Public Release Summary
on

Evaluation of the new active

MESOSULFURON-METHYL

in the product

Atlantis Selective Herbicide

National Registration Authority
for Agricultural and Veterinary Chemicals

February 2003

Canberra
Australia

54252

ISSN1443-1335

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FOREWORD

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is an independent statutory authority with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the NRA works in close cooperation with advisory agencies, including the Commonwealth Department of Health and Ageing (Therapeutic Goods Administration [TGA]), Environment Australia [EA] (Chemicals and the Environment Branch), the National Occupational Health and Safety Commission [NOHSC] (previously Worksafe Australia) and State departments of agriculture and environment.

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

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

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

More detailed technical assessment reports on all aspects of the evaluation of this chemical can be obtained by completing the order form in the back of this publication and submitting with payment to the NRA. Alternatively, the reports can be viewed at the NRA Library First Floor, 22 Brisbane Avenue, Barton, ACT.

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

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LIST OF ABBREVIATIONS AND ACRONYMS

AC	Active Constituent {source for product manufacture} (previously called the Technical Grade Active Constituent [TGAC])
ac	active constituent
ai	Active ingredient
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
BD	Bulk Density (soil)
bw	bodyweight
d	Day
DAT	Days After Treatment
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
EUP	End Use Product
Fo	original parent generation
FW	Fresh Weight
g	Gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
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
LC-MS/MS	Liquid Chromatography, Mass Spectroscopy

LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OM	Organic Matter
PHI	Pre-Harvest Interval
po	Oral
ppb	Parts per billion
PPE	Personal Protective Equipment
ppm	Parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	(See AC above)
TRR	Total Radioactive Residues
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of *ATLANTIS® SELECTIVE HERBICIDE (ATLANTIS®)*, which contains the new active constituent mesosulfuron-methyl (a sulfonylurea compound). The product also contains mefenpyr-diethyl, a crop-safener which exists in some currently registered products.

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

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

Written comments should be submitted by **21 March 2003**, and addressed to:

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Applicant
Bayer CropScience Pty. Ltd.

Product Details
It is proposed to register *ATLANTIS®*, containing 30g/L mesosulfuron-methyl and 90 g/L mefenpyr-diethyl, as a suspension concentrate. The product will be imported fully formulated and packaged in 5 L, 10 L and 20 L packs, from Germany.

Mesosulfuron-methyl is a member of the sulfonylurea group of herbicides. Its mode of action is to inhibit the biosynthesis of essential amino acids in susceptible plants, through inhibition of acetolactate synthase (ALS). With respect to weed resistance, mesosulfuron-methyl is classed as a Group B herbicide.

The application is for early post-emergence use (both with respect to the crop and weeds) in wheat. The weeds controlled or suppressed are wild oats (*Avena* spp), annual phalaris (*Phalaris paradoxa* only), brome grass (*Bromus diandrus*) and annual ryegrass (*Lolium rigidium*).

The rationale behind the product *ATLANTIS®*, is that it is an ALS-inhibitor herbicide for **post-emergence** use in wheat, to control or suppress the weeds above. It may also reduce the need for tank mixes (e.g. with Group-A grass herbicides) to achieve this.

The rate of product use is 330 mL/ha. *ATLANTIS®* is proposed for registration in all states.

It is not expected that this product would increase the rate of evolution of herbicide-resistance, or environmental load, by sulfonylurea herbicides, as it is expected to replace existing sulfoynlureas.

Additionally, as this product may replace tank-mixes in wheat which use Group-A herbicides (for grass control), then it may provide an alternative that could reduce the evolution of Group-A herbicide resistance.

A product containing mesosulfuron-methyl alone (with mefenpyr-diethyl) is expected to be registered in Italy by December 2003. Mesosulfuron-methyl (30 or 31.6 g/kg) with iodosulfuron-methyl (6.3 or 30 g/kg) [and 96.3 g/kg mefenpyr-diethyl] is contained in products that are registered in a number of overseas countries: France, Iraq, Pakistan, South Africa and Turkey. The company expects registration in all countries where wheat is commercially grown, by the end of 2003 or the middle of 2004.

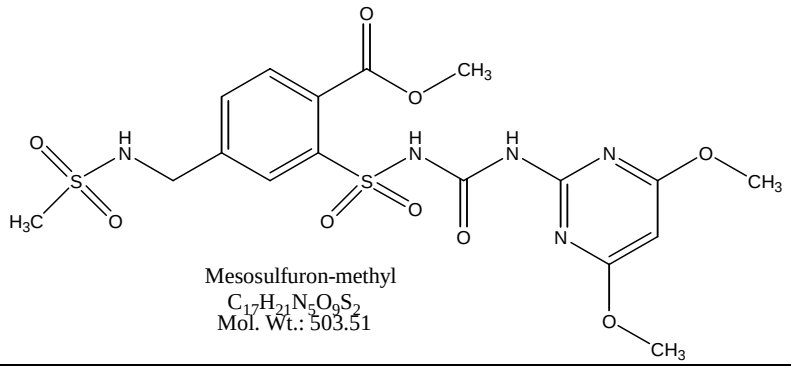
CHEMISTRY AND MANUFACTURE

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) has already approved a new active constituent (AC), mesosulfuron-methyl. Mesosulfuron-methyl is a new sulfonylurea herbicide for early-post emergence control of wild oats and phalaris, and suppression of brome grass and annual ryegrass in wheat.

The NRA is now considering registration of a formulated product [*ATLANTIS* ®] containing this new active constituent, mesosulfuron-methyl. The Chemistry and Manufacturing details of the new active constituent and product are presented below.

Particulars of Active Constituent

Chemical Characteristics

Common name:	mesosulfuron-methyl
IUPAC Name:	methyl 2-[3-(4,6-dimethyoxypyrimidin-2-yl)ureidosulfonyl]-4-methanesulfonamidomethybenzoate
CAS Name:	methyl 2-[[[[4,6-dimethoxy-2-pyrimidinyl)amimo]carbonyl]amimo]-sulfonyl]-4-[[methylsulfonyl)amino]methyl]benzoate
CAS number:	208465-21-8
Molecular weight:	503.51 Daltons
Empirical formulae:	$C_{17}H_{21}N_5O_9S_2$
Structure:	 Mesosulfuron-methyl $C_{17}H_{21}N_5O_9S_2$ Mol. Wt.: 503.51

Physical and Chemical Properties

Appearance:	Light yellowish crystalline powder
Odour*:*	Weakly pungent
Melting Point:	195.4 °C
Density:	1.48
Solubility in water:	21.4 mg/L
Solubility in organic solvents (g/L):	Isopropanol 0.096 Acetone 13.66 Acetonitrile 8.37 n-hexane $<2.3 \times 10^{-4}$ Methylene chloride 3.79 Ethyl acetate 2.03 Toluene 0.013
Dissociation Constants:	$pK_a = 4.35 \pm 0.04$ at 20 °C

Partition coefficient:	Log $P_{0/W}$ =1.90 at pH 4 Log $P_{0/W}$ =1.39 at pH 5 Log $P_{0/W}$ = -0.48 at pH 7 Log $P_{0/W}$ = -2.06 at pH 9 Log $P_{0/W}$ = -2.10 at pH 10
Vapour Pressure:	3.5×10^{-12} Pa @ 20 °C 1.1×10^{-11} Pa @ 25 °C 3.3×10^{-11} Pa @ 30 °C
Volatility:	2.434×10^{-10} Pa m^3mol^{-1} at pH 5 3.649×10^{-12} Pa m^3mol^{-1} at pH 7 1.145×10^{-13} Pa m^3mol^{-1} at pH 9
Hydrolysis:	DT_{50}[days] = 3.5 at pH 4 DT_{50}[days] = 253 at pH 7 DT_{50}[days] = 319 at pH 9
Photolysis:	DT_{50}[days] = 0.08 (1.8 hours) in air; Degradation in water, pH 7 was negligible (<3 %).
Flammability:	Not flammable
Oxidising properties:	Not an oxidising agent
Storage Stability:	Stable for at least 2 years at ambient temperature in sealed containers
Explosive properties:	Not explosive
Dangerous goods classification:	Not applicable – technical material not transported in Australia
Chemical Family:	Herbicide
Chemical Type:	Sulfonylurea
Mode of Action:	Inhibition of acetolactate synthase (ALS)

Summary of the NRA's Evaluation of AC

The Chemistry and Residues Evaluation Section of the NRA has evaluated the chemistry aspects of mesosulfuron-methyl active constituent (manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable. The chemical and physical properties of mesosulfuron-methyl active constituent have been adequately demonstrated. The mesosulfuron-methyl active constituent will be sourced from Germany.

Mesosulfuron-methyl is a new active constituent and there are **no** compendial specifications available for mesosulfuron-methyl. On the basis of the data provided it is proposed that the following minimum compositional standard be established for mesosulfuron-methyl:

Active constituent	**Minimum Requirement**
Mesosulfuron-methyl	Not less than 930 g/kg

Stability of the active constituent

Accelerated storage stability of mesosulfuron-methyl was tested when stored at 54 °C for 2 weeks in the presence of metal and metal ions. The results indicate negligible deterioration of the active content (max 3 %) over this time period. Testing was also performed by thermal DSC in air and nitrogen atmospheres, over a range of 30-360 °C. The test material was stable in the presence of iron, aluminium, aluminium acetate and ferric sulfate powders, over the range of 30-205 °C.

Storage stability data are acceptable to demonstrate that mesosulfuron-methyl active constituent is stable under normal storage conditions for a minimum of 2 years.

Toxicology
Other compounds of toxicological significance are not expected to occur in mesosulfuron-methyl as a result of the raw materials and the synthetic route used. The manufacturing process is not likely to produce toxic micro-contaminants such as nitrosamines, polychlorinated dibenzodioxins, polychlorinated dibenzofurans or polychlorinated phenols.

The Therapeutics Goods Administration [TGA] has considered the toxicological aspects of mesosulfuron-methyl, and advised that there are no toxicological objections to the approval of this active. An acceptable daily intake (ADI) of 1 mg/kg bw/day is recommended based upon a no observable effect level (NOEL) of 100 mg/kg bw/day in a 12/24 month rat study using a 100-fold safety factor.

Poison Scheduling
The National Drugs and Poisons Schedule Committee (NDPSC) has recommended that mesosulfuron-methyl be exempt from scheduling in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP).

The NRA has considered the findings and recommendations of its advisors on the above criteria and accepted their recommendations.

Packaging
The Applicant has indicated that only fully formulated product containing mesosulfuron-methyl will be imported into Australia. Accordingly, packaging details for the technical material are not required.

National Analytical Reference Laboratory
The Applicant has submitted appropriate analytical reference standards to the National Analytical Reference Laboratory (NARL).

Conclusion for the Active Constituent
The Chemistry Residues Program has evaluated the chemistry and manufacturing aspects of the application for approval of mesosulfuron-methyl active constituent. It recommended **approval** of mesosulfuron-methyl active constituent with a minimum content of not less than 930 g/kg, manufactured by Bayer CropScience GmbH (Germany), with Bayer CropScience Pty Limited as the approval holder [AC 54254].

