.

It is noted that the NOEC in the early life cycle test is very low, compared to the NOEC in the acute tests.

Aquatic invertebrates

Flumioxazin was moderately toxic (under flow-through conditions) to water fleas *(Daphnia magna)* with the 48-hour EC_{50} = 5.9 mg a.i./L (5.4 - 6.5 mg/L), based on the analysis of centrifuged water samples (soluble fraction), and rated as slightly toxic based on the analysis of non-centrifuged water samples EC_{50} = 17 mg a.i./L (14 - 22 mg/L). The NOEC was estimated at 8.54 mg ai/L from the non-centrifuged samples.

It is highly toxic to mysid shrimp, with 96-hour EC_{50} of 0.23 (0.19 - 0.28) mg ai/L, again under flowthrough conditions.

It is moderately toxic to oysters, with the EC_{50} (shell growth) of 2.8 (1.7 - 4.0) mg ai/L. At the highest test concentration, there was reduced feeding and several oysters had gaped shells (sign of severe stress for oysters).

In a life cycle study using *D. magna*, the LOEC was 105 µg ai/L with survival and reproduction of the adults being the effects observed at this concentration. The NOEC was 57 µg ai/L. The first deaths occurred on day-5. Again the *Daphnia* in the life cycle test were very much more sensitive to flumioxazin compared to the acute tests. In the 28-day life cycle study for mysid shrimp, the no observed effect concentration (NOEC) was 15 µg ai/L and the LOEC was 27 µg ai/L, from effects on both reproduction and growth at this concentration.

Aquatic plants

As expected for a herbicide, flumioxazin was very highly toxic to a number of alga species with EC_{50} ranging from 0.79 to 21 µg ai/L. It was also very highly toxic to duckweed with an E_bC_{50}= 0.41 µg ai/L.

Test conditions were static and analysis of the test solutions on termination of the studies (after 3 - 5 days) showed that flumioxazin was unstable and all results were based on initial concentrations. In these tests flumioxazin inhibited algae growth, but after a few days there were indications that the growth of these aquatic plants recovered.

Terrestrial invertebrates

Earthworms were relatively insensitive to flumioxazin with the 14-d LC_{50} > 984 mg ai/kg soil. Honeybees were also insensitive with the 48-h contact LD_{50} of > 105 µg ai/bee.

Soil microorganism processes

The effect of flumioxazin on soil respiration and nitrogen turnover in soil microorganisms was tested at 1.6 mg ai/soil, equivalent to 1.2 kg ai/ha, some 80 times above the proposed Australian rate.

Respiration was unaffected with production of CO_2 for treated-soil within 10% of control throughout the study. There was a decline in ammonium and in nitrate concentrations on day-14 but by day-28, there was no significant difference compared to control.

In conclusion, flumioxazin was considered to present a low risk to soil microflora at the Australian label rate.

Terrestrial plants

No studies were presented.

PREDICTION OF ENVIRONMENTAL HAZARD

Registration is sought for the control of various grasses and broadleaf weeds when mixed with glyphosate or paraquat/diquat, as a pre-emergent spray for use prior to sowing various crops, as per the directions for use. Residues from application would be expected on plant surfaces and soil. Surface water, uncultivated land and nearby non-target plants (e.g. trees and grasses) may be contaminated through over-spray, spray drift and/or run-off.

Estimated Environmental Concentrations

Concentration in soil

Given a direct application to bare soil, incorporation into the top 10 cm and a soil bulk density of 1.4 g/mL, the estimated environmental concentration (EEC) of flumioxazin in treated soil would be 10.7 µg ai/kg soil per application (15 g ai/ha). Assuming two applications per year, three months apart and a worst-case aerobic soil metabolism DT_{50} of 28 days, the maximum concentration is 11.8 µg ai/kg soil immediately after the second application.

With a worst-case DT_{50} of 78 days from the field study, the annual carry-over is about 4% assuming first order degradation and no soil accumulation is expected.

Concentration in water

In a worst-case scenario of a direct over-spray of a 15 cm deep body of water with the maximum single application rate of 15 g ai/ha, the EEC would be 10 µg ai/L. As the dissipation DT_{50} from the water column very fast, (< 4% after 3 d from the anaerobic metabolism study), hydrolysis is also fast (< 3 days) and flumioxazin is ready degradable in soil, no accumulation is expected.

