Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active PYROXASULFONE in the Product

SAKURA® 850 WG HERBICIDE

APVMA Product Number 63998

OCTOBER 2011

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PREFACE

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

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Aging, Office of Chemical Safety (OCS), Department of Sustainability, Environment, Water, Population and Communities (DSEWPaC), and State Departments of Primary Industries.

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

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

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

About this document

This is a Public Release Summary.

It indicates that the Australian Pesticides and Veterinary Medicines Authority (APVMA) is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

- the toxicology of both the active constituent and product
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop or animal safety.
- residue and trade aspects

Comment is sought from interested persons on the information contained within this document.

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of **SAKURA 850 WG HERBICIDE**

should be granted. Submissions should relate only to matters that the APVMA is required by legislation to take into account in deciding whether to grant the application. These grounds include **occupational health and safety, chemistry and manufacture, residues, safety and first aid, environmental fate and toxicity, trade** and **efficacy**. Submissions should state the grounds on which they are based. Comments received outside these grounds cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **Wednesday, 26 October 2011** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- Contact name
- Company or Group name (if relevant)
- Postal Address
- Email Address (if available)
- The date you made the submission.

All personal and ***confidential commercial information (CCI)***[1] material contained in submissions will be treated confidentially.

Written submissions on the APVMA's proposal to grant the application for registration that relate to the **grounds for registration** should be addressed in writing to:

Contact officer, Pesticides program
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Phone: 61 2 6210 4748
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[1] A full definition of "confidential commercial information" is contained in the Agvet Code.

Further information

Further information can be obtained via the contact details provided above.

Copies of full technical evaluation reports covering toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA on request.

Further information on public release summaries can be found on the APVMA website: http://www.apvma.gov.au

1 INTRODUCTION

Applicant

Bayer CropScience Pty. Ltd.

Details of Product

It is proposed to register Sakura 850 WG Herbicide, containing 850 g/kg pyroxasulfone as a water dispersible granule (WG) formulation. The product is intended for pre-emergence control of annual ryegrass, certain other grass weeds and toad rush in wheat (not durum wheat), barley and triticale. It is intended for application within 3 days prior to sowing, at an application rate of 118 g/ha.

Pyroxasulfone is a new active ingredient to the Australian market. It has been classified as a Group K mode of action for weed resistance management, and the product Sakura 850 WG Herbicide has been shown to be active against the widespread and increasing populations of annual ryegrass which are resistant to Group A, B and D herbicides. A comprehensive series of trials have shown that Sakura 850 WG Herbicide invariably performs at an equivalent but generally superior level to commercial standards in the control of annual ryegrass (*Lolium rigidum*), barley grass (*Hordeum leporinum*), annual phalaris (*Phalaris paradoxa*), silver grass (*Vulpia bromoides* and *myuros*) and toad rush (*Juncus bufonius*).

The active ingredient pyroxasulfone will be manufactured overseas, while Sakura 850 WG Herbicide will be formulated at either local or overseas facilities.

This submission has been assessed under a joint review arrangement where applications for registration of the same formulation and similar uses were submitted concurrently in Canada, USA and Australia. At this time, pyroxasulfone and products containing this new active constituent are not yet approved overseas.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of **Sakura 850 WG Herbicide**, and approval of the new active ingredient pyroxasulfone.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

Pyroxasufone is a new active constituent, which is a herbicide belonging to the N-phenylphthalimide class of chemical compounds used for the control of certain weeds in wheat, barley and triticale.

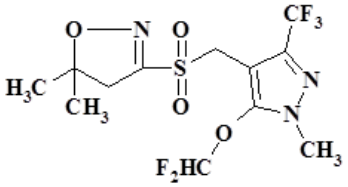
The active constituent pyroxasulfone is manufactured by

1. Ihara Chemical Industry Co., Ltd.
   2256 Nakanogo, Fujikawa-cho, Ihara-Gun, Shizuoka 421-3306, Japan

or

2. PI Industries Ltd.
   PLOT No. 237, GIDC, Ankleshwar Panoli-394 116(Gujrat), Distt-Bharuch, The Republic of India

The chemical active constituent pyroxasulfone has the following properties:

COMMON NAME:	Pyroxasulfone
IUPAC NAME:	3-[5-(Difluoromethoxy)-1-methyl-3-(trifluoromethyl)pyrazol-4-yl methylsulfonyl]-4,5-dihydro-5,5-dimethyl-1,2-oxazole
CAS NAME:	3-[[[5-(Difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl]sulfonyl]-4,5-dihydro-5,5-dimethylisoxazole
CAS REGISTRY NUMBER:	447399-55-5
MANUFACTURER'S CODE:	KIH-485
MOLECULAR FORMULA:	$C_{12}H_{14}F_5N_3O_4S$
MOLECULAR WEIGHT:	391.3
STRUCTURE:	

APVMA Active Constituent Standard for Pyroxasulfone Active Constituent

CONSTITUENT	SPECIFICATION	LEVEL
Pyroxasulfone	Pyroxasulfone	Not less than 960 g/kg

Physical and Chemical Properties of Pure Active Constituent and Technical Material

COLOUR	White
PHYSICAL STATE	Solid (crystalline)
ODOUR	Slight characteristic odour
MELTING POINT	130.7°C
VAPOUR PRESSURE AT 25˚C	2.4×10^{-6} Pa
WATER SOLUBILITY AT 20˚C	3.49×10^{-3} g/L
SOLUBILITY IN ORGANIC SOLVENTS	Acetone: > 250 g/L Dichloromethane: 151 g/L Ethyl acetate: 97.0 g/L Methanol: 11.4 g/L Toluene: 11.3 g/L n-Hexane: 0.0721 g/L
PARTITION COEFFICIENTS (N-OCTANOL/WATER)	log P_{OW} = 2.39 at 25°C at pH 8.7

2.2 End use product

Distinguishing name: Sakura 850 WG Herbicide

Formulation type: Water Dispersible Granule (WG)

Active constituents concentrations: Pyroxasulfone 850 g/kg

Physical and Chemical properties of the Product

APPEARANCE	Solid; homogeneous; tannish to yellowish; cylindrical; small to tiny pellets/granules; free from visible foreign matter
ODOUR	Halide to Alcoholic; earthy, husk-like, burnt plastic odor
ACIDITY/ALKALINITY	pH 7-10 (1% dilution)
DENSITY (BULK)	1.58
DUST CONTENT	1% maximum
PERSISTENT FOAM	Max. 60 mL foam after 1 minute
FLASH POINT	Not applicable
FLAMMABILITY	Not flammable
EXPLOSIVE PROPERTIES	Not explosive
OXIDISING PROPERTIES	No oxidising properties
CORROSIVE HAZARD	Not applicable
DIELECTRIC BREAKDOWN VOLTAGE	Not applicable, formulation is not intended for use around electrical equipment.
DANGEROUS GOODS CLASSIFICATION	Not dangerous good according to the Australian Code of Transport of Dangerous Goods by Road and Rail.

Recommendation

Based on a review of the chemistry and manufacturing details provided by the applicant, registration of **Sakura 850 WG Herbicide** is supported.

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

Pyroxasulfone is a novel pre-emergence herbicide discovered amongst a series of herbicidal 3-sulfonylisoxazoline derivatives. The product Sakura 850 WG Herbicide contains 850 g/kg pyroxasulfone as water dispersible granules. The product will be available in high-density polyethylene (HDPE) bottle or aluminium-foil lined polyethylene bag or polyethylene bag with outer fibre-board box in the following pack sizes: 1.18kg, 5kg, 10kg. Sakura 850 WG Herbicide will be used for the control of annual ryegrass and certain grass weeds and toad rush in wheat, barley and triticale. The use rate is 118 g product/ha (100 g pyroxasulfone/ha). It is expected that only one application is required per season by ground boom spray application.

Following oral administration in rats, pyroxasulfone was rapidly well absorbed, broadly distributed and fully excreted largely via the urine and faeces.

Pyroxasulfone was of low acute oral, dermal and inhalational toxicity in rats. It was a slight irritant to eyes and non-irritant to the skin of rabbits. It was not a skin sensitiser in mice. Sakura 850 WG Herbicide containing 850 g/kg of pyroxasulfone shared the same acute toxicity profile to pyroxasulfone with the exception it was a skin sensitiser in guinea pigs.

