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Public Release Summary
on

Evaluation of the new active

SULFOSULFURON

in the product

MONZA HERBICIDE
BY MONSANTO

National Registration Authority
for Agricultural and Veterinary Chemicals

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Australia

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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 Department of Health and Family Services (Chemicals and Non-prescription Drug Branch), Environment Australia (Risk Assessment and Policy Section), the National Occupational Health and Safety Commission 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.

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

This Public Release Summary is intended as a brief overview of the assessment that has been completed by the 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 it with payment to the NRA. Alternatively, the reports can be viewed at the NRA Library, Ground 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 Executive Manager—Registration, National Registration Authority for Agricultural and Veterinary Chemicals, PO Box E240, Kingston ACT 2604.

CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS

[This list should be modified to include all the acronyms and abbreviations that actually appear in the publication.]

ac	active constituent
ADI	acceptable daily intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
d	Day
EC_{50}	concentration at which 50% of the test population are immobilised
Fo	original parent generation
h	Hour
HPLC	high pressure liquid chromatography *or* high performance liquid chromatography
id	Intradermal
ip	Intraperitoneal
im	Intramuscular
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
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
mg	Milligram
mL	Millilitre
MRL	maximum residue limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
ng	Nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	no observable effect concentration/level
po	Oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
s	Second
sc	Subcutaneous
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
T-Value	a value used to determine the First Aid Instructions for chemical products that contain two or more poisons
TGAC	technical grade active constituent
WHP	withholding period

SUMMARY

This publication outlines the regulatory considerations and provides a summary of the data evaluated for the proposed registration of *Monza Herbicide By Monsanto* (*Monza*). *Monza* is formulated as a dry flowable water dispersible granule containing 750 g/kg of Sulfosulfuron. It is proposed that the product will be used for either pre or post-emergent management of grass and broadleaf weeds in wheat. The key will be the economic suppression of brome grass *(Bromus spp.),* which is threatening the viability of wheat production in some areas and for which current management methods are limited.

The NRA has assessed the data submitted by the applicant in support of the proposed use of Sulfosulfuron. The following information is provided for public comment before the NRA determines whether to register the product in Australia. Comments should be submitted by **8 January 1999** to the NRA at the address indicated on page 1.

Public Health Aspects

Toxicology

Sulfosulfuron, the active ingredient of *Monza*, has very low acute toxicity. It causes slight eye irritation but no skin irritation or sensitisation. The product, *Monza*, has not been studied, but a comparable formulation containing Sulfosulfuron was of very low oral, dermal and inhalational toxicity, caused slight eye irritation, but was not a skin irritant or sensitiser.

Following repeated oral administration of high doses of Sulfosulfuron, the kidney, ureters and urinary bladder have proven to be target organs in mice, dogs and rats. A consistent pattern of injury to the urinary tract has emerged in all three species, associated with the presence of crystals and stones. In dogs, urinary bladder lesions consisted principally of inflammation, ulceration and haemorrhage. Male mice exposed over a lifetime to high doses, displayed inflammation, increased division and plate-like transformation of the cells lining the urinary bladder, together with tumours which may have arisen from prolonged tissue injury and repair. There was extensive mortality among high dose rats from stone formation. Rats also showed increased cell division in the urinary bladder lining and single cases of benign and malignant bladder tumours. However, at low to moderate doses, which did not cause stone formation in the urinary tract, neither benign nor malignant tumours developed in mice or rats. Sulfosulfuron was not mutagenic in bacteria or cultured mammalian cells. Although in one study Sulfosulfuron caused chromosomal damage in cultured cells, negative results were obtained in a second *in vitro* study and in an *in vivo* study in mice. Sulfosulfuron did not have any effects on the reproduction of rats or the foetal development of rats and rabbits, and was not toxic to the nervous system of rats.

Based on an assessment of the toxicology and the potential dietary intake of residues, it was considered that despite significant adverse effects in some species at some treatment levels there should be no adverse effects on human health from the proposed use of Sulfosulfuron as a component of *Monza* in accordance with label directions.

Residues in Food and Trade Aspects

Residues in food

Results from Australian residue trials on wheat showed those Sulfosulfuron residues in the harvested wheat grain and straw were non-quantifiable (≤0.01 mg/kg). A maximum wheat forage residue of 0.017 mg/kg (equivalent to a dry weight residue of 0.07 mg/kg) was observed four weeks after application of the herbicide. A grazing restraint is not necessary since the wheat forage MRL (0.1 mg/kg) is based on the residues present at the earliest stage at which crop grazing may be considered.

When *Monza* is used according to the proposed use pattern on wheat, Sulfosulfuron residues in animal commodities as a result of animals having eaten wheat grain, straw or fodder are not expected to be quantifiable (≤0.005 mg/kg).

Trade

As the proposed use is expected to result in non-quantifiable residues, there should be no adverse effects on trade from use on wheat. The presence of non-quantifiable residues of Sulfosulfuron in wheat grain and straw indicates that the use of these commodities as animal feed would not be expected to result in quantifiable residues in animal commodities. Similarly, the low levels of Sulfosulfuron residues in wheat forage (≤0.1 mg/kg dry weight) are not expected to produce quantifiable residues in animal produce.

Occupational Health and Safety Aspects

Monza can be used safely by workers when handled in accordance with the control measures indicated in this assessment.

Based on available information, Sulfosulfuron and *Monza* cannot be determined to be hazardous substances according to the *National Occupational Health & Safety Commission* (NOHSC) Criteria for Classifying Hazardous Substances.

Monza is formulated overseas. Within Australia, exposure to the product would only occur during transport, storage or retailing, if packaging were breached. Should formulation be carried out in Australia in the future, workers will need to be protected by appropriate engineering controls, safe work practices and adequate training.

Monza is expected to be of low acute toxicity by all routes. It is a slight eye irritant but not a skin irritant nor a skin sensitiser. The main health hazards of repeated dosing were pathological changes in kidneys, bladder and ureters at high doses.

No information is available on human exposure to Sulfosulfuron. Exposure data derived from predicative models was used to assess the risk to end users of *Monza*. Based on the Occupational Health & Safety risk assessment no special controls or PPE is recommended for end users of the product.

No re-entry or re-handling restrictions are required for workers using *Monza*.

Instructions and safety directions on the product label enable safe use of the product.

Environmental Aspects

Environmental Fate

In laboratory studies, hydrolysis is a potential degradation route when conditions are acidic, with typical products being the aminopyrimidine and sulphonamide formed through cleavage of the sulfonylurea bridge. Aqueous photolysis is also a potential route, but with a greater variety of products. Some laboratory aerobic metabolism studies and sediment/water studies indicated that *Monza* would be "fairly degradable", although others indicated that degradation was not always assured, even in a soil with a low pH. Lower temperatures clearly slowed down degradation. The products formed included the hydrolysis products as well as the desmethyl product, and CO_2 in one study.

Batch equilibrium adsorption/desorption laboratory studies indicated the parent compound had high to very high mobility, with the results also suggesting that there was some correlation of adsorption with pH, although not with organic matter. The desmethyl product had similar high mobility, although the degradation products formed from hydrolysis of the sulfonylurea bridge generally had reduced potential for mobility; the sulphonamide having low to high mobility and the aminopyrimidine having medium mobility to being immobile. Adsorption of any of the degradation products studied did not appear to be correlated to pH or organic matter. A soil column test also indicated that *Monza* had the potential to leach when applied to an acidic sandy soil, although the field lysimeter study on a similar soil (pH = 6.1) indicated and that other factors when applied in the field might limit leaching of the parent, even after two applications; by contrast with results from the adsorption/desorption study, the sulphonamide was a significant component found in the leachate, although at sub-ppb levels. Another field lysimeter study also indicated that sandy soils with a neutral pH, while differing in the amount of leachate collected (7-13% of rainfall/irrigation received for bare columns, and <4% of rainfall/irrigation received when wheat was sown on the lysimeter), had generally low levels of residues in the leachate (<2ppb) with no parent detected (<0.001ppb).
From trials at 15 sites (USA and Europe), DT_{50}s ranged from 11d to 75d while DT_{90}s ranged from 83d to 358d with one outlier of 739d, possibly caused by differences in estimation techniques. The European studies indicated little potential for persistence of the parent with levels near or below the level of detection (LOD) 12 months after application. In the US studies, there appeared to be some potential relationship between the DT_{50} and the temperature of the site (longer DT_{50}s with colder soil temperatures). Given the above field half-life range (mean of 28d) and K_{oc} range of 5.3-89, the groundwater ubiquity score ranges from 2.5 to >6. Thus, at the lower limit of the score, *Monza* can not be clearly classified as a leacher or non-leacher, while at the upper limit, it is classified as a probable leacher. In the field studies, however, the residues were generally detected only in the first 0-15cm.