Hazard to Terrestrial Organisms

Birds

With the single oral dose LD_{50} for quail and mallards of > 2,250 mg ai/kg bw and the dietary LC_{50} of > 5520 mg ai/kg food for both species, the hazard to birds **was** calculated to be very low, based on expected concentrations in avian diets.

The most sensitive chronic NOEC for quail of 466 mg ai/kg food is 290 times higher than the estimated dietary intake and indicates no hazard is expected.

Earthworms

The 14-d LC_{50} for the earthworm was > 968 mg ai/kg soil, which is significantly higher than the worst case soil EEC of 0.010 mg ai/kg in the top 10 cm of soil.

Thus the proposed use of flumioxazin is not expected to be an acute hazard to earthworms. Environment Australia also expects the chronic hazard to be low given the very low acute toxicity, ready degradation and low application rate.

Beneficial arthropods

The hazard to honey bees is expected to be very low as the maximum application rate of 15 g ai/ha (equivalent to 0.15 µg ai/cm^2) is significantly lower than the most sensitive contact LD_{50} of > 105 µg ai/bee, assuming that a honeybee is approximately 1 cm^2 in surface area.

Terrestrial plants

As a herbicide with effects on grass and broadleaved weeds, flumioxazin is expected to cause adverse effects to a number of non-target broadleaf plants. At the maximum application rate of 15 g ai/ha, direct over-spray could be expected to be phytotoxic to a range of non-target plants. The product is applied tank mixed as a knockdown herbicide with glyphosate or paraquat/diquat, which are very phytotoxic by contact. It is not possible to extrapolate to Australian native plants, but clearly spray-drift could be toxic to non-target plants and should be avoided.

Remnant native vegetation on the margins of cereal paddocks can include threatened plant species, especially in WA. The absence of terrestrial plant data requires use of duckweed as a surrogate, and a 10 metre spray drift would mitigate the risk to these native plants species.

Soil microorganisms

The proposed use of flumioxazin is unlikely to be a hazard to soil microorganisms, as the LOEC for adverse effects on nitrogen mineralisation was 1.6 mg ai/kg soil.

This is higher than the soil EEC of 0.010 mg ai/kg soil.

Hazard to Aquatic Organisms

Direct over-spray

The worst-case scenario of a direct over-spray of a 15 cm deep body of water with *PLEDGE*® would result in an EEC of 0.010 mg ai/L.

Acute effects on fish are unlikely given the most sensitive LC_{50} of 2.3 mg ai/L for rainbow trout, which is significantly above the EEC. While the chronic 87 days NOEC of 7.7 µg ai/L is slightly lower than the EEC, and therefore indicate some risk, the rapid dissipation from water will limit any potential chronic hazard.

Acute effects on water fleas are also unlikely, with EC_{50} of 5.9 mg ai/L and a chronic NOEC of 57 µg ai/L, both higher than the EEC from direct over-spray.

Similarly, effects on mysid shrimp, used as a surrogate for sensitive invertebrates, are unlikely with an EC_{50} of 0.26 mg ai/L and a chronic NOEC of 15 µg ai/L.

However, there is a high hazard to algae, IC_{50} of 0.79 - 21 µg ai/L, and to duckweed, IC_{50} of 0.41 µg ai/L.

Despite the risk to algae and duckweed, the likelihood of a direct over-spray of natural waterways is minimal.

Spray-drift

Application of *PLEDGE*® may contaminate surface waters by spray drift, where the resulting concentration of flumioxazin is expected to be considerably lower than the EEC from direct over-spray. While the risk and extent of spray drift can be minimised, it must be assumed that some spray drift will occur and hence contamination of soil and water outside the target areas.

From German figures for spray-drift, the hazard was calculated to be acceptable to duckweed at 10 metres away from the edge of the sprayed field. A label restraint limiting use with waterbody 10 metres downwind would be sufficient to mitigate the risk. It should be noted that with duckweed as a surrogate for terrestrial plants, threatened terrestrial plants would also be protected by a similar buffer.