The NRA is also satisfied that the proposed importation and use of the active mesosulfuron-methyl would not be an undue toxicological hazard to the safety of people exposed to it during its handling and use.

Hence the active constituent mesosulfuron-methyl was approved in September 2002. The other active constituent in the product is mefenpyr-diethyl, which was approved in 1997.

FORMULATED PRODUCT

Product Name: *ATLANTIS® SELECTIVE HERBICIDE*
Formulation Type: Non-aqueous suspension concentrate (SC)
Active constituent concentration/s: 30 g/L mesosulfuron-methyl and
90 g/L mefenpyr-diethyl

Physical and Chemical Properties of the Product

Parameter	*Description*
Appearance/colour:	Brown liquid free from extraneous matter
Odour:	Aromatic
Formulation:	Suspension Concentrate (oil flowable)
Density:	1.04 g/mL at 20°C
pH:	5.9 (1% suspension)
Flash point:	> 100 °C (Setaflash Closed Cup)
Flammability Limits:	No data
Solubility in Water:	Forms a suspension
Auto-ignition Temperature	455 °C
Corrosivity Hazards:	None known
Dangerous Goods Class and Subsidiary Risk:	Not classified as dangerous goods for transport by road or rail
Poisons Schedule Number:	5
Chemical Family:	Sulfonylurea + pyrazoline dicarboxylate
Storage Stability:	Stable for at least 2 years when stored at ambient temperature

The specifications for this formulation type, a non-aqueous based suspension concentrate, are acceptable. Testing for the various physico-chemical parameters was performed using CIPAC methodology. The testing methodology used to assay the formulated product, *ATLANTIS® SELECTIVE HERBICIDE,* are acceptable.

Batch Analysis
Batch analysis showed the active and safener content (90 – 110% of the label claim), along with the various physico-chemical properties are satisfactory with regard to the product specifications.

Storage Stability and Shelf Life
The storage stability data demonstrate the active and safener content remain stable after 8 weeks storage at 40 °C (<3% deterioration). In addition, the results for pH, spontaneity of dispersion, suspensibility, wet sieve, pourability and foaming are satisfactory after this storage period. Cold stability of the product was also tested, after storage for 7 days at 0 °C. The report indicates there was no appreciable change in the appearance (no separation of oil or solid matter) and the product remained pourable. This testing was conducted in accordance with CIPAC MT 39, which is satisfactory.

The stability results are satisfactory to support a 2 year shelf life for the product when stored at ambient temperature.

Packaging
The product will be packaged in co-extruded blow-moulded containers made of polyamide/HDPE, which are fitted with polyethylene or polypropylene injection moulded closure and polyethylene induction sealing disc.

Bayer CropScience indicates the packaging complies with FAO Guidelines. The product will be available in pack sizes of 5, 10 and 20 L.

Labelling
The draft label is acceptable in respect of the chemistry aspects.

Recommendations
The Chemistry and Residues Program (CRP) has evaluated the chemistry and manufacturing aspects of *ATLANTIS® SELECTIVE HERBICIDE* (formulation process, composition and form of constituents, stability, and specifications for containers for the product) in data submitted by Bayer CropScience Pty Ltd to support their application to register *ATLANTIS® SELECTIVE HERBICIDE*. The CRP is satisfied that the chemistry requirements of Section 14(5) Agricultural and Veterinary Chemicals Codes have been met.

The CRP also advise that the product should remain within specifications for at least 2 years when stored under normal conditions.

TOXICOLOGICAL ASSESSMENT (INCLUDING METABOLISM AND TOXICOKINETICS)

Mesosulfuron-methyl is a sulfonylurea herbicide. Similar compounds currently registered in Australia include sulfometuron-methyl and thifensulfuron. *ATLANTIS*®, containing 30 g/L of mesosulfuron-methyl, is a suspension concentrate formulation for control of grass weeds.

Evaluation of Toxicology

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

Toxicokinetics and Metabolism

In rats, the absorption of mesosulfuron-methyl through the gastrointestinal tract was rapid but incomplete. Blood radioactivity was detected at 15 min after oral administration of 10 or 1000 mg/kg bw with peak plasma concentrations obtained at 2-4 hours. At the low dose, almost all of the radioactivity was excreted during the first 24 h after treatment with the majority (85-90%) of administered dose eliminated via the faeces including a portion excreted through the bile (7-9%), and only ~15% excreted in the urine. At the higher dose, the faecal to urinary excretion ratio increased. Parent mesosulfuron-methyl was the main component (76-87% of the administered dose) detected in the bile, urine and faecal extracts. More than 10 metabolites were detected in excreta, but only in trace amounts. In tissues examined, the highest radioactivity was detected in the liver and plasma. In a dermal absorption study with rats, absorption generally increased with time to reach a plateau at 24-72 h after treatment. A maximum of 9.3-13.9% of the applied mesosulfuron-methyl was absorbed. The majority of dermally-absorbed mesosulfuron-methyl was excreted between 24 and 72 h after dosing, with equal amounts in urine and faeces.

Acute Studies

The LD50 for mesosulfuron-methyl in rats was greater than 5000 mg/kg for both sexes when given by oral or dermal application. The LC50 was greater than 1330 mg/m^3, with no deaths when given by inhalation. Mesosulfuron-methyl was non-irritant to rabbit skin but slightly irritant to rabbit eyes. It was not a skin sensitiser in guinea pigs.

For *ATLANTIS*®, containing active constituent mesosulfuron-methyl (30 g/L) and mefenpyr-diethyl (90 g/L), the LD50 was greater than 2000 mg/kg bw for both sexes of rats when given orally. In a dermal study with rats, the product had a LD50 of greater than 5000 mg/kg bw.

The product was moderately irritant to rabbit skin and severely irritant to rabbit eyes, but was not a skin sensitiser in guinea pigs.

Short-Term Study

Dogs received mesosulfuron-methyl at 0, 400, 2000, 10000, or 20000 ppm in the diet for 4 weeks. No treatment-related changes were observed, except for ½ the dogs at 2000 ppm and above having oligospermia and a higher incidence of incipient maturation in the testes noted at 10000 and 20000 ppm.

Long-Term Studies

Mice received mesosulfuron-methyl at 0, 140, 1000 or 7000 ppm in the diet for 13 weeks. Decreased leukocytes, increased total bilirubin and loss of liver glycogen were observed in males at 1000 and 7000 ppm and increased total bilirubin was also noted in females at 7000 ppm. Reduced liver weight and atrophic tubules in the testes were observed in males at 7000 ppm. The NOEL was 140 ppm (28.5 mg/kg bw/day).

Rats received mesosulfuron-methyl at 0, 240, 1200, 6000 or 12000 ppm in the diet for 13 weeks. A white spot in the middle of lens surface was observed in 1/10 animals at 12000 ppm. Males at 1200 ppm and above had increased total bilirubin. The NOEL was 240 ppm (18 mg/kg bw/day).

Dogs were treated by dietary administration of mesosulfuron-methyl at 0, 2000, 10000, or 20000 ppm for 13 weeks. Decreased platelet and increased testes, epididymis and prostate weights were observed in males at 20000 ppm. The NOEL was 10000 ppm (348 mg/kg bw/day).

Mice received mesosulfuron-methyl at 0, 80, 800, or 8000 ppm in the diet for 78 weeks. Body weight gains were slightly lower in both sexes at 8000 ppm. WBC were increased in males and females at 8000 ppm. Oligospermia in the epididymides was noted at a higher incidence in 8000 ppm males. No treatment-related neoplastic findings were noted. The NOEL was 800 ppm (102.8 mg/kg bw/day).

Rats were fed mesosulfuron-methyl at 0, 160, 1600, or 16000 ppm in the diet for 52 or 105 weeks. Pelvic/caliceal mineralisation in the kidney, tubular atrophy in the testes and aspermia in the epididymides were observed in males at 16000 ppm at 12 months. Pelvic/caliceal mineralisation in the kidneys, Leydig cell hyperplasia in the testes and aspermia in the epididymides were at a higher incidence in 16000 ppm males at 24 months. No treatment related neoplastic lesions were observed. The NOEL was 16000 ppm (1000 mg/kg bw/day).

Dogs received mesosulfuron-methyl at 0, 400, 4000, or 16000 ppm in the diet for 52 weeks. WBC and neutrophil counts were higher in 16000 ppm males and increased mucous secretion in the stomach was observed in males at 16000 ppm. The NOEL was 4000 ppm (162 mg/kg bw/day).

Reproduction and Developmental Studies

In a dose-finding study, rats received 0, 160, 1600, or 16000 ppm of mesosulfuron-methyl in the diet from three weeks prior to mating throughout the pregnancy and lactation periods. In adults, two (of 10) females at 16000 ppm were killed prematurely; one was not pregnant and the other had no live pups at birth. Decreased live pups at birth associated with decreased implantation sites were recorded at 16000 ppm. Post-natal effects were not observed.

Rats received 0, 160, 1600, or 16000 ppm of mesosulfuron-methyl in the diet from 10 weeks prior to mating through 2 generations until terminated with the F2 weanlings. All reproduction parameters were normal for F0 parents and for F1 parents producing F2b litters. In the case of F2a litters, the conception rates were lower at 1600 and 16000 ppm. Correspondingly, the numbers of females littering and rearing live F2a pups were lower in the two groups. However, as this effect was only seen in the F2a litters, it was not considered of toxicological significance In the offspring, post-natal growth and development was unaffected.. The NOEL was 16000 ppm (1200 mg/kg bw/day).

In a dose-range finding study, mated female rats received mesosulfuron-methyl at 500 or 1000 mg/kg bw/day by gavage on days 7 through 16 of pregnancy. One of three rats from the high dose group had five oedematous foetuses at caesarean section, otherwise no treatment related changes were observed in this study.

Pregnant rats received mesosulfuron-methyl at 0, 100, 315, or 1000 mg/kg bw/day by gavage on days 7 through 16 of pregnancy. Maternal toxicity was not observed. There were no treatment-related abnormalities, skeletal defects or visceral findings in foetuses. The NOEL was 1000 mg/kg bw/day.

In a dose-range finding study, pregnant rabbits were administered mesosulfuron-methyl at 500 or 1000 mg/kg bw/day by gavage on days 6 through 18 of pregnancy. At 1000 mg/kg bw/day, food consumption was decreased for 5 days. No other treatment related changes were observed.

Mated female rabbits received mesosulfuron-methyl at 0, 100, 315 or 1000 mg/kg bw/day by gavage on days 6 through 18 of pregnancy. Maternotoxicity was not observed. There were no treatment related foetal skeletal and organ changes. The NOEL was 1000 mg/kg bw/day.

Genotoxicity Studies

Mesosulfuron-methyl was not genotoxic in a battery of genotoxicity studies including the Ames test, on *in vitro* HPRT mutation test and chromosome aberration test in cultured mammalian cells, unscheduled DNA synthesis in rat hepatocytes and a mouse micronucleus test.