Environmental Effects

The ecotoxicity profile of *Monza* suggests that it is typical of a sulfonylurea with very high toxicity to macrophytes (aquatic and terrestrial), potentially highly toxic to some algal and cyanobacteria species, but low to negligible acute toxicity to birds, fish, and invertebrates (aquatic and terrestrial). Results of chronic studies with reproductive and growth end-points indicated that *Monza* did not have any significant effects on birds, fish, water flea, mites and

wasps even at very high concentrations, although *Monza* residues have the potential to affect plants. No long-term effects were observed on soil microflora.

Environmental Hazard

Monza (direct spray) is not likely to pose a hazard to earthworms, birds and mammals due to its very low toxicity to these groups of animals. Hazard calculations do, however, indicate that it is likely to be hazardous to aquatic and terrestrial plants, even when allowing for lower residue levels by looking at low levels of drift (ie 1% at 5m). *Environment Australia* concludes, however, that the risk for both aquatic and terrestrial non-target organisms will be reduced considering that:

- drift from the application of herbicides by boom spray will be greatly reduced at longer distances, which is likely to be more typical in wheat growing districts,
- the exponential nature of the drift decay profile,
- the type of effect the hazard calculation was based on,
- the frequency at which drift would be problematic, and
- given appropriate label statements are made.

Efficacy and Crop Safety Aspects

Monza is in the sulfonylurea (Group B) mode of action herbicides. It was evaluated in Australia in a series of 80 field experiments in the period 1991 to 1996 for the control of brome grass, barley grass, wild oats, phalaris, wild radish and a range of other broadleaf weeds when applied either pre or post emergent (weed and crop) in wheat.

Applied post emergent, *Monza* provided control of paradoxa grass, wild radish, wild turnip, amsinckia, loose strife, capeweed and "economic control" of brome grass, barley grass, wild oats, toad rush, wild mustard, prickly lettuce, shepherds purse, volunteer peas, wireweed. *Monza*, applied pre-emergent, provided control of wild turnip and economic control of brome grass and barley grass.

Brome grass is a key weed of wheat in both Australia and overseas countries. There are no selective herbicides for the control of Brome grass in wheat, although Chlorsulfuron is registered pre emergent for suppression of brome grass only if populations are 20 plants/m^2 or less. Brome grass is currently managed by a number of methods, which prevent or control seed set the year prior to cropping wheat or exhaust seed reserves to a low level in the year of cropping. *Monza* should provide additional management options for this and other troublesome weeds in wheat.

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of *Monza Herbicide By Monsanto (Monza),* which contains the new active ingredient, Sulfosulfuron.

Responses to this Public Release Summary will be considered prior to registration of the product. They will be taken into account by the 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 Sulfosulfuron, covering toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the NRA on request (see order form on page 33). They can also be viewed at the NRA library located at the NRA's offices, Ground Floor, 22 Brisbane Avenue, Barton ACT 2604.

Written comments should be submitted by **8 January 1999** and addressed to:

[redacted]

Applicant
Monsanto Australia Limited

Product Details
Monza is to be manufactured and packed in the USA as a dry flowable water dispersible granule containing 750 g/kg of Sulfosulfuron.

It is proposed that the product will be will be registered in WA, NSW, VIC and SA for either pre or post-emergent management of grass and broadleaf weeds in wheat.

Monza is in the sulfonylurea group of chemicals (Group B). These chemicals are selective systemic herbicides that are absorbed by foliage and roots. Subsequently, they inhibit the plant enzyme, acetolactate synthase, which results in cell growth and division being stopped.

Products containing Sulfosulfuron in formulations, which are comparable to *Monza*, are registered in the following countries:

- Ireland (European Approval)
- Switzerland
- South Africa
- Poland
- Czech Republic

CHEMISTRY AND MANUFACTURE

The product proposed for registration in Australia is a water dispersible granule formulation under the trade name *Monza® Herbicide By Monsanto*.

The formulation storage stability and the physical and chemical properties of the formulated product were determined for formulation MON 37532. The differences between the proposed product formulation, (*Monza*, formulation MON 37503) and MON 37532 are considered minor and would not affect the chemistry aspects of the product.

MSDS for the inactive ingredients/excipients were provided and are acceptable.

Specifications applied to the finished product

Appearance	off-white, free flowing granules
Assay	72.5-77.5% w/w sulfosulfuron
Particle size	+10 mesh 1.0% maximum; +40 mesh 99.5% minimum
Water	<5%
Bulk density	0.62 g/mL

Packaging

The formulated product will be packaged in 600 g HDPE plastic bottles.

Stability of the Formulated Product

Samples of a formulated product (MON 37532, which is equivalent to Monza, was stable when stored at 54±2 °C in a beaker for 14 days (initial assay 74.8%; final assay 76.5%). The storage stability of the formulated product is acceptable.

Active constituent

The chemical active constituent in *Monza* is Sulfosulfuron and has the following properties:

Common name (ISO): Sulfosulfuron

Chemical name (IUPAC): 1-(4,6-dimethoxypyrimidin-2-yl)-3-[2-ethanesulfonylimidazo [1,2-*a*]pyr-idine)sulfonyl]urea

CAS Registry Number: 141776-32-1

Empirical formula: $C_{16}H_{18}N_6O_7S_2$

Molecular weight: 470.49 grams/mole

Physical form: solid

Colour: Munsell N9.5/90%R

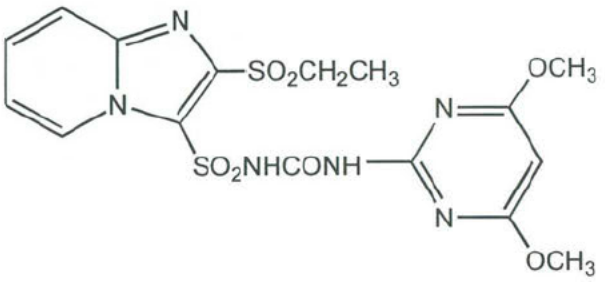
Odour: no obvious odour

Melting point: 201.0-201.7^{0}C

Octanol/water partition
coefficient (K_{ow}): log Pow<1

Vapour pressure at 25°C: 3.05×10^{-8pa}

Structural formula:



TOXICOLOGICAL ASSESSMENT

Evaluation Of Toxicology

The toxicological database for Sulfosulfuron, which consists primarily of toxicity tests conducted using animals, is extensive. In interpreting the data, it should be noted that toxicity tests generally use doses which are high compared to 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 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 at which no adverse health effects in humans would be expected.

Toxicokinetics and Metabolism

At low doses, rats absorbed >90% of orally administered Sulfosulfuron, while at high doses, absorption averaged approximately 40%. Metabolism of Sulfosulfuron occurred only to a limited extent. Sulfosulfuron and its metabolites were readily excreted, with urinary excretion as the major route of elimination for animals receiving a low dose, and faecal excretion predominating after a high dose. Expiration as carbon dioxide or volatiles was not a significant route of elimination. There was little evidence of bio-retention of Sulfosulfuron or its metabolites; tissue and blood levels were negligible, with no individual tissue containing levels exceeding 0.2% of the dose.

Acute Studies

In rats, Sulfosulfuron had oral and dermal LD50s >5000 mg/kg bw and an inhalation LC50 >3000 mg/m^3 (4h) (no deaths by any route of administration). Sulfosulfuron was slightly irritating to rabbit eyes but did not irritate rabbit skin or cause dermal sensitisation in guinea pigs.

MON 37532, a 750 g/kg WG formulation similar to *Monza*, had oral and dermal LD50s >5000 mg/kg bw in rats (no deaths by either route). Its inhalation LC50 exceeded 2600 mg/m^3 in rats (0/5 M and 1/5 F deaths following 4h exposure). MON 37532 was slightly irritating to rabbit eyes but did not irritate rabbit skin or cause dermal sensitisation in guinea pigs.

Short term Studies

Mice were treated with Sulfosulfuron by dietary administration for 4 wk at concentrations of 0, 10, 100, 1000 or 4000 ppm (M: 2.0, 17, 186 and 701 mg/kg bw/d and F: 2.7, 22, 274 and 987 mg/kg bw/d). There were no unscheduled deaths or treatment-related effects on feed

consumption, bodyweight or bodyweight gain, haematology or plasma biochemistry parameters, or gross- or histo-pathology. The test compound did not influence activity of the liver enzyme cytochrome P-450 activity, but induced a small (1.4-fold vs controls) but statistically significant increase in liver peroxisomal palmitoyl CoA oxidase activity in 4000 ppm males. Since activity of the enzyme was not measured at lower doses, a threshold dose for the effect could not be established.

In a dose-ranging study, Sulfosulfuron was administered in the diet to rats at 0, 20, 200, 2000 or 10000 ppm (1.3, 13.7, 136 and 669 mg/kg bw/d in males and 1.5, 15.6, 154 and 768 mg/kg bw/d in females) daily for 4 wk. There were no mortalities or significant differences among treatment groups in food consumption or mean body weights. There was a non-adverse cumulative bodyweight gain in females at 2000 and 10000 ppm, but no treatment-related effects on clinical signs, haematology, clinical chemistry, organ weights, and macroscopic or microscopic pathology.

Sulfosulfuron was administered by dermal application to rats at doses of 0, 100, 300 or 1000 mg/kg bw per application over a 28-day period (6 h/d, 5 d/wk). No local dermal irritation or other treatment-related effects were observed at any dose.