With the rapid dissipation of flumioxazin from water column and subsequent degradation, there is limited potential for a chronic hazard to be of concern.

Run-off

In a worst-case scenario, with 10% of applied run-off a treated paddock, calculations indicated an unacceptable hazard for both algae and duckweed. However, this is a worst--case scenario and when refined to a more realistic scenario the hazard to duckweed is low. It should be noted that this still assumes that all the runoff enters a pond and that there is no runoff from untreated land.

The hazard to aquatic plants from runoff is considered to be acceptable.

Leaching and Groundwater

The results from the column leaching studies show that flumioxazin leached significantly in sandy soils. Based on the K_{oc}s determined in these leaching studies and a half life of 18 days, calculations indicated that flumioxazin is an transitional leacher in sandy soils, but an improbable leacher on the silt loam and clay loam soils.

However, the field and the field lysimeter studies (sandy soil) clearly showed that there was no movement of flumioxazin to deeper soil profiles.

Leaching is not expected to be significant in areas where flumioxazin is proposed for use.

EFFICACY AND SAFETY ASSESSMENT

Justification and Use Pattern

The rationale behind the product *PLEDGE* ® is that it will be used as an additive to glyphosate-based or paraquat/diquat-based herbicides, which are used for knockdown of weeds prior to sowing winter crops (e.g. wheat, barley, lupins, canola, cotton, oats, faba beans, field peas, chick peas and lentils). The aim is to improve weed brownout prior to sowing these crops, and it has been shown to improve the control of several "difficult to control" species [e.g. bellvine (*Ipomea plebeia)*, capeweed (*Arctotheca calendula)*, marshmallow (*Malva parviflora)*, sow thistle (*Sonchus oleraceus)*, wireweed (*Polygonum aviculare)* etc.].

Farming systems across Australia have become dependent upon glyphosate for fallow and pre-sowing weed control, thus becoming at risk for the development of herbicide resistance. While paraquat/diquat herbicides have been available as an alternative, their efficacy has been variable. Addition of *PLEDGE*® to paraquat/diquat herbicides improves efficacy, to provide a viable alternative to glyphosate.

Hence this product is likely to have a genuine and important role in weed management in Australian agriculture.

EVALUATION OF EFFICACY AND CROP-SAFETY.

1. Adequacy of efficacy data

Trial design (controls, treatments, replicates etc.)
The application was well supported with statistically sound trial work. Trial design, layout and conduct were satisfactory.

Experimental conditions (e.g. pest pressure, weather conditions etc.)
Site selection, weeds present and weed pressure was satisfactory. All trials had sufficient weed pressure and located at suitable sites (soils and climates), reflective of the product's use.

Analysis of trial data, interpretation.
Trial data was appropriately analysed and interpretation of the experimental data was appropriate and satisfactory. Majority of the data were subject to appropriate statistical analyses and the conclusions drawn are supported.

Trial validation, location, date.
All trials have been conducted, analysed and interpreted by suitably qualified personnel. As stated above, trials were located at suitable sites (soils and climates), reflective of the product's use. This provides a representative range of climatic conditions, soil types, and production scenarios to test efficacy.

General applicability for commercial use.
The uses outlined and the methods used in the trials are applicable to commercial use.

2. Claims

Efficacy.
The efficacy data presented is adequate, well presented and generally the data support the label claims, except for sub clover. The data presented for clover only reflects suppression and not control

The reviewer strongly recommended that the wording under the "Weeds Controlled" column needs to be changed, to differentiate between what may be controlled and what may be suppressed. In southern farming systems, sub clover can be a major weed in the first crop sown after a pasture phase. The label needs to indicate that only **suppression** of this weed is likely. The applicant has agreed with this and amended the label accordingly.

Phytotoxicity.
There is no crop at the time of treatment, and there was no evidence of phyto-toxicity in crops planted after treatment.

3. Directions for use

These are clear and adequate.

4. Safety to non-target species

There is no direct, desirable, target-species that could be affected as this treatment occurs before sowing. There is no evidence that crops planted after treatment are affected.

Appropriate and adequate warnings have been included on the label to minimise or prevent damage to non-target species (e.g. the specific warnings against drift). Hence when used as directed, the product should not pose any threat to non-target species.