Other Studies

The medical surveillance of manufacturing plant personnel since 1996 has identified no reports of adverse effects on human health caused by mesosulfuron-methyl. Annual medical examinations (from 1997) also showed no substance-related disturbances to health. Dermal allergic reactions have not been detected during the handling of mesosulfuron-methyl to date and no reports of adverse effects and/or poisoning under conditions of experimental agricultural use have been documented.

Public Health Standards

Poisons Scheduling

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

On the basis of its toxicity, the NDPSC has exempted mesosulfuron-methyl from inclusion in a schedule of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). There are provisions for appropriate warning statements and first-aid directions on the product label.

NOEL / ADI

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

The ADI for mesosulfuron-methyl was established at 1 mg/kg bw/day based on a NOEL of 102.8 mg/kg bw/day in an 18-month dietary study in mice and using a 100-fold safety factor, in recognition of the extensive toxicological database available for mesosulfuron-methyl.

Acute Reference Dose (ARfD)

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

The ARfD is 2 mg/kg bw/day based on the LOEL of 2000 mg/kg bw for clinical signs of neurotoxicity in the acute oral study in rats, and a 1000-fold safety factor.

RESIDUES ASSESSMENT

Introduction

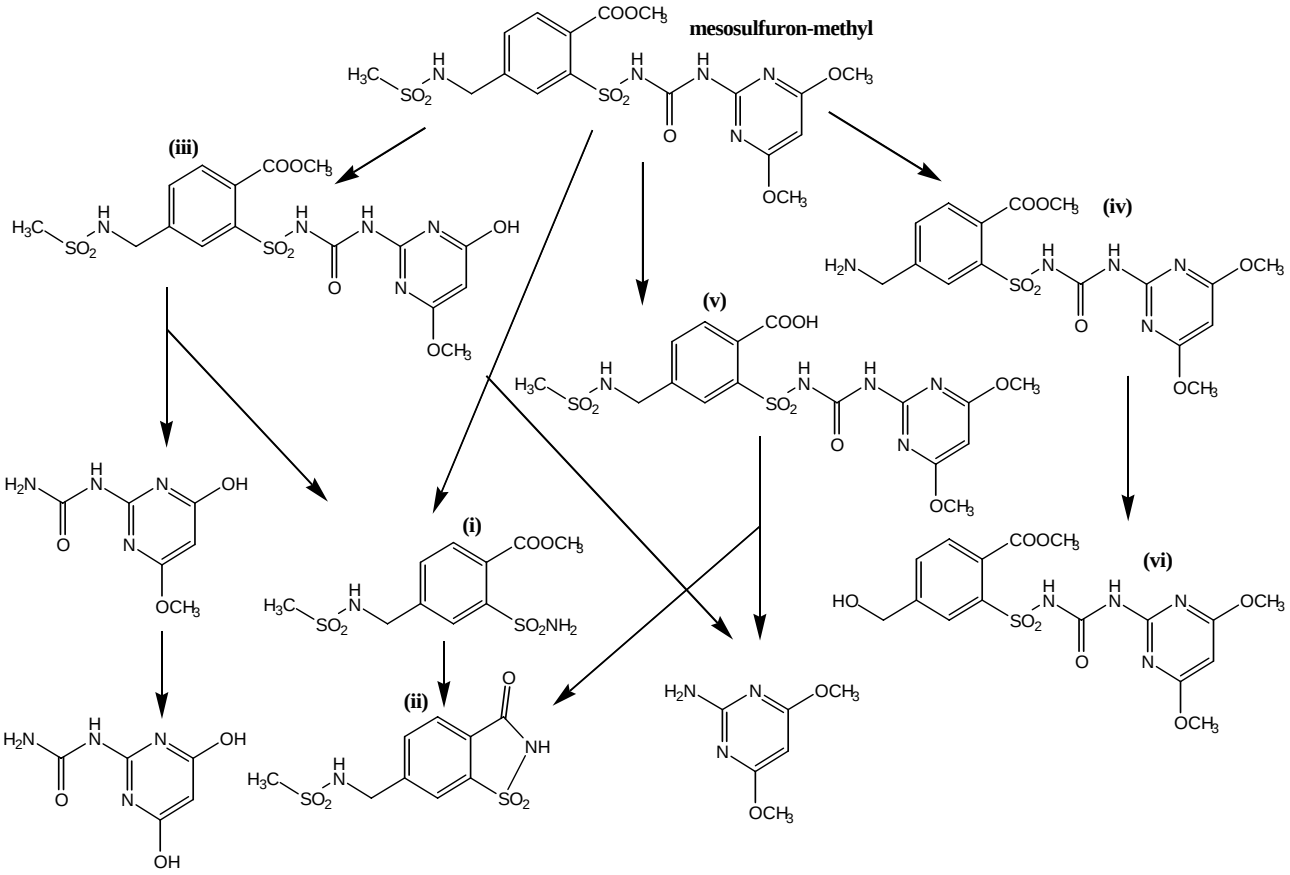
The application is for early post-emergence use (both with respect to the crop and weeds) of mesosulfuron-methyl in wheat. Application is not before the 3-leaf stage of the crop (Z 13) and application usually occurs between 4 and 7 weeks after sowing. In all cases on the label, the product rate is 330 mL/ha, or 10g-ac/ha.

Metabolism

Wheat plants were treated with [2-^{14}C-pyrimidyl]- or [U-^{14}C-phenyl]-mesosulfuron-methyl at rates up to 6× the proposed field application rate. Greater than 80% of the total radioactive residue (TRR) was generally extractable from straw and forage using acetonitrile/water. This compared to approximately 20% extraction efficiency in grain using the same solvent system. The TRR in **grain** at harvest was very low and no terminal metabolites were positively identified. Total radioactivity in **harvested straw and immature forage** was higher allowing the identification of 3 metabolites and the parent compound. The identified metabolites were the pyrimidyl-ring demethylated compound (iii) and 2 cleaved species containing the pyrimidyl-ring portion of the parent molecule (i, ii). Corresponding cleaved species containing the phenyl ring were not observed.

In **rats** dosed with [2-^{14}C-pyrimidyl]- or [U-^{14}C-phenyl]-mesosulfuron-methyl, excretion in the urine and faeces was rapid and extensive. Greater than 80% of the total dose was excreted in faeces in the first 24 hours after dosing with almost complete clearance of the dose after 3-7 days post-dosing. The primary component of the faecal radioactivity was unchanged parent compound. Only very low levels of radioactivity were observed in the tissues. Renal excretion was dose dependent, with a significantly lower amount of radioactivity excreted in the urine following a single high dose compared to a single low dose. Only moderate biliary excretion was observed in the period 0-12 hours after intraduodenal dosing, indicating that the majority of the radioactivity present in the faeces was not absorbed from the gastrointestinal tract. No individual transformation product accounted for more than 10% of the administered dose. Metabolism of the parent compound was mainly by cleavage of the sulfonylurea bridge to form (i) which cyclized to form (ii). Other transformations included O-demethylation at the pyrimidine ring to form (iii) and cleavage of the methanesulfonamidomethyl side chain (iv). Hydrolysis of the methyl ester to form the mesosulfuron acid metabolite (v) was a minor pathway.

In **laying hens** dosed with [U-^{14}C-phenyl]-mesosulfuron-methyl for 14 days at a dose rate equivalent to 10.2 ppm in the diet, an average of 92% of the total dose was eliminated in the excreta. Total radioactive residues in liver (0.023 mg equiv./kg), egg yolk (0.012), egg white (0.011), abdominal fat (0.002), undeveloped eggs (0.01), skin (0.004), muscle (<0.002) and sub-cutaneous fat (<0.002) were very low. The parent compound was the major residue in excreta (60% of TRR), liver (53%) and abdominal fat (70%).



Plant/animal metabolism of mesosulfuron-methyl

In a **lactating cow** dosed over 5 days with [U-^{14}C-phenyl]-mesosulfuron-methyl at a dose rate equivalent to 20.6 ppm in the diet, 78% of the total dose was eliminated in the faeces and urine. TRRs in kidney (0.058 mg equiv./kg), renal fat (0.032), liver (0.031) and milk (0.004) were very low. The parent compound was the major residue in milk (23% of TRR), liver (53%) and kidney (41%). The major residue in renal fat was an alcohol metabolite (vi) formed by oxidative deamination. Other metabolites in tissues included the sulfonylurea cleaved species (i) and its cyclized analogue (ii).

In animals the excretion of mesosulfuron-methyl residues was rapid and extensive. The pathway of metabolism was closely similar in rats, poultry and cows. The metabolism was less extensive in wheat but identified metabolites in wheat were also present in animals.

Analytical methods

Suitable analytical methodology was provided to determine residues of mesosulfuron-methyl in wheat grain, forage and straw. The method used for analysis of samples in Australian residue trials involved extraction with acetonitrile/triethylamine, liquid-liquid partitioning and solid phase clean up on a C18 cartridge. Quantitation was by LC-MS/MS with external calibration standards. Acceptable fortified recoveries were achieved for all matrices at 0.02 mg/kg which was specified as the LOQ of the method.

Suitable analytical methodology was also provided to determine mesosulfuron-methyl in muscle, fat, liver, kidney, milk and eggs. Residues are extracted with acetone and cleaned up by liquid-liquid partitioning. Acceptable fortified recoveries were achieved for all matrices at 0.01 mg/kg which was specified as the LOQ of the method.

Residue definition
Total residues in grain, forage, straw and animal commodities are expected to be very low. Several metabolites were identified in forage, straw and animal commodities at levels <10% of the TRR. The parent compound is an adequate residue definition in both plants and animals for the purpose of monitoring compliance with GAP and estimating dietary exposure.
The residue definition should be as follows:
Mesosulfuron-methyl mesosulfuron-methyl

Residues in wheat
Mefenpyr-diethyl is present in a number of registered products. Residue data provided with the application for *ATLANTIS*® and data previously evaluated for related products indicate that residues of mefenpyr-diethyl in grain and animal feeds are unlikely to exceed current MRLs when the product is used as directed. Further discussion of mefenpyr-diethyl residues is not presented here.

A total of 18 European and 7 Australian residue trials were provided showing the expected magnitude of mesosulfuron-methyl residues in wheat grain.

European trials were conducted at a slightly higher application rate (1.5×) to that proposed for Australia. Residues of mesosulfuron-methyl in harvestable grain collected 42-103 days after application at 15 g ai/ha were not detectable in all samples analysed (n=18).

In 8 Australian trials mesosulfuron-methyl was applied at varying stages of crop maturity resulting in pre-harvest intervals of 20-147 days after treatment. Sampling was conducted at timings consistent with the proposed 8 week harvest withholding period in all trials. Residues of mesosulfuron-methyl in grain were <0.02 mg/kg (n=58) at all sampling times following application at 10-20 g ai/ha (1-2× label rate).