Sulfosulfuron was administered orally by capsule to beagle dogs at 30, 100, 300 or 1000 mg/kg bw/d 5 d/wk for 4 wk. There were no clinical signs, deaths or treatment-related findings in haematology, clinical chemistry, gross- or histopathology up to and including the highest dose.

Subchronic Studies

Sulfosulfuron was administered in the diet for approximately 90 d to mice at concentrations of 0, 100, 1000, 3000 or 7000 ppm ([M/F]18 / 32, 163 / 313, 550 / 887 and 1144 / 2123 mg/kg bw/d). There were no unscheduled deaths, or treatment-related clinical signs or effects on feed consumption, bodyweight, bodyweight gain, haematology, clinical biochemistry, gross pathology or histopathology up to and including the highest dose tested.

In a 3 month toxicity/pilot reproduction study, Sulfosulfuron was administered in the diet to rats at 0, 20, 200, 2000, 6000 or 20000 ppm (1.2, 12.1, 123, 370, 1278 mg/kg bw/d males and 1.5, 14.6, 144, 448, 1489 mg/kg bw/d females). A subsequent group of pregnant females were administered the same dose range. There were no unscheduled mortalities and no statistically significant differences among treatment groups in food consumption or cumulative body weight gain. Mean body weights of high-dose animals in the main study decreased in males and in pregnant high-dose females. There were no treatment-related effects on clinical signs, ophthalmoscopy, haematology or clinical chemistry. At the high dose several kidney lesions were seen in conjunction with kidney and/or bladder stones. For the reproduction study phase there were no statistically significant differences among treatment groups in measures of mating, fertility or gestation length, pup weights at birth or during the first four days of lactation, or litter weights or survival. The NOEL was 6000 ppm (370 mg/kg bw/day).

Sulfosulfuron was administered orally by capsule to beagle dogs at 0, 30, 100, 300 or 1000 mg/kg bw/d, 5 d/wk for 3 months. One/5 males treated at 1000 mg/kg was sacrificed *in*

extremis on d 75. All other dogs survived until termination without significant effects on bodyweight, bodyweight gain, food consumption, or ophthalmology. Crystals and bacteria were observed in the urine at 300 and 1000 mg/kg. Creatinine phosphokinase activity was elevated in 1/5 of the 1000 mg/kg males, arising from degeneration of skeletal muscle. Red or purple areas of discolouration were noted in the urinary bladders of 1/5 females from each of the 100 and 300 mg/kg groups and 2/5 females treated with 1000 mg/kg, while the 1000 mg/kg male descendant showed evidence of urinary tract stone formation. At 300 and 1000 mg/kg, microscopic lesions included haemorrhage, ulceration and inflammation of the bladder lining. The NOEL was 100 mg/kg bw/d.

Long Term Studies

Mice received Sulfosulfuron in the diet for approximately 18 months at 0, 30, 700, 3000 and 7000 ppm ([M/F] 4.0 / 6.5, 93 / 153, 394 / 635 and 944 / 1388 mg/kg bw/d). Growth, feed consumption and survival were not compromised, but abdominal swelling or distension, urine stained fur, abnormal penile erections, biochemical evidence of kidney dysfunction and slightly depressed absolute and relative testis weights were observed among 7000 ppm males. Stones were found in the urinary bladder of many 3000 and 7000 ppm males, in addition to increased incidences of enlargement / distension of the ureter, bladder and / or kidney pelvis and kidney atrophy at 7000 ppm. Histopathological examination showed atrophy and dilation of the kidney pelvis, and inflammation, increased division and plate-like transformation of cells lining the bladder in 3000 and 7000 ppm males. Urinary bladder tumours were increased from zero among male controls to 1/60 and 5/60 in the 3000 and 7000 ppm male groups, respectively. The NOEL was 700 ppm (93 mg/kg bw/d).

Rats were fed diets containing Sulfosulfuron at 0, 50, 500, 5000 and 20000 ppm (0, 2.4, 24.4, 244 and 1178 mg/kg bw/d for males, and 0, 3.1, 30.4, 314 and 1297 mg/kg bw/d for females), for up to 22 months. Treatment resulted in significantly increased mortality for males in the 20000 ppm group, from urinary stones and related abnormalities in the kidneys, urinary bladder and ureters. By d 250, mortality rate had attained 37%, and so all remaining males in the 20000 ppm group were sacrificed on d 259. A slight increase in the mortality, which was also associated with urinary stones, was noted for females in the 20000 ppm group. There was an increased incidence of blood-like urine colour in the 20000 ppm males and slightly lower mean body weight gain in the 20000 ppm group, both sexes. At 5000 and 20000 ppm there were pathological changes in the kidneys and urinary bladder (stones, dilated renal pelvis, thickened bladder mucosa, increased cell division in the bladder wall) and secondary changes in biochemical and urinary parameters. Additionally, increased cell division in the parathyroid, defective bone formation and emaciation were noted in 20000 ppm females. One benign and one malignant tumour were observed in the urinary bladder of 2 different females in the 5000 ppm group. The NOEL was 500 ppm (24.4 mg/kg bw/day for males, and 30.4 mg/kg bw/day for females).

Sulfosulfuron was administered orally by capsule to beagle dogs at doses of 0, 5, 20, 100 or 500 mg/kg bw/d, 5 d/wk for 1 y. There was no premature mortality. No biologically significant influence occurred on bodyweight gain or terminal bodyweight. The only notable clinical sign was a yellow precipitate in the urine of males from the 500 mg/kg group. At the 6 month sampling point, urinalysis revealed the presence of unidentified crystals in 1/5 females at 20 mg/kg, and 1 dog/sex from the 500 mg/kg group. The 500 mg/kg females also

tended to have more red blood cells in the urine than the other groups. However, these findings were not replicated at the terminal sampling. A single 500 mg/kg male showed biochemical evidence of liver dysfunction. Treatment-related pathological abnormalities were confined to the 500 mg/kg group, comprising stones, mucosal thickening/irregularity, red mucosal foci, haemorrhage and oedema in the urinary bladder of 1 male and kidney pelvic inflammation in 1/5 females. The NOEL was 100 mg/kg bw/d.

Reproduction Study

A two-generation reproduction study was performed in rats at dietary levels of 0, 50, 500, 5000 and 20000 ppm Sulfosulfuron ([F0] 3.1 / 3.6, 32 / 36, 312 / 363 and 1313 / 1454 and [F1] 3.1 / 3.7, 31 / 37, 316 / 378 and 1379 / 1598 [M/F] mg/kg bw/d). Reproductive parameters and pup development, growth and survival were unaffected in both generations. Treatment-related effects were confined to adults. At 20000 ppm, two F0 and one FI males died prematurely, possibly from urinary stones. In either or both of the F0 and F1 20000 ppm groups, bodyweight gain and/or bodyweight were depressed during the premating period, and maternal food consumption, bodyweight and/or weight gain were significantly reduced during gestation and lactation. At 20000 ppm, relative kidney weights were increased in both generations. Relative liver weights were slightly increased in F0 males from 500 ppm, and in 20000 ppm males and females of the F1 generation. Gross treatment-related observations in F0 and/or F1 adults, comprised dilation of or stones in the kidney, ureter or bladder at 5000 and 20000 ppm. Histologically, the kidneys of 20000 ppm F0 and/or F1 females showed distension and increased cell division. Increased cell division in the prostate was present in F1 males at 5000 and 20000 ppm. The NOEL for adults was 500 ppm (approximately 30 mg/kg bw/d). No treatment-related effects occurred on pups up to and including the highest dose of 20000 ppm (approximately 1300 mg/kg bw/d).

Developmental Studies

Rats received single daily doses of Sulfosulfuron by gavage at 0, 100, 300 or 1000 mg/kg bw/d from the 6th to the 15th day of gestation. No treatment-related effects occurred on the dams or on gestation, foetal growth or development, at up to and including the highest dose tested.

Rabbits received single daily doses of Sulfosulfuron by gavage at 0, 50, 250 or 1000 mg/kg bw/d from gestation days 7 to 19. No treatment-related effects occurred on the dams or on gestation, foetal growth or development, at up to and including the highest dose tested.

Genotoxicity Studies

In both the presence and absence of metabolic activation, negative results were obtained when Sulfosulfuron was tested for mutagenicity in *S. typhimurium* and in cultured Chinese hamster ovary cells. An assay for chromosomal damage in cultured human lymphocytes was negative but chromosomal damage occurred in another study, at higher concentrations of the test compound in cultured Chinese hamster lung cells. A mouse bone marrow micronucleus test at oral doses of up to 5000 mg/kg bw revealed no chromosomal damage *in vivo*.

Other studies

In an acute neurotoxicity study, rats received a single dose of Sulfosulfuron by gavage at 0, 125, 500 or 2000 mg/kg bw. A Functional Observational Battery and a test for motor activity were run pre-test, 7 h post-dosing, and 7 and 14 d post-dosing. Fifteen days after dosing, half the animals were selected for neuropathological examination, while the remainder were killed approximately 3 wk post-dosing and were subjected to a gross external and internal necropsy. No treatment-related effects occurred at up to and including 2000 mg/kg bw, the highest dose tested.