5. Adequacy of precautionary advice

This is adequate.
There are no plant back issues involved (e.g. no herbicide residues that could delay planting of crops after treatment).

6. Compatibility of Proposed With-holding Period (WHP) with Good Agricultural Practice (GAP)

Again, there are no plant back issues.

The label specifically states that failed crops should not be grazed for 65 days after application of the product, and that treated weeds are not to be grazed. The reviewer strongly recommended that the wording could be amended to make it clear that the 65 days WHP refers to vegetation/crop grown immediately after treatment with Pledge.

Also, rewording of the "Withholding Period" was recommended to reflect that grazing is not confined to just "failed" crops.

Healthy crops may be grazed as a routine management practice, particularly in southern farming systems. Crops can also be cut for feeding and this is not accounted for on the label. Inclusion of a harvest withhold is also appropriate. Reworded statements could be:

"DO NOT graze treated areas, or cut treated crops for stock feed for 6 weeks after application"
"Harvest Withhold - Not required when used as directed"

The grazing statement on cotton remains unchanged.

The APVMA concurs with this suggestion, and the applicant also agreed. Hence the label has been changed accordingly.

7. Special Considerations

Nil.

8. Conclusion

The application is justified, conclusions from the data are valid and the product shown to have a place in Australian agriculture.

This submission for registration is supported, given the wording changes recommended in (2) and (6) above have been made.

The applicant was commended for submitting a well-written, logical and easy to follow application.

Hence registration of this product was recommended with respect to efficacy and crop-safety.

The APVMA has considered the above findings of its advisor and has accepted the recommendation.

LABELLING REQUIREMENTS

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

PLEDGE® 500 WDG HERBICIDE

ACTIVE CONSTITUENT: 500g/kg FLUMIOXAZIN

GROUP	G	HERBICIDE

For rapid knockdown and control of various grass and broadleaved weeds when mixed with glyphosate or paraquat/diquat herbicides prior to sowing wheat, barley, lupins, faba beans, field peas, chick peas and lentils as per the Directions for Use table in the attached booklet.

THIS PRODUCT CONTAINS FLUMIOXAZIN, WHICH CAUSES BIRTH DEFECTS IN CERTAIN LABORATORY ANIMALS.
WOMEN OF CHILD BEARING AGE ARE ADVISED NOT TO MIX, LOAD OR SPRAY THIS PRODUCT.
THEY SHOULD KEEP OUT OF AREAS THAT ARE BEING SPRAYED.

CONTENTS 1, 5 and 10 kg

SUMITOMO CHEMICAL AUSTRALIA PTY LTD
501 Victoria Avenue
Chatswood NSW
Tel: 02 9904 6499
A B N: 21 081 096 255

DIRECTIONS FOR USE

RESTRAINTS

DO NOT treat weeds under poor growing or dormant conditions (such as occur in drought, waterlogging, disease, insect damage or following frosts) as reduced control may result. Weeds should be actively growing at time of treatment.