An MRL of *0.02 mg/kg is appropriate for mesosulfuron-methyl in “GC 0654 Wheat”. The proposed withholding period of 8 weeks is acceptable.

Residues in animal feed commodities
Green forage
A grazing withholding period of 4 weeks was proposed to cover potential grazing of failed wheat crops. Samples of green forage were collected following application at around mid-tillering (Australian trials) or flag leaf stage (European trials).

In European trials residues in green forage collected 12-26 days after application at 15 g ai/ha (1.5×) were<0.03 (n=5), <0.05 (2), <0.1, 0.05 and 0.09 mg/kg fresh weight. As all European trials were conducted at exaggerated application rates and there are sufficient Australian trials available (n=10), the European trials will not be considered further for the purposes of setting an MRL.

In Australian trials residues in green forage collected 27-29 days after application at 10-20 g ai/ha were <0.02 (n=17) and 0.023 mg/kg fresh weight. The only quantifiable residues were observed in samples from 2× trials.

On the basis of results in the 10 Australian trials it is concluded that an MRL of *0.02 mg/kg is appropriate for mesosulfuron-methyl in “Wheat forage, green [fresh weight]”. A grazing withholding period of 4 weeks is required.

Straw

Straw from mature crops at harvest may be cut for livestock feed. The minimum time between application and cutting of straw would be equivalent to the harvest withholding period ie. 8 weeks.

In European trials residues in straw collected 43-103 days after application at 15 g ai/ha were <0.015 (n=14), <0.05 mg/kg (2), 0.05 and 0.09 mg/kg. As all European trials were conducted at exaggerated application rates and there are sufficient Australian trials available (n=8), the European trials will not be considered further for the purposes of setting an MRL.

In Australian trials residues in straw collected 46-60 days after application at 10 g ai/ha were all <0.02 mg/kg (n=8). In samples collected 46-60 days after application at 20 g ai/ha (2×) residues in straw were <0.02 mg/kg in 6 out of the 7 trials where samples were analysed. Residues greater than the LOQ were only observed as a result of higher application rates or applications closer to harvest than would occur under GAP.

It is concluded that an MRL of *0.02 mg/kg is appropriate for mesosulfuron-methyl in "AS 0654 Wheat straw and fodder, dry".

Residues in animal commodities

The maximum anticipated dietary exposure of livestock to mesosulfuron-methyl residues is shown below.

Feed	% in diet	Residue, mg/kg	% DM	Maximum anticipated dietary exposure, ppm in diet
Cattle				
Forage	100	*0.02 (MRL, FW [1])	25[2]	**<0.08**
Sheep				
Forage	100	*0.02 (MRL, FW)	25[2]	**<0.08**
Pig				
Wheat grain	100	*0.02 (MRL)	-	**<0.02**
Poultry				
Wheat grain	100	*0.02 (MRL)	-	**<0.02**

1. FW= residue expressed on fresh weight basis
2. Estimated dry matter content of green forage

Based on the results of the available metabolism studies and the maximum anticipated dietary exposure for livestock, the predicted residues of mesosulfuron-methyl in all tissues, milk and eggs are <0.01 mg/kg. It is appropriate to establish the following MRLs at the limit of analytical quantitation:

MO 0105 Edible offal (Mammalian) *0.01
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
PE 0112 Eggs *0.01

Processing studies

Since residues >LOQ are unlikely to occur in any raw agricultural commodity, no processing data were required.

Storage stability

Samples of wheat grain, forage and straw were stored frozen for up to approximately 2 years prior to determination of residues. Storage stability data were provided and indicate that residues in fortified samples do not degrade significantly when stored frozen for 24 months. The results obtained in the residue trials are considered an accurate reflection of the residues present at sampling.

Dietary risk assessment

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

The Acceptable Daily Intake (ADI) for mesosulfuron-methyl is 1 mg/kg bw/day, based on a NOEL of 100 mg/kg bw/day and a safety factor of 100.

The NEDI for mesosulfuron-methyl is equivalent to less than 1% of the ADI. It is concluded that the chronic dietary exposure is small and the risk is acceptable.

The acute dietary exposure to mesosulfuron-methyl is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR, using 97.5th percentile food consumption data from the 1995 National Nutrition Survey of Australia.

The Acute Reference Dose (ARfD) for mesosulfuron-methyl is 2 mg/kg bw based on a LOEL of 2000 mg/kg bw and a 1000-fold safety factor.

The NESTIs for all relevant commodities are equivalent to less than 1% of the ARfD for the population 2 years and over and children 2-6 years old. It is concluded that the acute dietary exposure is small and the risk is acceptable.

Bioaccumulation potential

The log P_{ow} for mesosulfuron-methyl ranges from –2.1 at pH 10 to 1.9 at pH 4. According to the FAO Manual the compound should not be designated as fat soluble.

Conclusion

Adequate residues data were provided to support the registration of *ATLANTIS* ® for use on wheat.

Recommended amendments to the MRL Standard:

Table 1

Compound	Food		MRL (mg/kg)
Add:			
Mesosulfuron-methyl	GC 0654	Wheat	*0.02
	ML 0106	Milks	*0.01
	MM 0095	Meat [mammalian]	*0.01
	MO 0105	Edible offal (mammalian)	*0.01
	PE 0112	Eggs	*0.01
	PM 0110	Poultry meat	*0.01
	PO 0111	Poultry, edible offal of	*0.01

Table 3

Add:	Mesosulfuron-methyl	Mesosulfuron-methyl

Table 4

Compound	Animal Feed Commodity		MRL (mg/kg)
Add:			
Mesosulfuron-methyl		Wheat forage, green [fresh weight]	*0.02
	AS 0654	Wheat straw and fodder, dry	*0.02

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

Withholding periods:
The following withholding periods are required in conjunction with the above MRLs:
Harvest: Do not harvest for 8 weeks after application
Grazing: Do not graze or cut for stockfeed for 4 weeks after application

Summary

Residues in Food

Metabolism studies indicate that the excretion of mesosulfuron-methyl in animals is rapid and extensive. The transformation pathway was closely similar in rats, poultry and cows. Metabolism was less extensive in wheat with very low terminal residues observed in grain and straw. The metabolic pathways were adequately elucidated in animals and the target crop.

A residue definition of mesosulfuron-methyl *per se* is adequate for the purposes of monitoring compliance with GAP and estimating human dietary exposure.

Residue trials conducted in Europe and Australia show low mesosulfuron-methyl residues occur in wheat grain, forage and straw. Residues are not expected to exceed the limit of analytical quantitation in any crop fraction.

The livestock dietary exposure from consumption of treated crops and grain is low. Residues in animal tissues, milk and eggs are not expected to exceed the limit of analytical quantitation.

The risk to human health from dietary exposure to residues of mesosulfuron-methyl is low. The use of mesosulfuron-methyl on wheat is unlikely to unduly prejudice trade or commerce between Australia and places outside of Australia.

Suitable amendments to the *MRL Standard* are recommended for Table-1, Table-3 and Table-4. The following withholding periods are required in conjunction with the proposed MRLs:
Harvest: Do not harvest for 8 weeks after application
Grazing: Do not graze or cut for stockfeed for 4 weeks after application

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Relevant export commodities

Wheat grain is a significant export commodity with total exports valued at $3.5 billion (1999, Australian Commodity Statistics). Major export markets include Egypt, Iran and Indonesia.

Cattle, pigs, sheep and poultry are all significant export commodities. All of these species may consume straw, forage and/or grain from wheat crops treated with *ATLANTIS* ®.

Overseas registration status and MRLs

A product containing mesosulfuron-methyl alone (with mefenpyr-diethyl) is expected to be registered in Italy by December 2003. Mesosulfuron-methyl (30 or 31.6 g/kg) with iodosulfuron-methyl (6.3 or 30 g/kg) [and 96.3 g/kg mefenpyr-diethyl] is contained in products that are registered in a number of overseas countries: France, Iraq, Pakistan, South Africa and Turkey. The company expects registration in all countries where wheat is commercially grown, by the end of 2003 or the middle of 2004.

No MRLs for mesosulfuron-methyl are currently established in overseas countries and the compound has not been considered by Codex.

Potential Risk to Australian Trade

Residues of mefenpyr-diethyl arising from the use of *ATLANTIS* ® are expected to comply with currently established MRLs. No changes to the current MRLs for mefenpyr-diethyl are proposed. Hence the trade situation with respect to mefenpyr-diethyl residues should be unchanged as a result of the registration of *ATLANTIS* ®.

Residues of mesosulfuron-methyl are expected to be less than the limit of analytical quantitation in wheat grain, forage, straw and all commodities derived from livestock consuming treated crops or grain.

It is concluded that the proposed use of *ATLANTIS* ® is unlikely to unduly prejudice trade between Australia and places outside of Australia.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

NOHSC has conducted a risk assessment on mesosulfuron-methyl and mefenpyrdiethyl in *ATLANTIS® SELECTIVE HERBICIDE*. The product is applied at 10 g-ac/ha and 30 g-ac/ha respectively, as a suspension concentrate formulation, for the post-emergence control of selected grass weeds in wheat. *ATLANTIS®* can be safely used by workers when handled in accordance with the control measures indicated in this assessment.

The active constituents mesosulfuron-methyl and mefenpyr-diethyl alone are not classified as hazardous. However, the formulated product *ATLANTIS®* is classified as hazardous based on the NOHSC Approved Criteria for Classifying Hazardous Substances.

ATLANTIS® is a brown aromatic suspension concentrate with low acute oral and dermal toxicity in rats. There are no data on inhalation toxicity. It is a moderate skin irritant and severe eye irritant but is not a skin sensitiser.

Formulation, repackaging, transport, storage and retailing
The new active ingredient and the product will be formulated in Germany and imported to Australia fully packaged and labelled and ready for sale. The product will be packaged in 5, 10 and 20 L co-extruded polyamide/HDPE bottles with 63 mm neck. Transport workers, store personnel and retailers will handle the packaged product and will only become contaminated if the packaging is breached.

Advice on safe handling of the product during routine handling, prior to use, is provided in the Material Safety Data Sheet (MSDS) for *ATLANTIS®*.

Use and exposure
ATLANTIS® will be used for the post-emergence control of grass weeds in wheat, applied once per season. The maximum recommended product rate is 330 mL product per hectare (10 g mesosulfuron-methyl and 30 g mefenpyr-diethyl). The draft label states that standard boom sprayers only are recommended and must be fitted with by-pass or mechanical agitation. Spray volumes of 50 to 80 L/ha are recommended on the label. The product will not be applied by aircraft.

The product is available as a suspension concentrate. The main acute hazards associated with the product are moderate skin irritation and severe eye irritation. During mixing and loading, workers, may be exposed by the dermal and ocular routes. Inhalation is unlikely given the product presentation. Personal protective equipment (cotton overalls or equivalent clothing, elbow-length PVC gloves and goggles) to limit dermal and ocular exposure should be worn during mixing and loading.