A subchronic neurotoxicity study was performed with Sulfosulfuron in rats at 0, 200, 2000 or 20000 ppm in the diet ([M/F] 12 / 14, 122 / 141 and 1211 / 1467 mg/kg bw/d). A Functional Observational Battery and a test for motor activity were run pre-test and 4, 8 and 13 wk post-dosing. After 14 week's treatment, half the animals were selected for neuropathological examination and the remainder were subjected to a gross external and internal necropsy. All animals survived to scheduled sacrifice without displaying treatment-related clinical signs. There was an apparent dose-related trend towards reduced bodyweight gain among treated males, such that both terminal bodyweight and cumulative weight gain were depressed by approximately 6 and 10%, at 20000 ppm. High dose males also consumed slightly less food than controls. However, there were no treatment-related effects on the appearance, behaviour or activity, or remarkable gross post-mortem findings. Neurohistopathology revealed minor focal or multi-focal degeneration in the skeletal muscle and/or spine, sural nerve or sciatic nerve of some 20000 ppm rats, but the lesions were insufficiently severe or frequent to be ascribed to treatment. Therefore, there were no neurotoxic effects up to and including the highest dose of 20000 ppm (1200 mg/kg bw/d).

PUBLIC HEALTH STANDARDS

Poisons Scheduling

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

The NDPSC recommended that formulations containing Sulfosulfuron should be exempt from scheduling. There are provisions for appropriate warning statements and first-aid directions on the product label.

NOEL/ADI

The most sensitive species tested was the rat with a NOEL of 24 mg/kg bw/day in a 2-year dietary study. In order to calculate an Acceptable Daily Intake (ADI) for humans, a safety factor is applied to the NOEL in the most sensitive species. The magnitude of the safety factor is selected to account for uncertainties in extrapolation from animal data to humans, variation within the human population, the quality of the experimental data, and the nature of the potential hazards. Using a safety factor of 100, an ADI of 0.2 mg/kg bw/day was established for Sulfosulfuron.

RESIDUES ASSESSMENT

Metabolism

Plants:

Metabolism studies were conducted in the USA on wheat using two ^{14}C-labelled forms of Sulfosulfuron. Wheat plants were treated pre- and post- emergence with the labelled formulation at rates of 52.5 g ai/ha and 150 g ai/ha (2.8x and 8x the recommended use rate, respectively). Samples of forage, straw and grain were collected and analysed. Post-emergent wheat was found to have the highest level of radioactivity, with the magnitude of the residues being greatest in wheat foliage and forage, followed by straw, and then grain. A total of six Sulfosulfuron metabolites[†] were identified in wheat commodities, but the parent Sulfosulfuron was found to be the largest component of the total residue (>58%), while each metabolite typically contributed less than 10%. In fact, greater than 70% of the total residue was made up of components containing the intact imidazopyridine moiety. The maximum radioactive residue level for each sample type after treatment at 150 g ai/ha was: 0.013 mg/kg (grain), 1.1 mg/kg (straw), 5.2 mg/kg (foliage) and 2.9 mg/kg (forage). Similarly, the maximum residue levels after treatment at 52.5 g ai/ha were: 0.0055 mg/kg (grain), 0.40 mg/kg (straw), 2.6 mg/kg (foliage) and 1.0 mg/kg (forage).

Animals:

Animal metabolism studies were conducted in rats, lactating goats, and laying hens. Common metabolic trends were observed in all three animal types.

In rats treated with ^{14}C-labelled Sulfosulfuron, it was determined that >90% of the oral dose was absorbed, and the extent of absorption was unaffected by pre-treatment with repeated doses of Sulfosulfuron. At low doses, the major route of Sulfosulfuron elimination is via the urine, whereas at high doses the faeces became the preferred route of excretion. The half-life for whole-body Sulfosulfuron elimination was estimated to be between 1.1 and 3.2 days.

In lactating goats orally dosed with ^{14}C-labelled Sulfosulfuron for three days, most of the dose (60 to 84%) was excreted within 24 hours of the last dose (40 to 46% in the faeces and 29 to 38% in urine). The remainder of the radioactivity was primarily associated with the gastrointestinal tract (7.7 to 10.9%). Milk accounted for less than 0.05% of the administered dose, and the edible tissues (muscle, liver, kidney and fat) contained a total of 0.11 to 0.17% of the administered radioactivity. The metabolite profile in goats was relatively uncomplicated, with the dominant residue being the parent Sulfosulfuron. For that portion of Sulfosulfuron that does undergo metabolic breakdown in the goat, the metabolic pathways involve oxidative demethylation and sulfonylurea bridge cleavage (both reactions seen in wheat metabolism) and oxidation/sulfonation of the aminopyrimidine ring (absent in wheat).

In hens orally dosed with ^{14}C-labelled Sulfosulfuron for five days, 84 to 89% of the dose was eliminated via the excreta. Egg whites accounted for less than 0.006% of the administered dose, while egg yolks contained 0.00087 to 0.0052% of the total radioactivity. The edible

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[†] The six metabolites were the desmethyl form of Sulfosulfuron, the sulfonamide, the guanidine, the urea, the sulfamic acid, the oxamic acid and the aminopyrimidine forms. Note that the desmethyl, sulfonamide, and guanidine forms all possess the intact imidazopyridine moiety.

tissues (muscle, skin, blood, liver, kidney and fat) contained a total of between 0.016 and 0.032% of the administered radioactivity. The metabolic profile in hens was identical to that found in lactating goats.

Overall, the metabolic pathway in animals appears to be slightly different from that in wheat. Of the six Sulfosulfuron metabolites identified in wheat, only two were found in animal metabolism studies. The cleavage of the sulfonylurea bond appears to be of greater significance in wheat, whereas the demethylation and oxidation of the pyrimidine ring appear to be more important in animals. However, the significance of the observed variations in the metabolic pathways is minimal, since the sum of the common metabolites plus the parent Sulfosulfuron accounts for most of the residues in both wheat and animal tissue samples.

Analytical Methodology

A detailed description of the analytical method used for determining residues in plant and animal tissues was provided. The parent Sulfosulfuron and its metabolites with an intact imidazopyridine group (desmethyl, sulfonamide and guanidine) are degraded to a common chemophore (the ethyl sulfone) by acid hydrolysis. The concentration of the ethyl sulfone is then determined by HPLC after a series of extractions and solid-phase clean-up steps. The residue is then expressed in terms of Sulfosulfuron equivalents. The limit of quantitation of the validated method is 0.004 mg/kg for animal tissues and milk, and 0.01 mg/kg for plant tissues.

Residue Definition

The residue definition for Sulfosulfuron is the *"sum of Sulfosulfuron and its metabolites which can be hydrolysed to 2-(ethylsulfonyl)imidazo[1,2-a]pyridine, expressed as Sulfosulfuron"*.

Residues Trials

Residue data were presented for wheat commodities (forage, grain, hay, and straw), eggs, milk and edible tissues of lactating dairy cattle. Sulfosulfuron wheat residue trials were conducted in both the USA and Australia.

Wheat residue trials conducted in the USA: During the 1995 growing season, 25 wheat trials were conducted in 17 US states, where winter wheat was planted at 17 test sites and spring wheat was planted at eight test sites. In all trials, Sulfosulfuron was applied at 40 g ai/ha (~2x recommended use rate) using the post-emergent mode of application. Additionally, the pre-emergent and pre-plant incorporation treatment modes were tested at eight locations. Samples of wheat forage, grain, hay, and straw were collected from each treatment plot and analysed for residues. Sulfosulfuron residues in all grain samples were below the limit of quantitation (LOQ; 0.008 mg/kg) irrespective of whether the herbicide was applied pre- or post-emergence. In contrast, the post-emergent Sulfosulfuron residues in wheat forage, hay and straw were higher than the corresponding pre-emergent residues. The maximum residues for wheat hay and straw after post-emergent application were 0.230 mg/kg and 0.076 mg/kg, respectively (31 days and 66 days after treatment). For wheat forage from post-emergence treated sites, the maximum residues were 3.036 mg/kg (immediately after application), 0.696

mg/kg (after 14 days) and 0.44 mg/kg (after 30 days). These values demonstrate that the Sulfosulfuron residues decline rapidly in wheat. There were no significant differences in the residue levels present in winter and spring wheat.