CROP SITUATION	WEEDS CONTROLLED	RATE (mL/ha)	STATE	CRITICAL COMMENTS
PRIOR TO SOWING wheat, barley. oats, canola, lupins, Chick peas, Faba beans, field peas, Lentils and cotton	Refer to the glyphosate, glyphosate- trimesium and paraquat/diquat product labels for details of the grass and broadleaf weeds controlled.	30 g/ha of Pledge plus the label rate of tank mix partner plus an adjuvant°	All States	Observe the restraints, rates, mixing and general instructions on the knockdown-herbicide labels. product labels.
	The addition of Pledge 500 WDG Herbicide to glyphosate will increase the speed of brownout and may improve final control of the following weeds: Bellvine *(Ipomoea plebeia)* Bladder ketmia *(Hibiscus trionum)* Caltrop *(Tribulus terrestris)* Capeweed *(Arctotheca calendula)* Cow vine *(Ipomea ioncophylla)* Doublegee *(Emex australis)* Erodium False castor oil *(Datura stromonium)* Liverseed grass *(Urochloa panicoides* Marshmallow *(Malva parviflora)* *Medicago spp.* Noogoora burr *(Xanthium occidentale)* Paterson's Curse *(Echium plantagineum)* Seedling Lucerne *(Medicago sativa)* Shepherd's Purse *(Capsella bursa-pastoris)* Sowthistle *(Sonchus oleraceus)* Sunflower (*Helianthus annus*) Redroot amaranth *(Amaranthus retroflexus)* Subterranean clover *(Trifolium subterranean)*** Volunteer canola *(Brassica napus)* Wild radish *(Raphanus raphanistrum)* Wireweed *(Polygonum aviculare)* If one of the above weeds is the dominant weed. and there is no specific rate for it on the Glyphosate product label, consult the label's generic annual-weed rate range. Select from within this range to suit the weed-stage, weed density, conditions etc of your situation.	--		Addition of Pledge 500 WG Herbicide to knockdown products will increase the speed at which treated weeds develop visible symptoms of phytotoxicity (compared to the results achieved with tank mix partner products alone) and may improve the final control of certain broadleaved weeds. To ensure uptake of Pledge 500 WDG Herbicide. **DO NOT** sow crops for at least one hour after application. Always refer to the tank-mix partner product label in case a longer interval is required. ®Always apply with Hasten Spray Adjuvant or Kwickin Spray Adjuvant at 0.5 - 1 L/1 00L (use the lower rate on smaller, actively growing weeds), or Uptake' Spraying Oil at 500 mL/100L.

**** SUPPRESSION ONLY.**

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

WITH-HOLDING PERIODS :
HARVESTING : NOT REQUIRED WHEN USED AS DIRECTED.

GRAZING / STOCK-FEED :
Wheat, barley, oats, canola, lupins; chickpeas, faba beans, field peas and lentils : **DO NOT** graze crop or treated vegetation for 6 weeks after application.
Cotton: **DO NOT** graze failed crop.

GENERAL INSTRUCTIONS

Apply <u>ONLY</u> as a tank mix with glyphosate, glyphosate-trimesium or paraquat/diquat herbicides.

MIXING

To ensure even mixing, half-fill the spray tank with clean water and add the required amount of Pledge 500 WGD Herbicide. Mix thoroughly. Add the knockdown herbicide and remaining water. Mix thoroughly. Add spray additive near the end of the filling process to minimize foaming. Always maintain adequate agitation during application and use the tank *mix* promptly.

APPLICATION

Refer to the Direction for Use and General Instructions of the knockdown herbicide label.

SPRAYER CLEANUP

After Pledge 500 WDG is applied, the following steps must be taken to clean the spray equipment:

1. Completely drain the spray tank, rinse the sprayer thoroughly, including the inside and outside of the tank and all in-line screens.
2. Fill the spray tank with clean water and flush all hoses, booms, screens and nozzles.
3. Add 1 litre of 3% household ammonia for every 100litres of water, circulate through sprayer for five minutes, then flush all hoses, booms, screens and nozzles for a minimum of fifteen minutes.
4. Drain tank completely.
5. Add enough clean water to the spray tank to allow all hoses, booms; screens and nozzles to be flushed for two minutes.
6. Remove all nozzles and screens and rinse them in clean water.

Equipment with Pledge 500WG residue remaining in the system may result in crop injury to the subsequently treated crop.

COMPATIBILITY

Pledge 500 WG Herbicide is compatible with:

Roundup[2] CT Herbicide
Roundup Max Herbicide
Roundup Dry Herbicide
Nufarm Glyphosate CT Herbicide
Spray.Seed[3] 250 Herbicide and
Touchdown[3] Broadacre Herbicide.

RESISTANT WEEDS WARNING

GROUP	G	HERBICIDE

Pledge 500 WG Herbicide is a member of the diphenyl ether group of herbicides. The mode of action of Pledge 500 WG Herbicide is to inhibit protoporphyrinogen oxidase. For weed resistance management, Pledge 500 WG Herbicide is a Group G Herbicide.

Some naturally-occurring weed biotypes resistant to Pledge 500 WG Herbicide and other Group G 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 Pledge 500 WG Herbicide or other Group G Herbicides.

Since the occurrence of resistant weeds is difficult to detect prior to use, Sumitomo Chemical Australia Pty Ltd accepts no liability for any losses that may result from the failure of Pledge 500 WG Herbicide to control resistant weeds.