During spray application exposure may occur via the dermal, ocular or inhalation routes. The final spray will contain less than 1% product. There should be no acute hazards associated with the final spray.

The main potential hazards associated with repeat exposure to product are systemic effects (effects on liver, kidney, haematopoietic system and male reproductive organs). Hence NOHSC used the UK Predictive Operator Exposure Model (POEM) and the Pesticide Handlers Exposure Database (PHED) to estimate applicator exposure in the absence of worker exposure data. The repeat dose risk assessment indicated no specific personal protective equipment requirements during mixing and loading or application.

Entry into treated areas
Workers may be exposed to the product during re-entry activities such as irrigation, crop checking, thinning, or weeding. Harvesting is expected to be mechanical and therefore would not result in significant worker exposure. No post-application worker exposure data were available.

Given the low application rate of the active ingredients mesosulfuron-methyl and mefenpyr-diethyl (10 g and 30 g per ha, respectively) and the relatively low toxicity associated with each ingredient, NOHSC does not consider re-entry workers to be under any significant risk following the application of *ATLANTIS*®, once the spray has dried.

Recommendations for safe use
Users should follow the instructions and Safety Directions on the Product label. Safety Directions include the use of cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow-length PVC gloves and goggles when preparing the spray.
The personal protective equipment recommended should meet the relevant Standards Australia standards specified below:

AS 2161-1978 Industrial Safety Gloves and Mittens (Excluding Electrical and Medical Gloves)
AS 3765-1990 Clothing for protection against hazardous chemicals
AS 1337-1992 Eye Protection for Industrial Applications

To ensure there is no risk from exposure to wet spray, the following re-entry statement should be included on the product label:

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

Information provision
Bayer CropScience Pty Ltd has produced a MSDS for *ATLANTIS*®. This should contain information relevant to Australian workers, as outlined in the NOHSC National Code of Practice for the Preparation of Material Safety Data Sheets. Employers should obtain the MSDS from the supplier and ensure that employees have ready access to it.

Conclusion
ATLANTIS® can be used safely if handled in accordance with the instructions on the product label. Additional information is available on the MSDS for *ATLANTIS*®.

SUMMARY

The new active ingredient and the product will be formulated in Germany and imported to Australia fully packaged and labelled and ready for sale. The product will be applied once per season at the maximum recommended product rate of 330 mL product per hectare (10 g mesosulfuron-methyl and 30 g mefenpyr-diethyl), via standard boom sprayers in 50 to 80 L of water. The product will not be applied by aircraft.

The final spray will contain less than 1 % product. There should be no acute hazards associated with the final spray. Instructions and Safety Directions are provided on the product label to minimise exposure to the product.

Environmental Assessment

Introduction

Bayer CropScience Australia Pty Ltd has applied for the registration of a new product *ATLANTIS* ®, containing the active constituent (AC) mesosulfuron-methyl at 30 g/L plus the crop-safener mefenpyr-diethyl at 90 g/L.

Mesosulfuron-methyl is a sulfonylurea herbicide to be used for the post-emergence control of annual wild oats and annual phalaris and for the suppression of brome grass and annual ryegrass in wheat as per the directions for use on the label.

Environmental Fate

Hydrolysis

Mesosulfuron-methyl hydrolyses fairly rapidly under acidic pH conditions (3.5 days at 25°C and pH 4) but hydrolysis is significantly slower under neutral and alkaline pH conditions (>253 days at pH 7 and 9, extrapolated values). The major degradation pathway involves cleavage of the sulfonylurea bridge leading to formation of an amino pyrimidine derivative, two phenyl degradates (a bisulfonamide and a saccharide derivative), and a free acid, with formation of the latter three individual degradates being dependent on the pH. No other degradate fractions were detected during the test, which was carried out under sterile conditions in the dark, indicating the degradates were stable to chemical hydrolysis under these conditions.

Photolysis

Aqueous photolysis of mesosulfuron-methyl had an experimental half-life of 30-62 days, which increased significantly when normalised to natural sunlight. However, photodegradates were formed at less than 4% of the applied radiolabel. Thus under natural environmental conditions, photodegradation is not expected to be a significant degradation pathway for mesosulfuron-methyl in the aquatic environment. On the soil surface, the half-life was calculated to be >300 days, indicating photolysis from soils is also not a significant degradation pathway. While not volatile, modelled atmospheric photolysis indicated half-life times of <0.1 day, suggesting rapid degradation in the atmosphere due to reaction with hydroxy radicals.

Aerobic and Anaerobic Soil Metabolism

Mesosulfuron-methyl is fairly degradable in soil under both aerobic and anaerobic conditions. Several transformation :processes were observed in the aerobic degradation studies. These included complete degradation of the molecule by ring opening (as indicated by significant elimination of $^{14}C0_2$ in the range of 14-49%), formation of non-extractable residues (up to 62%), and formation of a number of metabolites through ester and ether demethylation, followed by sulfonylurea cleavage, thus following a similar degradation pathway to hydrolysis. Most of the individual metabolites (known and unknown) were formed in amounts <10%, with only the urea and the free acid reaching values >10% of applied radioactivity in some soils during the course of the studies. Nevertheless, for all metabolites, a general decline was observed over the test period, with all metabolites reaching peak values in less than 365 days, indicating their transient nature. The experimental aerobic degradation half-life times (DT_{50}) of mesosulfuron-methyl at 20°C exhibited large differences in degradation times between soil types, which ranged between 8.2 and 68 days. The differences could not be easily explained by soil characteristics. At 10°C the route of degradation was the same as under standard conditions, however, degradation rates were about one third slower, and metabolism was less pronounced.

The anaerobic half-life times in a sandy water-logged soil were in good agreement with the half-life times observed in aerobic soils, with DT_{50} values for mesosulfuron-methyl between 27 and 30 days. Anaerobic degradation formed the same metabolites as aerobic degradation, but with only the amino pyrimidine occurring in amounts >10% of applied radioactivity, and with the urea component and the free acid contributing negligibly to the route of degradation of mesosulfuron-methyl under anaerobic conditions. The experimental studies suggest the parent compound is unlikely to accumulate in soils under aerobic or anaerobic conditions.

Degradation in Water / Sediment

Mesosulfuron-methyl was degraded in a rapid to moderate rate by microbially induced processes in two water/sediment samples from different river systems, each differing in their sand and clay content, percentage organic carbon, pH, and microbial biomass. The rate of dissipation of mesosulfuron-methyl from water varied with the sediment type, with adsorption of residues to the sediment being three times lower in the sandy sediment with the lowest microbial biomass. A corresponding formation of non-extractable radioactivity was observed in each sediment, with higher amounts formed in the heavier (more clayey) textured sediment with the higher microbial biomass. The DT_{50} values in water were 14 and 57 days, and in the whole systems were 25 and 73 days, respectively, indicating mesosulfuron-methyl is readily to slightly degradable.

The metabolism of mesosulfuron-methyl in both water/sediment systems followed similar pathways and formed most of the same metabolites as observed in hydrolysis and aerobic/anaerobic degradation with the hydroxypyrimidine, acid phenol and saccharide derivatives predominating. However, a number of unknown substances were also detected in minor amounts in both water/sediment systems. In the water phases, up to 21% of unknown metabolites was present at the end of the 140 day incubation period, while in the sediment extracts unknown metabolites were <5% AR. In the Kies system, the percentage of unknown metabolites increased to 38% (day 252) for the phenyl label and 44% AR (day 309) for the pyrimidyl label. However, it was concluded that information derived from day 252 to 365 days did not represent natural conditions due a shift from anoxic to oxic conditions.

Adsorption / Desorption

Results of adsorption/desorption studies in nine agricultural soils of varying characteristics from locations in France, Germany, UK and the US, indicate mesosulfuron-methyl will have a high to very high mobility in soils. The K_{oc} values ranged between 26 and 354, and were not correlated with texture, organic carbon or pH. A poor correlation between Koc and pH is surprising in light of the significantly higher solubility of mesosulfuron-methyl under alkaline pH conditions.

The mobility of the major soil metabolites (occurring at >10%) indicates that the free acid will be highly mobile, and the urea will have medium to low mobility in soils. Of the three soil types used in the study, the lowest mobility occurred in the soil with the highest clay and organic carbon, with no apparent effect of pH on mobility. The amino pyrimidine metabolite exhibited a medium to high mobility depending on the soil type, with mobility correlated to the percentage of silt.

Leaching

Leaching of mesosulfuron-methyl applied twice, about 1 year apart, in spring to outdoor lysimeters with "worst-case" sand, soil showed that, over the 3-year monitoring period, 3-8.5% of the originally applied material was found in the leachate. The combined total of precipitation/irrigation received over that period was 2903 mm. Mean radioactivity concentration in leachate water exceeded the EU groundwater limit of 0.10 μg/L a.i. equivalent during each of the three years of monitoring (maximum 1.192 μg/L).

However, none of the known metabolites or the less polar unknown components reached the EU groundwater limit in the leachate water. No parent compound was detected in the leachate water.

Similar results were observed in a second study (autumn application), in which there was a combined three-year total precipitation/irrigation of 2809 mm. Only 0.05% of applied radioactivity was detected in the leachate water in the first year. In the second year, a maximum of 19% of the originally applied material was detected in the leachate, with the amount declining to 3-3.5% by the third year. The high concentration measured in the second year was attributed to the high amount of leachate water generated by extremely high precipitation rates (1161 mm) which flushed out of residual radioactivity retained in the soil during the first year. Mean radioactivity concentration in leachate water exceeded the EU groundwater limit of 0.10 μg/L a.i. equivalent only in the second year of monitoring (maximum 1.2 μg/L). However, no mesosulfuron-methyl was detected in the leachate.

The majority of radioactivity present in the leachate water was due to 2 unidentified polar metabolites. The metabolites are thought to be small, bound, break-down products, such as urea and guanidine, generated by biodegradation which are incorporated into the water soluble organic carbon fraction of the soil. The leachate water was not toxic to the most sensitive species, duckweed, in the toxicity tests, but rather had a growth promoting effect.

Computer modelling studies, simulating the long-term (20 years) leaching behaviour of mesosulfuron-methyl and its main metabolites, and using climate and soil data from nine regions in Europe, indicated annual leachate; concentrations below 0.1 μg/L (the EU groundwater limit), except at one location, over the simulation period, even when worst-case scenarios were adopted. Modelling studies simulating the long-term (14 years) leaching behaviour using Australian soil and climatic data from areas identified as potentially vulnerable to leaching (Clare, Lameroo, Minnipa (SA) and Walpeup in the Wimmera/Mallee region), indicated no substantial generation of drainage at any of the sites, except Clare, which had the highest rainfall. The highest herbicide concentration in leachate was correlated to the highest drainage/rainfall, while the second highest concentration in leachate was correlated to the sandiest texture (Walpeup). However, the predicted mean herbicide concentrations in groundwater were low and even the maxima never exceeded 0.1 μg/L. The data suggest leaching groundwater concentrations are unlikely to exceed 0.1 μg/L in most Australian wheat growing areas, which fall in the climatic zones having mean annual rainfall between 300 and 600 mm.