Wheat residue trials conducted in Australia: A series of 12 residue trials were conducted in three Australian states during the 1996 growing season. Since the results from the US trials indicated that the post-emergent use-pattern produced the highest Sulfosulfuron residues, the Australian trials involved the post-emergent application of Sulfosulfuron to wheat crops at rates of 20 g ai/ha (1x) and 40 g ai/ha (2x). Samples of wheat forage, straw and grain were collected from each of the trial sites, and were analysed for their residue content. Sulfosulfuron residues in all wheat grain samples were below the limit of quantitation (LOQ; 0.01 mg/kg) ie the results were comparable with those from the US trials. Likewise, in the Australian trials the Sulfosulfuron residues in wheat straw were all below the LOQ. This is comparable to the results of the US trials: although a maximum residue of 0.076 mg/kg was obtained for wheat straw, most of the residues were below the LOQ. In the Australian trials, wheat forage samples were collected from plants that were at the tillering stage of growth (the earliest stage at which grazing of a crop may be considered). A maximum forage residue of 0.017 mg/kg was observed (27 days after post-emergent treatment with 20 g ai/ha Sulfosulfuron), with most samples being below the LOQ. This is comparable to the results from US trials where forage residues ranged from <LOQ to 0.044 mg/kg, 30 days after treatment with 40 g ai/ha.

Overall, the residue trials indicate that when *Monza* is used in accordance with the label instructions, there are no detectable residues in wheat grain and straw. The maximum residue for wheat forage was 0.017 mg/kg, which is equivalent to a dry weight residue of 0.068 mg/kg. Hence, the Table 4 entry for wheat straw and forage (dry) has been set at 0.1 mg/kg. No grazing restraint is necessary for forage, since the MRL is based on the residues present at the earliest stage at which crop grazing may be considered.

Animal Transfer Studies

Lactating dairy cows were administered encapsulated Sulfosulfuron at 1x, 3x, and 10x the calculated maximum dietary burden (8 mg/kg) for 28 consecutive days. At the 8 mg/kg dose rate, the Sulfosulfuron residues in raw milk were all at or below the LOQ (0.004 mg/kg). The Sulfosulfuron residues in skim milk were approximately the same as those in raw milk, and there was no evidence of residue accumulation in the cream (ie Sulfosulfuron is not lipophilic).

In animals treated with 8 mg/kg Sulfosulfuron, the residues in fat and muscle tissue were below the LOQ (0.004 mg/kg). However, the residues were significantly higher in liver (0.10 mg/kg) and kidney (0.12 mg/kg). The exposure of 8 mg/kg is based on the unlikely scenario of dairy cows grazing on a wheat pasture field immediately following application of Sulfosulfuron, for a 28 day period. A more appropriate estimate of the exposure rate (based on forage residues determined in Australian trials) is 0.1 mg/kg. Thus, when the liver and kidney residue levels are adjusted to account for the 80-fold over-estimate of dietary burden, the calculated residues are below the LOQ (0.004 mg/kg).

No animal transfer studies were conducted with poultry. However, wheat grain is widely used in the poultry diet. Therefore, it is appropriate to set Sulfosulfuron MRLs (at or about the LOQ) for poultry meat, offal and eggs on the basis of the metabolism study with laying hens, and the observation that all wheat grain residues were less than the LOQ. The Sulfosulfuron MRLs for poultry meat, offal and eggs have been set at *0.005 mg/kg.

Rotational Crops

Four representative rotational crops (lettuce, radish, barley and rye) were planted in soil that had been treated with 40 g ^{14}C-labelled Sulfosulfuron/ha (2x), and allowed to lay fallow for between 30 days and 361 days. Sulfosulfuron was found to be phytotoxic to barley and lettuce at the 30 day planting interval, and to a lesser extent radish. A normal barley crop was only attained after a soil fallow period of 89 days. The minimum recommended recropping interval for rotational crops is 10 months (ie 300 days).

In soil, Sulfosulfuron was found to primarily break down into sulfonamide and aminopyrimidine. Rotational crops readily absorb the sulfonamide metabolite, whereas aminopyrimidine is bound to soil. Any aminopyrimidine uptake by the crops is believed to undergo conversion to smaller molecules that are incorporated into natural plant tissues.
The levels of ^{14}C-labelled Sulfosulfuron residues present in radishes, lettuce, barley grain and rye grain were all below the LOQ (0.01 mg/kg). In contrast, the total residues detected in animal feed commodities (ie barley forage, hay and straw) exceeded the analytical method LOQ, even when a recropping interval of 361 days was observed. However, the results from an animal transfer study conducted with dairy cattle indicate that it is unlikely that feeding rotational crops to animals will result in detectable residues in animal tissues or milk.

Estimated Dietary Intakes

The risk to human health from the registration of *Monza* is considered to be extremely low. The chronic dietary risk is estimated by the theoretical daily maximum intake (TMDI) calculation. The TMDI calculation shows that the intake is equivalent to 0.03% of the ADI for Sulfosulfuron (0.2 mg/kg bwt/day). Therefore, it is concluded that the risk to human health via chronic dietary exposure is acceptable.

Bioaccumulation Potential

The solubility of Sulfosulfuron is limited in both aqueous and organic solvents. In water, the solubility of Sulfosulfuron is pH-dependent (17.6 mg/L at pH 5, 1627 mg/L at pH 7, and 482 mg/L at pH 9). Within organic solvents, the solubility of Sulfosulfuron is extremely low in non-polar solvents (heptane <1 mg/L, xylene 160 mg/L), and higher in polar solvents (330 mg/L in methanol, 710 mg/L in acetone, 1010 mg/L in ethyl acetate and 4350 mg/L in dichloroethane). Therefore, Sulfosulfuron is not considered lipophilic, and is unlikely to have bioaccumulatory or bioretentive properties. This conclusion is further supported by the lack of any significant accumulation of Sulfosulfuron or its metabolites in animal tissues, and the observation that Sulfosulfuron is rapidly excreted in urine.

Recommended Amendments to the MRL Standard

The following Table 1 and Table 4 entries have been recommended for inclusion into the *MRL Standard*:

Table 1

Compound			Food	MRL (mg/kg)
Add:				
Sulfosulfuron				
	MO	0105	Edible offal (mammalian)	*0.005
	PE	0112	Eggs	*0.005
	MM	0095	Meat (mammalian)	*0.005
	ML	0106	Milks	*0.005
	PO	0111	Poultry, Edible offal of	*0.005
	PM	0110	Poultry meat	*0.005
	GC	0654	Wheat	*0.01

Table 4

Compound			Animal Feed Commodity	MRL (mg/kg)
Add:				
Sulfosulfuron				
	AS	0654	Wheat straw and fodder, dry	0.1

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

Withholding Periods

A withholding period is not required when the product is used as directed.

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Trade

Establishment of Sulfosulfuron MRLs at or about the limit of quantitation for wheat grain (0.01 mg/kg) and animal commodities (0.005 mg/kg) would not be expected to result in trade issues. No Codex Alimentarius Commission MRLs have been established for Sulfosulfuron. However, permanent or temporary registration and MRLs (0.01 mg/kg) have been established in Ireland (European Approval), Switzerland, the Czech Republic, Poland, South Africa and Slovakia. Additionally, complete registration packages have been submitted for registration in the USA, Canada and India. The use pattern of Sulfosulfuron is similar in all countries for which registration is currently being sought. Consequently, the potential risks to the Australian wheat trade are considered negligible.

Risk Assessment and Management

The proposed use pattern and residue results indicate that it is unlikely there will be measurable Sulfosulfuron residues in wheat grain and straw from treated plants. Low Sulfosulfuron residues have been detected in wheat forage (four weeks after application of the herbicide), and an MRL of 0.1 mg/kg has been set for forage on a dry weight basis. The risk associated with feeding animals with treated commodities, and the potential for Sulfosulfuron residues occurring in animal commodities, is considered negligible. Adherence to the proposed use pattern would be expected to effectively manage the residue risk identified with the use of *Monza*.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Sulfosulfuron is not a hazardous substance according to National Occupational Health and Safety Commission (NOHSC) Approved Criteria for Classifying Hazardous Substances.

Sulfosulfuron is a solid odourless substance with a low vapour pressure. It is not classified as dangerous goods. Sulfosulfuron is of low acute toxicity by all routes. It is a slight eye irritant but not irritant or sensitising to skin. It has low systemic toxicity and is not genotoxic, neurotoxic or teratogenic, and has no reproductive toxic potential.

The main adverse health effects noted in experimental animals repeatedly dosed with Sulfosulfuron were pathological changes in the kidneys, urinary bladder and ureters at high doses.

Monza is non-hazardous according to NOHSC criteria.

The formulation has low acute toxicity by all routes, is a slight eye irritant but not a skin irritant or a skin sensitiser.

Monza is formulated as water dispersible granules which are odourless and off-white in colour. It has low vapour pressure and the particle size varies from +10 mesh (1% maximum) - +40 mesh (99.5% minimum). The granules are not expected to be friable.

Monza is formulated overseas and will be imported into Australia in high density polyethylene plastic bottles with neck size 40 mm and simple screw cap.

Australian worker exposure to the product would occur only if packaging were breached during transport, storage or retailing. Advice on safe handling, storage and transport of *Monza* is provided in the product Material Safety Data Sheet (MSDS).

Should formulation be carried out in Australia in the future, workers will need to be protected by appropriate engineering controls, safe work practices and adequate training.

End Use

Monza will be applied by ground boom equipment, using a spray volume of 50-100 L/ha. For both pre- and post-emergent spraying, the working strength solution will be a 0.025% - 0.05% concentration of the EUP or 0.02% - 0.04% concentration of Sulfosulfuron.