Strategies to minimize the risk of herbicide resistance are available. Contact your farm chemical supplier, consultant or local Department of Agriculture.

PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS

DO NOT apply Pledge 500 WG Herbicide under weather conditions (e.g. wind), or from spraying equipment, that may cause spray to drift onto nearby susceptible crops/plants, cropping lands or pastures.

A 10 meter buffer should be present between sprayed areas and any adjacent vegetation. Care should be taken to avoid damage to adjoining native grasses or grass crops.

Pledge 500 WDG Herbicide should **not** be applied through misting equipment or any other method likely to cause excessive drift.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

DO NOT contaminate streams, rivers or waterways with the product or used containers.
DO NOT apply Pledge if wind is likely to cause drift onto natural and impounded lakes, waterways, streams or rivers.
A 10 meter buffer should be present between sprayed areas and natural and impounded lakes, dams, waterways, streams or rivers.

STORAGE AND DISPOSAL

Store in locked room or place away from children, animals, food, feedstuffs, seed and fertilisers. Store in the closed, original container in a dry, cool well-ventilated area out of direct sunlight. Shake empty container into spray tank.

DO NOT dispose of undiluted chemicals on-site. Puncture, or shred and bury empty containers in a local authority landfill.

If not available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose, clear of waterways, desirable vegetation and tree roots. Empty containers and product should **NOT** be burnt.

SMALL SPILL MANAGEMENT

Sweep up material and contain in a refuse vessel for disposal in the same manner as for containers (see Storage and Disposal).

PRECAUTION STATEMENTS

WARNING: This product contains flumioxazin which causes birth defects in certain laboratory animals. Women of child bearing age are advised not to mix, load or spray this product. They should keep out of crops being sprayed.

SAFETY DIRECTIONS

Poisonous if absorbed by skin contact or swallowed. Will irritate eyes and skin. Avoid contact with eyes and skin. Wash hands after use. When opening the container and preparing spray wear cotton overalls buttoned to the neck and wrist and a washable hat and elbow-length PVC gloves and face shield or goggles. After each days' use, wash gloves, face shield or goggles and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre (Tel. 131126).

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet (MSDS).

NOTICE TO BUYER

Sumitomo Chemical Australia Pry Ltd will not accept any responsibility whatsoever and howsoever arising and whether for consequential loss or otherwise in connection with the supply or use of these goods other than responsibility for the merchantable quality of the goods and such responsibilities mandatory imposed by Statutes applicable to the sale or supply of these goods. To the extent allowed by such statutes the liability of Sumitomo Chemical Australia Pty Ltd is limited to the replacement of the goods or (at the option of Sumitomo Chemical Australia Pty Ltd) the refund of the price paid and is conditional upon a claim being made in writing and where possible sufficient part of the goods to enable proper examination being returned to Sumitomo Chemical Australia Pty Ltd.

APVMA Approval No: Batch No: Date of Manufacture:

THIS PRODUCT IS NOT CONSIDERED TO BE A DANGEROUS GOOD UNDER THE AUSTRALIAN CODE FOR THE TRANSPORT OF DANGEROUS GOODS BY ROAD AND RAIL	
IN A TRANSPORT EMERGENCY DIAL: 000 POLICE OR FIRE BRIGADE	F0R SPECIALIST ADVICE IN AN EMERGENCY ONLY PHONE: 1800 024 973 TOLL FREE - ALL HOURS - AUSTRALIA WIDE

[1] Trademark of Dow AgroSciences LLC; [2] Registered trademark of Monsanto Company USA; [3] Registered trademark of a Syngenta Group Company

GLOSSARY

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

References

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

APVMA PUBLICATIONS ORDER FORM

To receive a copy of the full technical report for the evaluation of **flumioxazin** in the product ***PLEDGE® 500 WG HERBICIDE***, please fill in this form and send it, along with payment of $30 to:

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

Alternatively, fax this form, along with your credit card details, to:

David Hutchison, Pesticides Division at (02) 6272-3218.

Name (Mr, Mrs, Ms, Dr)_____
Position _____
Company/organisation _____
Address _____
Contact phone number (___) _____

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

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

___ Bankcard ___ Visa ___ Mastercard

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

Signature_____ Date _____