The majority (22-33%) of the applied radioactivity remaining in the soil after three years was in the top 50 cm with only 1-2% detected at lower levels. Soil analysis performed at the end of the 3-year period detected only the parent compound in the upper soil layers at an equivalent concentration of ≤0.83 μg/kg.

It appears from these studies that mesosulfuron-methyl or its major soil metabolites do not have significant leaching potential under the test conditions. The results suggest no perceivable risk to groundwater contamination from mesosulfuron-methyl or its major metabolites under most Australian wheat growing conditions.

Field Dissipation

Field dissipation studies conducted at six locations in Europe using a mesosulfuron-methyl formulation (*ATLANTIS*®), applied in a single applications in either spring or autumn at a rate of 3.5 L/ha (105 g a.i./ha), resulted in DT_{50} values between 44 and 76 days for mesosulfuron-methyl, with a mean value of 65 days. The DT_{90} values were between 146 and 252 days, with a mean value of 216 days.

The field dissipation half-life times are in agreement with the disappearance times observed in laboratory trials, while the modelled half-life times, using normalised soil moisture and temperatures, showed slightly faster degradation rates than measured field and laboratory rates, with expected DT_{50} values of between 30 and 48 days (average 38 days) at 20°C and a soil moisture content of 100% of field capacity. Nevertheless the time to 90% degradation of mesosulfuron-methyl is significantly less than one year, indicating that it is unlikely the herbicide will be detected in soil a year after application at the recommended application rate.

Field dissipation studies showed that during the 12-month monitoring period, concentrations of mesosulfuron-methyl in the top 10 cm of soil following treatment were in the range of 0.0019 mg/kg to 0.1312 mg/kg. After one year, residue concentrations in the top 0-10 cm had fallen at each location to a maximum of 0.007 mg/kg (in Germany) and a minimum of 0.0019 mg/kg (in Italy). Mesosulfuron-methyl could only be detected occasionally in low concentrations in soil layers deeper than 10 cm after application. Thus mesosulfuron-methyl, applied at rates 10.5 times the maximum proposed rate, does not show a significant downward movement in the soil profile.

Environmental Toxicology

Birds

According to the study results mesosulfuron-methyl was practically non-toxic to both Bobwhite quail and Mallard duck in acute and short-term (5-day) dietary toxicity studies. The studies reported acute oral LD_{50} values greater than 2,000 mg/kg body weight and dietary LC_{50} values greater than 5000 ppm (equivalent to a mean daily mesosulfuron-methyl intake of 720 and 1210 mg/kg bodyweight/day for Bobwhite quail and Mallard ducks respectively).

The subchronic dietary treatment of these species in reproduction toxicity studies had no effect on the growth and survival of adult birds or their reproductive performance (including egg production and hatchability or offspring growth and survival).

The No Observed Effect Level (NOEL) was 1000 ppm (equivalent to a mean daily mesosulfuron-methyl intake of 93 and 126 mg/kg bodyweight/day for Bobwhite quail and Mallard ducks respectively). No studies assessing the avian toxicity using the formulated product were provided.

Aquatic Organisms

The most sensitive aquatic species to the technical grade mesosulfuron-methyl (95.3%) is the aquatic plant species *Lemna gibba* with an E_bC_{50} of 0.62 μg/L and an NOEC of 0.18 μg/L. The technical grade mesosulfuron-methyl (94.6%) is also highly toxic to the freshwater green algae, *Pseudokirchneriella* subcaμpitata, with an EC_{50} value equal to 0.18 mg/L, and an NOEC of 0.018 mg/L, and is at worst slightly toxic to the marine diatom, *Skeletonema costatum*, and the freshwater diatom, *Navicula pelliculosa*.

The formulated product (*ATLANTIS* ®), which contains 30 g/L mesosulfuron-methyl and 90 g/L mefenpyr-diethyl, and a mean measured content of 2.97% w/w mesosulfuron-methyl and 8.93% mefenpyr-diethyl, is moderately toxic to freshwater green algae and highly toxic to the aquatic plant species *Lemna gibba*, with the latter having 7 day E_rC_{50} = 50.7 μg/L, and an NOEC of 5.6 μg/L.

Technical grade mesosulfuron-methyl (94.6%) is very slightly acutely toxic to Rainbow trout, Bluegill sunfish, mysid shrimp, *Mysidopsis bahia*, and *Daphnia magna*, with all species having acute LC_{50} values >100 mg/L. In chronic tests, technical grade mesosulfuron-methyl was very slightly toxic to Rainbow trout and *Daphnia magna*, with NOEL values for Rainbow trout of 32 mg/L, and for *Daphnia* of 5.6 and 32 mg/L.

The formulated product is moderately acutely toxic to Rainbow trout and *Daphnia magna*, with LC_{50} values of 3.2 mg/L and 3.4 mg/L, respectively. The product is slightly to moderately chronically toxic to *Daphnia magna*, with 21day NOEL values between 0.1 to 1.0 mg/L.

The toxicity of the several metabolites of mesosulfuron-methyl was tested against algae and *Lemna gibba*. The hydroxypyrimidine metabolite was moderately toxic to *Lemna gibba* and slightly toxic to green algae, while the acid phenol was practically non-toxic to the Duckweed, and the saccharide derivative was practically non-toxic to Duckweed and green algae. The leachate water from lysimeter studies, which contained no detectable mesosulfuron-methyl but a number of unidentified polar metabolites, was not toxic to duckweed, but rather had a growth promoting effect.

The toxicity of the technical grade substance is higher toward algae and Duckweed, whereas the toxicity of the formulated product is higher than the technical grade substance to fish and Daphnia.

Terrestrial Invertebrates

The formulated product (*ATLANTIS* ®), containing 2.97% mesosulfuron-methyl and 8.93% mefenpyr-diethyl, was classified as harmless to the terrestrial invertebrates *Typhlodromus pyri* (predatory mites), *Paradosa spp*. (ground dwelling spider), *Chrysoperla carnea* (foliage dwelling predator - lacewing) and *Aphidius losiphi* (parasitoid wasp), when exposed under laboratory conditions to concentrations equal to application rates of up to 10 g a.i/ha (the proposed Australian use rate) and 15 g a.i/ha (European use rate), and a 5% drift rate of 330 mL/ha and 500 mL/ha.

The highest mortality rate (38%) (corrected mortality = 27.4) in terrestrial invertebrate studies was observed in *Typhlodromus pyri*, exposed to 330 mL/ha (equivalent to 10 g a.i./L). However, the deaths were considered not to be substance-related because the mortality rate in groups exposed to the 500 mL/ha (equivalent to 15 g a.i./ha) and to the 5% drift rate of 500 mL/ha was only slightly increased (corrected mortality = 8.33% in both), but was not significantly different compared to the control. No mortalities were observed in the 5% drift rate of 300 mL/ha. As in the 500 mL/ha treatment group, the mortality in the 330 mL/ha after one week was not significantly different from the control. Reproduction of the treated mites was not affected.

Maximum mortalities in spiders exposed to the test substance were 0%, and in lacewings, 4.7%, while in wasps exposed to the 500 mL/ha treatment, the maximum corrected mortality was 17.5%. While no deaths occurred in the control group, the authors concluded that the mortality of wasps was not affected by the formulated product (*ATLANTIS* ®).

Honey Bees

Technical mesosulfuron-methyl (purity not provided) was moderately toxic to honey bees in an oral toxicity test, where bee mortality rates were 33% at the highest test concentration compared to the control, while in a contact toxicity test, no mortalities were observed. The resulting 72 hour oral LD_{50} was 5.6 μg a.i..(measured) per bee and the contact LD_{50} was >13 μg a.i..(measured) per bee.

The formulated product (*ATLANTIS* ®), containing 8.93% mefenpyr-diethyl and 2.97% mesosulfuron-methyl, was slightly toxic to honey bees in an acute oral and contact toxicity test, where no mortalities were observed in bees exposed to nominal test concentrations up to the highest concentration of 100 μg/bee, except for 2 bee deaths in the 50 μg/bee test system. The resulting contact 48 h LD_{50} was determined to be > 100 μg preparation/bee and the oral 48 h LD_{50} was > 115.8 μg/L.

Earthworms
No mortalities, toxicity effects, or significant weight difference, compared to the controls, were observed in adult earthworms exposed to technical mesosulfuron-methyl (94.6%) in artificial soil at nominal concentrations of up to 1000 mg/kg soil for 14 days. The resulting 14-day NOEC was therefore 1000 mg/kg dry substrate, indicating the technical substance is very slightly toxic to earthworms.

Earthworms exposed (in two separate tests) for an 8 week period to the technical grade mesosulfuron-methyl (95.7%) at nominal spray rates of 15 g/ha and 150 g/ha also exhibited no mortalities in either adults or offspring, and no obvious behavioural differences compared to controls. Consequently the LC_{50} values were greater than a nominal 15 g a.i./ha (7.91 g a.i./ha measured), and a nominal 150 g a.i./ha, respectively in each test, which are the equivalent of 0.01 and 0.1 mg mesosulfuron methyl per kg in a soil 10 cm deep and with a density of 1.5 g/cm^3.

Mortalities and lethargic behaviour were observed in adult earthworms exposed for 14 days to the formulated product, containing 30 g/L mesosulfuron-methyl and 90 g/L mefenpyr-diethyl, at the highest test concentration of 320 mg/kg. The LC_{50} value after 7 and 14 days test duration was determined to be 253 mg/kg (dry weight), and the 14-day NOEC was determined to be 100 mg/kg, classifying the formulated product as slightly toxic to earthworms.

However, earthworms exposed to the formulated product for 8 weeks at nominal spray rates of 500 g/ha (0.33 mg product/kg) and 2500 g/ha (1.67 mg product/kg) exhibited no mortalities or behavioural abnormalities, and similar biomass turnover to the control, and no differences in the weight of adult worms and the number of offspring compared to the control.

Soil Nitrification and Respiration
Mesosulfuron-methyl, technical (96%) when applied at rates equivalent to 15 g/ha (0.02 mg/kg soil) and 75 g/ha (0.10 mg/kg soil) had a negligible effect on the nitrogen turnover in a silty sand and a loamy silt soil over the 28 day measurement period.

The formulated product (*ATLANTIS*®), containing 2.97% mesosulfuron-methyl and 8.93% mefenpyr-diethyl, when applied at rates of up to 2.5 L/ha (proposed rate of use is 330 mL/ha) induced negligible effects on soil microbial nitrogen turnover, with the highest deviation in nitrogen turnover compared to the control of -12.2% on day 7, in the loamy sand. Therefore, the studies concluded that under normal conditions of use mesosulfuron-methyl is not expected to lead to any long-term detrimental effects on nitrogen turnover in soil.

Mesosulfuron-methyl, technical (96%) when applied at concentrations of 0.02 and 0.1 mg/kg soil rates, (equivalent to 15 and 75 g/ha) had a negligible effect on short-term (28 days) soil respiration in two different soils, with the highest deviation in oxygen consumption on day 28 being +3.6% compared to the control.