The product is to be applied once per crop. A work rate of 100 ha/d is assumed under Australian conditions. Based on this work rate, it is estimated that a farmer will use *Monza* between 1-8 days per year. Contract workers may apply the spray at 140 ha/d and handle the product for up to 28 days per year.

The main route of exposure will be skin contamination. Based on the acute and repeat-dose toxic potential of Sulfosulfuron and the concentration of the active ingredient in the spray

(max 0.04%) it is unlikely that a worker will be exposed to the volume of spray required to produce adverse health effects.

Monza is formulated as large granules that are not expected to be friable. Therefore, generation of significant quantities of dust is not likely during routine use. The product is a slight eye irritant. Given the high dilution of the working strength solution (0.05% EUP), it is not expected to be an irritant to the eyes.

No worker exposure studies or surrogate studies were submitted. Therefore, the risk assessment was conducted using exposure data derived from the UK Predictive Operator Exposure Model (POEM) and the Pesticide Handlers Exposure Database (PHED).

Using the UK POEM data, adequate margins of exposure (MOE) were obtained for workers performing combined functions of open mixing, and applying spray in closed cabs with and without the use of gloves. Using the PHED data, adequate MOE were obtained for mixer/loaders using open-pour, applicators in open cabs and workers performing combined tasks under these conditions. All categories of workers wore long pants and long-sleeved shirts but no gloves.

Based on the risk assessment, no significant short-term or long-term risk is identified with use of Sulfosulfuron. No personal protective equipment is recommended.

Monza will be sprayed on wheat as a pre or post-emergent spray. Workers are not expected to re-enter treated fields shortly after spray application. Therefore, a re-entry period (REP) is not recommended at this stage.

Recommendations for Safe Use

Transport, storage & retailing

Workers involved in transport, storage or retailing should be protected by safe work practices and training.

End Users

Users should follow the instructions and Safety Directions on the Product label.

MSDS

The MSDS for *Monza* 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 their employees have ready access to it.

Conclusions

Sulfosulfuron and *Monza* can be used safely if handled in accordance with the instructions on the product label. Additional information is available on the product MSDS.

ENVIRONMENTAL ASSESSMENT

Monza is to be registered for use only in Victoria, New South Wales, South Australia and Western Australia. It is to be used at a maximum rate of 25g/ha to control or suppress certain weeds in wheat, particularly brome grass (*Bromus* spp), either pre- or post-emergence (crop and weed). As a Group B Herbicide, the company recommends that it be used as part of an Integrated Weed Management program. For post-emergent application, *Monza* can be applied as early as the one-leaf stage.

The pH of the soil that wheat could be grown on would range from 5 to 8.5 and are of a highly diverse nature, with the black clays (Qld), red-brown earths (NSW and SA), solonised brown soils (Vic), grey-brown clays and red clays (Vic and NSW), and the red sandy earths (WA). For the application of sulfonylureas, however, the alkaline sodic soils from South Australia into northern New South Wales and southern Queensland are the most vulnerable. For the prevention of carryover and movement of the sulfonylurea, label restraints indicate that the product should not:

- be sprayed when very dry conditions prevail,
- used on flood irrigated crops, and
- applied to soils with pH >8.5

Crop safety statements indicate that below average rainfall (preventing uptake), greater than recommended rates of application, pH >6.5 and low soil temperatures increase the risk of carryover. Crop rotation guidelines are also given.

Summary of Environmental Chemistry and Fate Studies

Degradation and Metabolism studies

Hydrolysis

A single experiment indicated that hydrolysis was quickest at pH4, with a $t_{½}$ of 7d, but other half-lives were >48d indicating that *Monza* was only slightly hydrolysing at 25C in the environmental pH range. The major hydrolysis products respectively for the labelled pyrimidine ring and imidazopyridine ring were the aminopyrimidine and the sulphonamide which were not further degraded.

Photolysis

Single experiments are available for the determination of quantum yield, and aqueous and soil photolysis. The theoretical half-lives in natural water are estimated respectively to be 2-4d and 22-33d in European summer and winter conditions. The aqueous half-life for photolysis was 2.9d (average of both labels and for a 12light:12dark day). As well as the sulphonamide and aminopyrimidine formed at >10% of applied activity, the *N*-hydroxy urea (>10% of applied), oxamic acid, sulphonic acid and sulphone derivatives, and three unknowns (5-10% of activity) were also found. A low level of CO_2 (6.2%) was also formed from ^{14}C-imidazopyridine *Monza*. The soil (pH = 5.5) photolysis half-life was 48d (mean of the two labels) with similar degradation products (as for hydrolysis). The dark controls essentially

had a similar half-life and degradation products, indicating degradation was through hydrolysis and cleavage of the sulfonylurea bridge.

Aerobic metabolism

In an aerobic metabolism study, the DT_{50} and DT_{90} values at 20°C on a loamy sand soil of pH 5.8 respectively were 53d and 176d (average of both labels); ie "fairly degradable". Extractable activity decreased through the study period with a corresponding increase in non-extractable residues. Some CO_2 was observed but with greater total volatiles produced in the ^{14}C-pyrimidine *Monza* treatment (13% of applied). Some of the products peaked at around 100d for both labels, with levels of 28% of applied ^{14}C-imidazopyridine *Monza* activity observed for desmethyl *Monza*, and levels of 29% and 3.4% of applied ^{14}C-pyrimidine *Monza* activity respectively observed for desmethyl *Monza* and aminopyrimidine.

Another study of aerobic soil metabolism was performed using 3 soils with sandy loam (pH of 5.3), silt/silty clay/loam (pH of 6.7) and clay loam (pH of 7.9) textures. The DT_{50}s were respectively 92d, 194d and 226d (ie "very slightly degradable" with half-lives greater than, or equal to, the length of the study) while the DT_{90}s were respectively 306d, 643d and 750d, indicating some correlation of DT_{50} or DT_{90} with pH. A higher moisture content (70% maximum water holding capacity cf 40% MWHC) did not seem to affect the DT_{50} of the clay loam soil while a lower temperature (10°C cf 20°C) increased the DT_{50} of the clay loam soil to >365d.

A third study of aerobic soil metabolism was performed using 2 soils with sandy loam (pH of 6.8) and loam (pH of 7.6) textures. The DT_{50}s were respectively 35 and 32 (ie "fairly degradable"; means of the labels) while the DT_{90}s were respectively 219 and 258 (means of each label). The products formed were similar to those observed with loamy sand soil above, but with low levels of the guanidine derivative characterised.

Sediment/water systems

A study of metabolism and degradation in two sediment/water systems (river and pond) was performed with the water (pH ≥ 7.5) aerated for the 100d study period. The DT_{50}s for the non-sterile sediment/water test systems at 20°C were 20-32d (whole systems) indicate that *Monza* is "fairly degradable". A lower temperature treatment (5-7°C) had a predictable longer DT_{50} of 58d with the sterile controls (20°C) all >100d. In the sediment, non-extractable residues increased over the test period (about 55% the applied initial activity) with the dissipation from water to sediment, and within sediment from extractable to non-extractable residues, clearly facilitated by biological activity. The major degradation product was desmethyl *Monza* (not formed to any significant extent in the sterile controls). The hydrolysis products, the sulphonamide and aminopyrimidine, were found in all treatments but appeared to further degrade in the non-sterile treatments.

A study of metabolism and degradation in a strictly anaerobic sediment/water system was performed with an eutrophic pond water/sediment system. The DT_{50} was 147d (mean of both labels). The 5°C treatment was biphasic with essentially no degradation occurring after 60-120d (ie $t_{½} >> 365$ d). The major degradation products were the sulphonamide (65%) and the urea (26%), as well as some lower levels of the aminopyrimidine (13%). The data suggested little metabolism, with the main degradation through abiotic processes. The formation of the urea was unusual, but apparently formed through the hydrolysis of the aminopyrimidine and/or the parent by an exogenous ammonia source.

Mobility studies

Batch equilibrium adsorption/desorption studies
Batch equilibrium adsorption/desorption studies were conducted on the parent compound, *Monza*, and three degradation products, the sulphonamide, desmethyl *Monza* and aminopyrimidine, using four to five soils with varying pH and organic carbon content. Some degradation of the parent compound occurred in the aqueous phase during equilibration (up to 8% of the sulphonamide was formed). All results for the parent were calculated from concentrations determined by HPLC.
All processes in all studies were described by Freundlich isotherms, with the slopes of the isotherms generally indicating that adsorption and desorption were not generally affected by the concentration of compound. The parent compound had the greatest potential for mobility ($K_{ads,oc}$ of 5.3 to 89 - classified as having high to very high mobility), although the desmethyl degradation product was similar ($K_{ads,oc}$ of 37 to 116 - classified as having high mobility). The two products formed by hydrolysis of the sulfonylurea bridge, the sulphonamide and aminopyrimidine, were less mobile with the sulphonamide classified as having low to high mobility ($K_{ads,oc}$ of 61 to 261) while the aminopyrimidine was even less mobile (classified as having medium mobility to being immobile - $K_{ads,oc}$ of 260 to 8280).