The primary target of toxicity following repeated administration of pyroxasulfone repeat in these species appeared mainly to be the muscular and the nervous systems. The data available also suggests that the both dogs and rats were equally sensitive to the effects of pyroxasulfone because the one year studies in dogs and rats as well as the 2-year carcinogenicity study in rats all yielded a NOEL of approximately 2 mg/kg bw/d. While the toxic endpoints in dogs were muscular and sciatic nerve degeneration, the effects in rats include bladder mucosa hyperplasia and bladder transition cells papilloma in addition to cardiomyopathy and sciatic nerve effects. Other effects produced by pyroxasulfone include cardiac toxicity (increased cardiomyopathy in mice and rats), liver toxicity (centrilobular hepatocellular hypertrophy) and kidney toxicity (increased incidence of chronic progressive nephropathy in dogs).

Pyroxasulfone was not considered to be genotoxic *in vivo*, and was not a reproductive toxicant in rats or teratogenic in rats and rabbits. Furthermore, pyroxasulfone did not produce immunotoxic effects in mice or rats.

Although pyroxasulfone produced neurotoxic effects in dogs (impaired hind limb function, and ataxia, tremors, and axonal/myelin degeneration of the sciatic nerve), mice and rats (sciatic nerve lesions), specific neurotoxicity tests did not reveal neurotoxic effects. However, in a developmental neurotoxicity study in rats, pyroxasulfone was associated with offspring toxicity causing slight but dose related decreases in absolute brain weight accompanied by a decrease in the thickness of the hippocampus, corpus callosum and cerebellum. These effects were seen in the absence of maternal toxicity.

The product Sakura 850 WG Herbicide was of low acute oral, dermal and inhalational toxicity in rats, is not a skin irritant in rabbits but is a slight eye irritant in rabbits and a skin sensitiser in guinea pigs.

3.2 Evaluation of toxicology

The toxicological database for pyroxasulfone, which consists primarily of toxicity studies conducted in rats, mice, rabbits and dogs, is considered sufficient to determine the toxicology profile of pyroxasulfone and characterise the risk to humans. 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.

The toxicology assessment of pyroxasulfone was conducted as part of a Global Joint Review (GJR) by scientists from the United States Environmental Protection Agency (US EPA), Health Canada Pest Management Regulatory Agency (PMRA) and the Office of Chemical Safety (OCS) within the Department of Health and Ageing. Since the assessment report relies significantly on the core toxicological monograph prepared between the agency partners, the OCS adopted the no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) with scientific justification for the adoption of these NOAEL/LOAEL positions. Additional data submitted after the preparation of the core toxicological monograph was assessed by OCS separate from the GJR process.

Chemical class

Pyroxasulfone is a derivative of 3-sulfonylisoxazoline, which exerts herbicidal activity by blocking biosynthesis of very-long chain fatty acids (VLCFAs) by inhibition of VLCFA enlongase catalysis of the fatty acid elongation step. This inhibition results in a build-up of fatty acid precursors.

Toxicokinetics/metabolism

Orally administered radiolabelled pyroxasulfone was shown to be quickly absorbed and excreted in rats, with an elimination half-life ranging from 15–173 hours with the longer half-life corresponding to a high orally administered dose (700 mg/kg bw). At lower administered oral doses (10 mg/kg bw) absorption was rapid (T_{max} of 1.1-7 hours with 77-88 % absorption) while at a higher dose (700 mg/kg bw) absorption was slower (T_{max} 7.0-17.3 hours, with 22-26% absorption). The main excretory routes were the urine and faeces, while limited enterohepatic circulation was also demonstrated. Following absorption pyroxasulfone was widely distributed, with high concentrations observed in the bladder, prostate, adrenals, kidney, liver, abdominal fat, uterus, and blood. Absorbed pyroxasulfone was extensively metabolized to a number of compounds (at least 30 chromatographic regions). There was no significant sex difference in the metabolism of pyroxasulfone. Compared with low dose animals, there appeared to be saturation or induction of metabolism at the high dose, which resulted in an altered metabolic profile. The major metabolites in the urine of rats were produced by the cleavage between the pyrazole and isoxazoline ring structure of

pyroxasulfone. Additionally, a major portion of the radioactivity detected in urine was highly polar and multi-component, containing 5-methyl-5-isoxazoline carboxylic acid and an uncharacterised component identified as M-30. Unabsorbed pyroxasulfone constituted the major fraction of radiolabel eliminated by the faecal route. The largest notable fractions of radiolabel detected in bile consisted of conjugated compounds co-eluting with a sulphate conjugate of hydroxy-pyroxasulfone and a glucuronide of uncharacterised component M-13. The metabolism of pyroxasulfone was defined to proceed by two separate routes, with the first involving the cleavage of the sulfonyl group, with either subsequent sequential oxidations of the sulfonyl group on the pyrazole moiety or glutathione conjugation and subsequent hydrolysis of the isoxazoline moiety; and the second route involving sequential oxidations of parent pyroxasulfone.