The formulated product (*ATLANTIS*®), containing 2.97% mesosulfuron-methyl and 8.93% mefenpyr-diethyl, when applied at concentrations of 0.59 mg/kg and 2.94 mg/kg (equivalent to 0.50 L/ha and 2.50 L/ha), also had negligible effects on soil respiration, with deviations in oxygen consumption of +9.6 on day 0. These results suggest that mesosulfuron-methyl will not have any significant effects on the activity of soil microorganisms.

Sludge Respiration and Bacterial Inhibition
Technical mesosulfuron-methyl (96%) did not have any inhibitory effects on the respiration of activated sewage sludge at concentrations of up to 1000 mg/L.

The study concluded that the range EC50 of mesosulfuron-methyl substance technical was therefore greater than 1000 mg/L.

Exposure of the freshwater bacterium, *Pseudomonas putida*, to technical mesosulfuronmethyl (96%), resulted in an EC50 of 298 mg/L, indicating the test substance is practically nontoxic to these organisms.

Non-target Vegetation
A screening test using the a test substance referred to as the herbicide AE F130060 (a 20% wettable powder formulation) showed that mesosulfuron-methyl is active pre-emergence as well as post-emergence to monocots and dicots at application rates above 20 g/ha.

A vegetative vigour study using the formulated product, containing 3.02% mesosulfuron-methyl and 8.64% mefenpyr-diethyl, indicated the lowest EC_{50} was 0.91 g a.i./ha for tomatoes. However, important crop plants were affected at applications rates as low as 0.27 g/ha (or 2.7% of the recommended application rate of 10 g a.i./ha).

Environmental Hazard

Accumulation in Soils
Studies applying the herbicide at more than 10 times the Australian rate showed maximum concentration of mesosulfuron-methyl declined over the monitoring period, with 50% field dissipation ranging from about 6 to 11 weeks, and 90% dissipation ranging from about 5 to 9 months. Given the herbicide is applied only once a year, these results indicate that mesosulfuronmethyl is unlikely to accumulate in the soil from year to year.

Under Australian conditions, the maximum single application rate of *ATLANTIS*® is equivalent to 488.4 g/ha product, comprising 10 g/ha of active mesosulfuron-methyl and 30 g/ha of mefenpyr-diethyl. This application rate is expected to result in an EEC for the formulated product of 407 μg/kg in the top 10 cm of soil with a bulk density of 1.2 g/cm^3 and assuming that 100% of spray reaches the soil. The EEC for the equivalent concentration of active ingredients in the formulation is 33 μg/kg, comprising 8 μg a.i./kg mesosulfuron-methyl and mefenpyr-diethyl 25 μg a.i./kg soil.

Hazard to Birds
A low risk to birds is indicated by the low expected residue concentrations in feed, which are far below the toxic end points for both chronic and acute toxicity studies for the two species tested, bobwhite quail and mallard duck.

Hazard to Terrestrial Organisms and Soil Micro-organisms
A low risk to terrestrial organisms including predatory/parasitic arthropods, soil microorganisms, earthworms, and honey bees, is indicated from use of *ATLANTIS*®. The formulated product is classified as harmless to earthworms, predatory mites, a ground dwelling spider, a lacewing, a wasp, while being classified as slightly toxic to honey bees. The technical substance had negligible effects on nitrogen turnover and soil respiration.

The EEC calculated for the top 10 cm of soil (BD = 1.2 mg/cm^3) is far below the toxicity endpoints for all of these organisms.

The hazard to terrestrial organisms is further minimised by the single seasonal application, the very low application rates, and the expected lack of persistence in soil environments.

Hazard to Plants

As with any herbicide, a potential hazard to non-target plants is possible. A screening test showed that mesosulfuron-methyl is active pre-emergence as well as post-emergence to monocots and dicots at application rates above 20 g/ha.

A vegetative vigour study using the formulated product indicated important crop plants were affected at applications rates as low as 0.27 g/ha (or 2.7% of the recommended application rate of 10 g a.i./ha).

The draft label warns users not to apply to crops undersown with legumes, or to any crop other than wheat, and not to apply under weather conditions, or from spray equipment, that may cause drift to nearby susceptible plants, crops, cropping lands or pastures. Application with ground spaying equipment should help to minimise drift.

The draft label warns not to apply *ATLANTIS* ® by aircraft.

Consideration of spray drift values based on European studies indicate the use of buffer zones of at least 3 metres will reduce the risk to non-target plants.

Aquatic Hazard

The hazard from *ATLANTIS* ® usage to aquatic organisms is expected to be greatest toward duckweed, which are the most susceptible aquatic organisms.

Trout, daphnids and algae are not indicated as being at risk from 10% spray drift after a single spray of the herbicide at maximum label application rates, while the hazard to duckweed is unacceptable at this spray rate. Again based on European studies, calculations show a buffer zone of 3 m is expected to reduce the hazard to duckweed to acceptable levels during ground spraying.

Thus with an appropriate label statement drawing attention of the toxicity of mesosulfuron-methyl to certain aquatic plants and duckweed, the hazard is expected to be manageable.

The potential for aquatic exposure from 10% run-off into a 1 ha pond 26 cm deep, indicates a concern that may be mitigated by some form of risk management, such as not applying the product if heavy rain is expected, and by the use of buffer zones between water courses and sprayed areas to prevent direct run-off. The potential for run-off is lowered by the relatively high water solubility, which will result in the product being carried into the soil profile during rainfall events rather than being lost solely through run-off.

Adherence to the label instruction of an eight-hour interval between application and any expected rainfall further reduces the run-off potential.

Potential for Movement to Ground Water

The potential for groundwater or subsoil contamination is possible as adsorption and desorption studies indicate mesosulfuron-methyl has a relatively high soil mobility, with the mobilities of the main metabolites being the same order of magnitude as the parent compound.

However, field dissipation studies at 10 times the proposed application rates only occasionally detected the herbicide below 10 cm. Leaching into ground water of mesosulfuron-methyl or its major metabolites is therefore not expected to be a major route of contamination under Australian wheat growing conditions. This has been confirmed by modelling studies.

Conclusions

The proposed use of *ATLANTIS* ® is not expected to be a hazard to birds, fish, aquatic invertebrates, bees, earthworms, most beneficial insects and soil microbes.

There is a potential hazard to duckweed and to a lesser extent, algae, using worst case scenarios for run-off and spray drift. However, with more realistic assumptions and taking into account the low use rates and use pattern, the hazard is lower and should be acceptable using good agricultural practice and by adhering to the recommendations from the label warning statements.

EFFICACY AND SAFETY ASSESSMENT

Justification and Use Pattern

The rationale behind the product *ATLANTIS* ®, is that it is an ALS-inhibitor herbicide for **post-emergence** use in wheat, to control or suppress the weeds above. It may also reduce the need for tank mixes (e.g. with Group-A grass herbicides) to achieve this.

It is not expected that this product would increase the rate of evolution of herbicide-resistance, or environmental load, by sulfonylurea herbicides, as it is expected to replace existing sulfoynlureas. Additionally, as this product may replace tank-mixes in wheat which use Group-A herbicides (for grass control), then it may provide an alternative that could reduce the evolution of Group-A herbicide resistance.

The application is for early post-emergence use (both with respect to the crop and weeds) in wheat. Application is not before the 3-leaf stage of the crop (Z 13). Application to the weeds occurs between 4 and 7 weeks after sowing, when the weeds are at the 1-leaf to 3-leaf stage (Z 11 - Z 13,21).

The label-claims are that the weeds controlled are wild oats (*Avena* spp) and annual-phalaris/paradoxa-grass (*Phalaris paradoxa* only), and the weeds suppressed are brome grass (*Bromus diandrus*) and annual ryegrass [ARG] (*Lolium rigidium*). Control or suppression is claimed in All States, except for ARG, where the states claimed are NSW, ACT, Victoria, SA and WA. In all cases, the product rate is 330 mL/ha.

Evaluation of Efficacy and Crop Safety

1. Adequacy of efficacy data

Trial design (controls, treatments, replicates)
The application was well supported with statistically sound trial work. Comparisons with appropriate alternative herbicides were carried out and all treatments were applied at the appropriate growth stages.

Analysis of trial data, interpretation.
Trial data was appropriately analysed and interpretation of the experimental data was appropriate. All of the experiments were carried out under standard conditions, although drought conditions and flooding affected the finish of some trials. These problems were adequately covered in discussion and there were a sufficient number of unaffected sites to provide reliable interpretation. A concern was raised about weed densities treated (in relation to resistance management), and this is discussed below.

Trial validation, location, date.
The trials were conducted over a five year period, across the major wheat growing regions of Australia. 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. The selective control and/or suppression of the target weeds in wheat crops will provide a useful weed management tool to producers.

2. Claims

Efficacy.
The efficacy data presented is extensive. The applicant has defined the target species for which control can be expected (wild oats, annual phalaris) and those which are likely to be only suppressed (brome grass, annual ryegrass). Data indicates that this product is more of a suppressant but this is clearly shown on the label.

Phytotoxicity.
Some phytotoxity effects were noted in the experiments and appeared to be crop variety based. Allowances for this have been made, on the label. There it is specified, the varieties for which the product is safe, and noting two varieties (Westonia and Brookton) for which unacceptable damage was noted.

3. Directions for use

These are adequate. However, as suppression of weeds is largely expected rather than death, consideration should be given to adding advice on making the crop competitive by correct fertilization (including trace elements), by controlling disease, and by adequate seeding rates.

This was considered by the company, who felt this was un-necessary, as growers are doing their upmost to grow a competitive crop. Further, the proposed advice is well known to growers and not new. Hence this advice will not be placed on the label. The NRA has accepted this argument.

4. Safety to non-target species

Adequate information has been provided.

5. Adequacy of precautionary advice

This is adequate. To address concerns regarding the likelihood of brome grass germinating slightly ahead of the wheat, the following words have been included on the label:

> *"Apply when the majority of brome grass is at the 1 to 3 leaf stage (Z 11 – Z 13,21). Efficacy on larger plants that may have emerged before the crop may be poor."*

This statement leaves it up to the grower to avoid situations (e.g. dry sowing et al) that may result in larger weeds.

To address review concerns associated with appropriate use of the product under resistance management guidelines, the following statement has been included on the label:

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

This alerts growers to use the product within an appropriate integrated weed management (IWM) program. The NRA has accepted the proposed label statement.

9. Recommendations

Hence registration of this product was recommended with respect to efficacy and crop-safety. The NRA has considered the above findings of its advisor and has accepted the recommendation.

LABELLING REQUIREMENTS

MAIN PANEL

CAUTION

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

Atlantis®

SELECTIVE HERBICIDE

Active Constituent: 30 g/L MESOSULFURON-METHYL
Crop Safener: 90 g/L MEFENPYR-DIETHYL
Solvent: 711 g/L HYDROCARBON LIQUID

GROUP B HERBICIDE

For the post-emergence control of wild oats and annual phalaris, and suppression of brome grass and annual ryegrass in wheat.