Soil column studies
The leaching behaviour of *Monza* on aged sandy soil was determined in a laboratory 30cm soil column with the equivalent of 20cm rainfall of water applied over a 100d period. The activity recovered in the leachate was 30-39% of applied, with most of the activity as parent (25-39% of applied). Some parent was also found in the soil (19-23% of applied) with most of the activity (47-49% of applied) retained in the first 5cm of the soil column.

Field lysimeter studies
The leaching behaviour of *Monza* on a (European) sandy soil (pH = 6.1) was determined with field lysimeters. The study was conducted over a two year period after application of *Monza* at the proposed European maximum rate of 30g ai/ha, with one lysimeter also receiving a second application at the beginning of the second year. Rainfall and irrigation received at the lysimeter site was about 1000 mm each year, with the volumes collected roughly half that of the rainfall. Soil temperatures varied from 0 C to 26 C. Results indicated that only low levels of the applied activity leached (around 7-8% of applied activity) with leaching roughly equal for both years. In contrast to the column study, the concentration of the parent was <1% of the applied activity while the major degradate found in the leachate from the one- and two-application lysimeters were respectively the sulphonamide (50% the leachate activity) and an unknown (29% of the leachate activity). The sulphonamide was also found in the two-application lysimeter at levels of 17% of the leachate activity.

The leaching behaviour of *Monza* on sand (Washington, US; pH = 7.1) or sandy loam (California, US; pH = 7.2) soils was determined with field lysimeters. The study was conducted over an 18month period after application of *Monza* at the nominal rate of 70g ai/ha. Treatments included supplementary irrigation. The DT_{50}s for *Monza* (mean of the labels) at the sandy loam and sand soil sites were respectively 19d and 37d, and the DT_{90}s respectively were 739d and 194d. The major degradates were the sulphonamide (about 6ppb) and the aminopyrimidine (about 8ppb) which tended to reach a maximum around 184d then decreased

to slightly lower levels. Another minor product, the guanidine, reached a maximum level of 1-2ppb 183-275DAT and then declined; the urea was much more variable with no clear trends (maximum of 4ppb reached). Most residues remained in the top 0-15 cm and were not found deeper than the 15-30cm soil layer. The level of activity in the leachate was generally low, with peak activity levels never exceeding 2 ppb for any one lysimeter in any one month and with mean activity levels generally well below 1ppb. No *Monza* was found in any leachate sample, with activity associated with polar degradation products.

GUS

Given a field half-life range of 11-75d (mean of 28d) and K_{oc} range of 5.3-89, the groundwater ubiquity score (GUS) ranges from 2.5 to >6.0. Thus, at the lower limit of the score, *Monza* can not be clearly classified as a leacher or non-leacher, while at the upper limit, it is classified as a probable leacher.

Field Dissipation studies

From trials at 15 sites (USA and Europe), DT_{50}s ranged from 11 d to 75d while DT_{90}s ranged from 83d to 358d with one outlier of 739d, possibly caused by differences in estimation techniques. The European studies indicated little potential for persistence of the parent with levels near (ie 0.7µg/kg) or below the LOD (ie 0.5µg/kg) 12 months after application for those sites in which sulfosulfuron was applied at 20g/ha. In the US studies, there appeared to be some potential relationship between the DT_{50} and the temperature of the site (longer DT_{50}s with colder soil temperatures). The residues were generally detected only in the first 0-15cm. Application of the herbicide to a crop led to lower soil residues, while application at a higher (50%) rate led to higher (about 50%) residues. For the European sites, under bare soil conditions, the levels of the sulphonamide and desmethyl metabolites were a maximum of 3.2µg/kg in the 0-20cm soil horizon and declined to 0.7-2.7µg/kg 18 months after treatment (not stated which metabolite or at what time after application maximum reached).

Accumulation studies

While limited data were provided in this area, it is considered unlikely that *Monza* would accumulate in plants, aquatic organisms or soils. *Monza* might persist in soil, however, under certain conditions (eg cold temperatures, high pH) and cause injury to non-target plants.

Summary of Environmental Effects Studies

Avian toxicity tests

Mallard ducks and northern bobwhite quail and were used in oral dose acute toxicity studies, acute dietary toxicity studies, and reproduction studies. The LD_{50}s determined for these species were both >2250mg ai/kg body weight, indicating that *Monza* is practically non-toxic (USEPA classification) to the birds when orally dosed. The dietary LC_{50}s determined for these species were >5620 mg ai in feed/kg body weight. These results indicate that *Monza* is *practically non-toxic* (USEPA classification) to birds when ingested with food.

Results of reproductive studies on the Mallard duck and Northern Bobwhite quail indicate a NOEC of ≥1250mg ai in feed/kg body weight for both species, based on mortality, overt clinical signs of toxicity, gross necropsy examinations, adult body weight, adult feed consumption, reproductive parameters, egg shell thickness, body weight of hatchlings or 14-day old survivors.

Fish aquatic invertebrate toxicity studies
Monza is considered "*practically non-toxic*" (USEPA classification) in acute tests to the test species trout (*Oncorhynchus mykiss*), bluegill sunfish (*Lepomis macrochirus*), carp (*Cyprinus carpio*), sheepshead minnow (*Cyprinodon variegatus*) and water flea (*Daphnia magna*). *Monza* did not have any significant effects on trout (*Oncorhynchus mykiss*) and water flea (*Daphnia magna*) in subchronic tests at levels of about 100mg/L.

Aquatic plant toxicity studies
The toxicity of *Monza* varied from moderately to very highly toxic for the algae, cyanobateria and aquatic macrophyte species tested. The lowest EC_{50}/IC_{50} obtained was for the green algae, *Selenastrum capricornutum*, of 367µg/L and 188µg/L, although the IC_{50} for *Lemna*, while not being able to be calculated, was clearly about 1µg/L. The lowest NOEC, however, was for the duckweed, *Lemna gibba*, of 0.5µg/L. The cyanobacteria species was also relatively sensitive with an EC_{50} of 770µg/L, while the diatoms, *Skeletonema costatum* and *Navicula pelliculosa*, were quite insensitive with IC50s >103mg/L and >87mg/L, respectively. The green algae, *Scenedesmus subspicatus*, was relatively insensitive to *Monza* also, with an EC_{50} of 3.1mg/L.

Non-target Terrestrial Invertebrates, including soil microflora, studies
Laboratory toxicity tests on the honey bee (contact and oral), earthworm (*Eisenia foetida*), soil microflora (2 soils), carabid beetle (*Bembidion tetracolum*), spiders (Family: Lycosidae), mite (*Typhlodromus pyri*) and wasp (*Aphidius rhopalosiphi*) were performed using internationally recognised guidelines or guidelines being developed by the International Organisation for Biological Control (IOBC) or ESCORT (European Standard Characteristics Of beneficials Testing). Reference compounds (ie positive controls) were used to indicate the relative toxicity of *Monza* to known toxicants. Most studies were acute in nature, although some had reproductive parameters included (eg mites and wasps).

The results of the laboratory studies indicate that *Monza* is likely to be "*not harmful*" at field rates up to 38g/ha to non-target arthropods. No long-term effects (ie effects observed on Day 28 but system had recovered at next sampling time at Day 63) were observed on soil microflora.

Mammal toxicity studies
Summaries from other parts of the submission indicate *Monza* to be practically non-toxic when ingested, either as the TGAC or as the formulation.

Plant toxicity studies
Summaries from other parts of the submission indicated that *Monza* should be considered potentially very highly toxic to a broad range of plants, with possible effects of residues even after some time, as is typical of the sulfonylurea class of chemicals. Persistence of *Monza* is likely to depend on the pH and temperature of the soil.

Hazard arising from use

The main hazard of *Monza* is from exposure to non-target plants, which may occur through:
- Lateral transport of the chemical in subsurface/groundwater flow;

- Contaminated rising water tables and/or irrigation water associated with accumulation of *Monza* in confined aquifers;
- Spray drift to non-target areas; and
- Surface run-off to non-target areas.
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The latter two points have the greater potential for effect, although if ionised, the sulfonylurea would tend not to degrade or bind as readily as in its non-ionised form.

Australian literature indicates that the alkaline sodic soils are the most vulnerable, with sodic soils also tending to disperse leading to surface sealing, poor water infiltration and highly compacted soil with low microbial activity. This property might promote surface run-off in fallow situations. Lower temperatures would also decrease the rates of chemical and microbial degradation, and surplus rainfall over evaporation could provide a driving mechanism for leaching. Literature also concludes that sulfonylureas have "substantial" leaching potential in the sandy and alkaline soils of Australia which is likely to lead to persistence in alkaline subsoils lacking organic matter and biological activity (eg the pH(water) in subsoils was stated to be as high as 10.2). This was also indicated from Australian field studies conducted for efficacy and crop safety which demonstrated that effects up to 12 months after application of *Monza* were seen as low as rates of 10g ai/ha (ie 0.5 x the minimum application rate of 20g ai/ha) in most crops, and linked to carryover of residues in alkaline soils (pH 8.5 to 8.6) of South Australia and Victoria. The label carries various warnings dealing with carryover with respect to pH, low temperatures and soil moisture.