*** L**

IMPORTANT: READ THE ATTACHED BOOKLET

(label code)

* 1, 5, 10, 20 L

ATLANTIS SELECTIVE HERBICIDE

STORAGE AND DISPOSAL
Store in the closed, original container in a cool, well-ventilated area. Do not store for prolonged periods in direct sunlight. Triple or preferably pressure rinse containers before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and bury empty containers in a local authority landfill. If no landfill is available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should not be burnt.

SAFETY DIRECTIONS
Will damage the eyes. Will irritate the skin. Avoid contact with eyes and skin. When preparing spray wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow-length PVC gloves and goggles. If product on skin, immediately wash area with soap and water. If product in eyes, wash it out immediately with water. Wash hands after use. After each day's use wash gloves, goggles and contaminated clothing.

FIRST AID
If poisoning occurs contact a doctor or Poisons Information Centre (telephone 13 11 26). If swallowed, do NOT induce vomiting. Give a glass of water.

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

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

NRA Approval No.: 54252/….

Atlantis® is a Registered Trademark of Bayer.

REAR PANEL

FOR 24 HOUR SPECIALIST ADVICE
IN EMERGENCY ONLY
PHONE 1800 033 111

*

BAR CODE

Bayer CropScience Pty. Ltd.
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391-393 Tooronga Rd
East Hawthorn Vic. 3123

Phone: (03) 9248 6888
Fax: (03) 9248 6800
Website: www.bayercropscience.com.au
Technical Enquiries: 1800 804 479

Bayer CropScience

Batch Number:
Date of Manufacture:

(label code)

CAUTION

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

ATLANTIS SELECTIVE HERBICIDE
Active Constituent: 30 g/L MESOSULFURON-METHYL
Crop Safener: 90 g/L MEFENPYR-DIETHYL
Solvent: 711 g/L HYDROCARBON LIQUID

GROUP B HERBICIDE

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

SAFETY DIRECTIONS
Will damage the eyes. Will irritate the skin. Avoid contact with eyes and skin. When preparing spray wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow-length PVC gloves and goggles. If product on skin, immediately wash area with soap and water. If product in eyes, wash it out immediately with water. Wash hands after use. After each day's use, wash gloves, goggles and contaminated clothing.

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NRA Approval No.: 54252/….

IMPORTANT: READ THIS BOOKLET BEFORE USE

DIRECTIONS FOR USE

Restraints

DO NOT use if rainfall or irrigation is to occur within 8 hours of application.
DO NOT apply to crops undersown with legumes.
DO NOT apply to wheat before the 3-leaf stage (Z13).
DO NOT apply without surfactant/wetting agent.
DO NOT apply to paddocks where there is a high risk of weeds resistant to Group B herbicides.
DO NOT apply to the wheat varieties Westonia and Brookton

Note

Atlantis is a sulfonylurea herbicide. Atlantis will substantially reduce the growth of many weeds rather than give complete plant kill. Refer to the critical comments in the Directions for Use Table below, for directions on specific weeds.

CROP	WEED	STATE	WEED STAGE	RATE /ha	CRITICAL COMMENTS
Wheat	Brome grass (great brome) *(Bromus diandrus)*	All States	1 to 3 leaf (Z11 to Z13,21)	330 mL	**Suppression of brome grass.** Will substantially reduce the growth of brome grass and its ability to compete with the crop and will reduce seed set but may not give a significant reduction in plant numbers. Apply generally within 4 to 7 weeks after sowing. Apply when the majority of brome grass is at the 1 to 3 leaf stage (Z11 to Z13,21). Efficacy on larger plants that may have emerged before the crop may be poor. Do not use for suppression of dense brome grass populations (>150 plants/m^2).
	Annual ryegrass (*Lolium rigidum)*	NSW, ACT, Vic, SA, WA only	1 to 3 leaf (Z11 to Z13,21)		**Suppression of ryegrass.** Will substantially reduce the growth of ryegrass and its ability to compete with the crop and will reduce seed set but may not give a significant reduction in plant numbers. Apply generally within 4 to 7 weeks after sowing. Do not use for control of dense annual ryegrass populations (>200 plants/m^2).

CROP	WEED	STATE	WEED STAGE	RATE /ha	CRITICAL COMMENTS
Wheat	Wild oats (*Avena* spp.)	All States	1 to 3 leaf (Z11 to Z13,21)	330 mL	Apply generally within 4 to 7 weeks after sowing. Do not use for control of dense wild oat populations (>150 plants/m^2). Application to wild oats at more advanced growth stages or to dense populations will result in suppression of wild oats only. Growth of wild oats and the ability to compete with the crop will be reduced but plants numbers may not be significantly reduced.
	Annual phalaris, paradoxa grass (*Phalaris paradoxa* only)		1 to 3 leaf (Z11 to Z13,21)		Apply generally within 4 to 7 weeks after sowing. Do not use for control of dense phalaris populations (>300 plants/m^2). **Other phalaris species may not be adequately controlled with Atlantis.**

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

WITHHOLDING PERIODS
Harvest: DO NOT HARVEST FOR 8 WEEKS AFTER APPLICATION
Grazing/Stockfood: DO NOT GRAZE OR CUT FOR STOCKFOOD FOR 4 WEEKS AFTER APPLICATION

GENERAL INSTRUCTIONS

Atlantis is a selective sulfonylurea herbicide. It is predominantly a foliar herbicide with less activity via the soil. Atlantis will not reliably control weeds that emerge after spraying. Results are best under good growing conditions and application to weeds or crop under stress should be avoided.

Resistant Weeds Warning **GROUP B HERBICIDE**

Atlantis Selective Herbicide is a member of the sulfonylurea group of herbicides and has the inhibitor of ALS mode of action. For weed resistance management Atlantis is a Group **B** herbicide. Some naturally-occurring weed biotypes resistant to Atlantis, and other Group **B** herbicides, may exist through normal genetic variability in any weed population. These resistant individuals can eventually dominate the weed population if these herbicides are used repeatedly. These resistant weeds will not be controlled by Atlantis or other Group **B** herbicides.

Do not rely exclusively on Atlantis for weed control. Use as part of an integrated weed management program involving herbicides with other modes of action and non-chemical methods of control. Avcare resistance management strategies are available from your local agricultural chemical supplier. Refer to these strategies for details of how to manage the build up of resistant weeds on your farm.
Since occurrence of resistant weeds is difficult to detect prior to use Bayer CropScience Pty. Ltd. accepts no liability for any losses that may result from the failure of Atlantis to control resistant weeds.

Use of Surfactant / Wetting Agent
Atlantis must always be applied with the addition of a non-ionic wetting agent (e.g. BS1000® at 0.25% v/v).

Crop Safety
- Do not apply to any crop other than wheat.
- Do not apply to the wheat varieties Westonia and Brookton
- Wheat should be at the 3 leaf stage (Z13 growth stage), or more advanced, before application of Atlantis.
- Do not apply to wheat that is physically damaged (e.g. by hail, wind, insect attack).
- Some crop yellowing and growth retardation may occur within 5 weeks of application. Growth retardation will be increased if the crop is affected by root disease (e.g. cereal cyst nematode, rhizoctonia, take-all (haydie)), nutritional stress, waterlogging, drought stress, excessively cold conditions or previous herbicide treatment.
- Application to very dry sandy soils followed by soaking rainfall may cause significant crop effects.
- Crop damage will be increased in highly alkaline soils (soil pH > 8.5 as determined by soil in water suspension).
- Do not apply to crops not actively growing due to cold and wet conditions or drought stress.
- Do not overlap when spraying or double spray corners.
- The following wheat varieties have been tested for crop safety. Application to wheat varieties other than those listed below may result in crop damage.

Ajana	Carnamah	Hartog	Nyabing	Sunbrook	Sun 230 A
Amery	Cunderdin	Janz	Ouyen	Suneca	Tamaroi
Arrino	Cunningham	Kalannie	Pelsart	Sunland	Tasman
Batavia	Diamondbird	Kamilaroi	Perenjori	Sunlin	Wallaroi
Baxter	Dollarbird	Karlgarin	Rosella	Sunmist	Yallaroi
Bowey	Frame	Leichardt	Rowan	Sunsoft	Yanac
Calingiri	Goldmark	Machete	Silverstar	Sunstate	
Camm	Goroke	Meering	Stiletto	Sunvale	

Crop Rotation Recommendations
Minimum re-cropping intervals apply for all crops following Atlantis application.
The application of a Group B herbicide in the crop following Atlantis use may result in increased crop effects. Consult the manufacturer of Atlantis for advice in these situations.
Rainfall of less than 250 mm following Atlantis use will result in extended re-cropping intervals.
Use on soils with a pH greater than 8.5 (soil in water) has not been extensively tested and is not recommended. For advice on crops not listed below, contact your local reseller or Bayer CropScience representative.

CROP	MINIMUM RECROPPING INTERVAL
wheat	1 day
faba beans	11 months
canola	9 months
lentils	11 months
medic	21 months
peas	9 months

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

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

Equipment
Ground Sprayers
Standard boom sprayers only are recommended and must be fitted with by-pass or mechanical agitation. It is recommended that 50 to 80 L water/ha is applied as a FINE/MEDIUM spray as defined by ASAE S572 standard.
Aircraft
Do not apply Atlantis by aircraft.

Sprayer Clean Up
The sprayer must be decontaminated before being used to spray crops other than cereals. Ensure that the following operation is carried out in an area that is clear of waterways, desirable vegetation and tree roots, and preferably in an area where drainings can be contained.
1. Drain sprayer completely and wash out tank, boom and hoses with clean water.
2. Drain again.
3. Fill the tank with clean water and add 300 mL of chlorine bleach (containing 4% chlorine) per 100 L of water with agitation running.
4. Flush some bleach solution through booms and hoses and allow remainder to agitate in tank for 10 minutes.
5. Remove nozzles and filters and leave to soak in a bleach solution of 500 mL per 10 L of water while tank cleaning is in progress.
6. Drain tank and repeat the procedure of flushing with bleach solution.
7. Flush the tank, boom and hoses with clean water.

Compatibility
The compatibility of Atlantis with crop protection products other than wetting agent as recommended, is being further evaluated. Contact your local Bayer CropScience representative for further information on compatible products.

Re-entry Period
Do not allow entry into treated areas until the spray has dried.

When prior entry is necessary and if exposure to the treated crop is likely, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

Undersown Clovers and Medics
DO NOT apply to crops undersown with legumes.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Very toxic to aquatic plants and algae. DO NOT contaminate streams, rivers or waterways with the chemical or used container.

PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS
DO NOT apply under weather conditions, or from spraying equipment, that may cause spray to drift onto nearby susceptible plants/crops, cropping lands, pastures, waterways or wetlands. **DO NOT apply within 3 metres of non-target vegetation or waterbodies.**

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GLOSSARY

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

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

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