The following hazard evaluations follow the USEPA approach to establish a Q-value from the Estimated Environmental Concentration (EEC) and lowest effects concentration, such as an LC_{50}. The highest rate of product use (single application) is used as it is considered the worst case: for the product, 25g/ha is equivalent to 19g ai/ha.

Acute Hazard From Overspray

Hazard to terrestrial organisms

The levels of residues on avian and mammalian food items (eg leaves, berries, grass and insects) resulting from direct application can be worked out using the modified Kenaga nomogram. The hazard is clearly negligible with the Q-values all below 1×10^{-3}. The hazard of *Monza* to mammals and birds will therefore not need to be discussed further.

When the scenario of direct application to soil is considered, the resulting Q-value is 3.2×10^{-5} derived from a calculated expected environmental concentration (EEC) of 27µg/g (5cm depth of mixing) and the LD_{50} for the most sensitive invertebrate species, *Eisenia foetida*. The Q in this case is well below the level of concern for the species of earthworm tested, *Eisenia foetida* and it is concluded that there is a low level of concern for soil arthropods and micro-flora.

However, there remains some concern for non-target plants. For soil in which only 10% drift was considered, an equivalent application rate of 1.9g/ha would result. The most sensitive endpoint was for the radish with an $EC_{25\ (vigour)}$ of 0.108g/ha, while the next lowest end-point was an $EC_{25\ (seed\ germination)}$ of 1.23g/ha for onion. Using each of these endpoints, the Q-value

would respectively be 18 and 1.5 and is therefore of concern. This will be discussed further below in the context of "scenario realism".

Hazard to aquatic organisms

The Estimated Environmental Concentration (EEC) and Q for the worst case situation of direct overspray onto shallow water (depth of 15cm) are 13µg/L and 13 using the most sensitive species IC_{50} (*Lemna minor*) of 1µg/L. When compared to other sensitive species tested, the green alga (*Selenastrum capricornatum*) and the cyanobacterium (*Anabaena flos-aquae*), the Q-value was of two orders-of-magnitude less (Q-value = 0.034 and 0.017, respectively, for endpoints of 367µg/L and 770µg/L).

For spray drift onto a shallow pond, assuming 10% of the applied formulation will drift, effectively 10% of the worst case situation (ie 10% of 13µg/L) giving 1.3µg/L in this case. Q is therefore 1.3 and is still of concern. This will be discussed further below in the context of "scenario realism".

Other scenarios to refine hazard:

The above estimates of Q are arguably not realistic. In the above worst case aquatic estimate, an IC_{50} was used and was without regard to interactions with other species and other intricacies expected to occur in ecosystems. Therefore, it is initially assumed that:

- there is no degradation at all given the stability of *Monza* under alkaline conditions,
- drift of 1% of application rate at 5m, and
- run-off (from 100ha) of 1% of application rate into a 15 cm deep pond and surface area of $1.8 \times 10^7 cm^2$ (aquatic scenario only).
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Potential acute aquatic Q-values using mitigating factors above

Using 1% spray drift at 5m away, Q would be 0.13 based on the IC_{50} for *Lemna*. As Q is ≥0.1 it is considered that *Monza* presents an unacceptable acute risk. However, the risk is more likely to be marginal considering that drift to water from the application of herbicides by boom spray will be greatly reduced at longer distances, which is likely to be more typical in wheat growing districts. For instance, at 30m, allowing 0.2% for drift, the Q-value would be only 0.026, well below 0.1. The overall risk is acceptable considering the appropriate label statements.

The risk from run-off indicates a Q-value of 0.07 for duckweed. As Q is <0.1 for duckweed, it is considered that *Monza* presents an acceptable acute aquatic risk.

Potential chronic aquatic Q-values

Chronic data is limited although no aquatic hazard to fish and invertebrates is apparent with the NOEC for both water flea and trout ≥ 100mg/L. The algae and *Lemna* toxicity results could essentially be considered "chronic" given that a number of generations of plants takes place in the test.

Potential acute terrestrial Q-values

Using 1% spray drift at 5m away, Q would be 1.8 based on the $EC_{25\ (vigour)}$ for radish. As Q is ≥0.1 it could be considered that *Monza* presents an unacceptable acute risk. However, as with the aquatic scenario above, the risk will be reduced considering that drift to non-target vegetation from the application of herbicides by boom spray will be greatly reduced at longer

distances, which is likely to be more typical in wheat growing districts. For instance, at 30m, allowing 0.2% for drift, the Q-value would be reduced to 0.36. While still of concern, given the exponential nature of the drift decay profile, the type of effect (for vigour only, the next lowest effect was an $EC_{25\ (seed\ germination)}$ of 1.23g/ha for onion) and the frequency at which drift would be problematic, the overall risk is acceptable given the appropriate label statements.

Potential chronic terrestrial Q-values

Chronic data is limited although the following points can be made:

- The persistence of the sulfonylurea in alkaline soils is likely to affect non-target plants as demonstrated in Australian crop safety studies; and
- Problems associated with drift would remain, as demonstrated above, but would be acceptable with appropriate label statements and given that the sulfonylurea would only be applied once per season.

Conclusion

The sulfonylurea exhibits typical very high toxicity to aquatic and terrestrial plants and negligible toxicity to birds, fish, aquatic and terrestrial invertebrates, and microflora. Its very high toxicity to plants indicates that it is potentially hazardous to aquatic and terrestrial plants. However, the risk for both aquatic and terrestrial non-target organisms will be reduced because of the limited movement of the sulfonylurea off-field and appropriate label statements.

EFFICACY AND SAFETY ASSESSMENT

Justification

Brome grass is a key weed that can be managed with the use of *Monza* in both Australia and overseas countries. There are no selective herbicides for the control of Brome grass in wheat, although Chlorsulfuron is registered pre emergent for suppression of brome grass only if populations are 20 plants/m^2 or less. Brome grass is managed by a number of methods, which prevent or control seed set the year prior to cropping wheat or exhaust seed reserves to a low level in the year of cropping. The serious nature of *Bromus spp.* infestations in wheat and the current limitations on control methods provide sufficient justification for the development of a new herbicide able to provide weed management with enhanced wheat yields.

Proposed Use Pattern

Applied post emergent, *Monza* provided control of paradoxa grass, wild radish, wild turnip, amsinckia, loose strife, capeweed and suppression of brome grass, barley grass, wild oats, toad rush, wild mustard, prickly lettuce, shepherds purse, volunteer peas, wireweed. *Monza*, applied pre-emergent, provided control of wild turnip and suppression of brome grass and barley grass.

Suppression of the above weeds can give significant economic benefit. In the case of the key weed brome grass, trials have demonstrated yield improvements at the proposed label rate of 20 g ai/ha. It has also reduced the brome grass seed numbers in the final wheat sample, which has the economic benefit of less dockage and less, need to grade.

The performance of *Monza* applied post emergent to *Bromus* spp. varied significantly with rate, the pH of the soil, the amount of surfactant added and the growth stage of the *Bromus* spp. at application.

Evaluation of Efficacy

The herbicide MON 37500 was evaluated in Australia in a series of 80 field experiments in the period 1991 to 1996 for the control of brome grass, barley grass, wild oats, phalaris, wild radish and a range of other broadleaf weeds applied either pre or post emergent in wheat. A number of formulations of MON 37500 were tested during this period and these have been demonstrated to be equivalent. Trials and results cited in this assessment will refer to the formulations tested generically as the end use product *Monza*.

Adequate trial data was presented to support the performance claimed. Relatively good post emergent control was demonstrated on a number of broadleaf weeds in particular and for the control of wild radish, wild turnip and volunteer peas. Weeds more difficult to control or on which there is only a small database, a rate of 20 g ai/ha is proposed for paradoxa grass, amsinckia, wild mustard, with the latter being suppression only. The level of control achieved on wild oats and barley grass was similar to brome grass, and is proposed to be labelled for suppression only at the 20 g ai/ha rate.

In all trials wheat showed a high level of tolerance to Monza with no detrimental effects evident. It was thought prudent to add a warning not to use the product on barley or oats as farmers are used to using sulfonylurea herbicides on these crops and severe damage could result if this occurred.

Sufficient data was presented to justify the plant-back periods recommended on the label.

Resistance Management

The concept of population management is crucial to brome grass control not only because of potential for resistance, but also because of the carry over of brome grass seeds resulting from the relatively low level of control.

Monza will form part of an Integrated Weed Management program, which may include:

- rotation with herbicides having different modes of action
- use in tank mixes with herbicides having different modes of action
- chemical fallowing
- pasture topping
- knockdown herbicides prior to sowing
- use of selective grass herbicides in alternative crops - grain legumes, canola etc.
- grazing
- cultivation

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.
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Toxicokinetics	The study of the movement of toxins through the body.
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