In a separate study in rats, following a single oral administration of 250 mg/kg bw, the concentration of pyroxasulfone in milk, as in the plasma, peaked (C_{max}) at 2 h (T_{max}) after which it decreased in both samples. The levels in milk and plasma at 96 h were approximately 35-fold and 266-fold less than their respective C_{max} values. The elimination half-lives of the test substance from milk and plasma were comparable i.e. 21.4 h and 22.5 h. The milk:plasma ratio of radioactivity level increased throughout the study with the exception of sporadic decrease at 48 h.

In rats administered a daily oral dose of pyroxasulfone (10 mg/kg bw) for 26 days during pregnancy, the level of pyroxasulfone in the pup stomach contents was very low and approximately half the level detected in maternal plasma. Following cessation of dosing (post-natal day 10 -13), the amount of radioactivity in both pup stomach and maternal plasma dropped rapidly. The lower concentrations of radioactivity in pup stomach content compared to maternal plasma indicated that there was limited transfer of radioactivity to the milk.

The metabolism of pyroxasulfone was also considered in mice. Pyroxasulfone was rapidly absorbed in mice (T_{max} = 2 h). Approximately 78% of the administered dose was excreted in the urine after 120 h with most of the urinary radiolabel (73%) excreted in the first 24 h after dosing. The remainder of radioactivity was excreted in the faeces. Only about 0.2% of radioactivity was left in the animals after 120 h. Concentration of radioactivity was highest in the liver and heart by 2 h post administration although radioactivity was extensively distributed into various other tissues. Whole body autoradiography indicated that 2 h after dosing, radioactivity was absorbed from the gastro-intestinal tract into various tissues and organs with high concentration in the liver and gall bladder (indicative of first-pass elimination). By 24 h radioactivity in most tissues was close to or indistinguishable from background levels. Pyroxasulfone was extensively metabolised in the urine of mice. Fifteen metabolites were resolved by HPLC and three oxidative products identified. One minor metabolite was identified as a glucuronide or sulphate conjugate. Unchanged pyroxasulfone was not present in the urine. No data on the metabolic profile of radiolabelled compounds in faeces was noted.

In a female dog administered pyroxasulfone, oral absorption was at least 51%, with 77% of the administered dose excreted in the first 24 h. Since no biliary excretion study was carried out, the true extent of absorption could not be determined. Radioactivity was excreted equally in both urine and faeces (approximately 50% in each sample). C_{max} was slightly higher in the blood than the plasma and the C_{max} was achieved at 8 h (T_{max}) in both samples. The rate of clearance of radioactivity was slower in blood than the plasma (approx. 90 h in the blood and 41 h in the plasma). After 120 h, the levels of radioactivity in tissues were highest in the liver and blood. The kidney, plasma and heart contained the next highest concentration. Unchanged compound was found only in faeces. Urine samples contained several specifically known metabolites (designated M-3, M-7 and M-8), with structures proposed for three other uncharacterised metabolites.

Acute toxicity studies

Pyroxasulfone is of low acute toxicity in rats by the oral (LD_{50} >2000 mg/kg bw, no deaths), dermal (LD_{50} >2000 mg/kg bw, no deaths) and inhalational route (4-hr LC_{50} >6560 mg/m^3, no deaths). Additionally, it is not a skin irritant in rabbits or a skin sensitiser in mice, but is a slight eye irritant in rabbits.

Sakura 850 WG Herbicide is of low acute toxicity in rats by the oral (LD_{50} >2000 mg/kg bw, no deaths), dermal (LD_{50} >2000 mg/kg bw, no deaths) and inhalational route (4-hr LC_{50} >5800 mg/m^3, no deaths). The product is not a skin irritant in rabbits, but is a slight eye irritant in rabbits and a skin sensitiser in guinea pigs.

Systemic effects

Pyroxasulfone was administered in diets at doses up to approximately 2500 mg/kg bw/d in mice and rats and 10 mg/kg bw/d in dogs. Studies were performed for varying lengths of time according to approved test guidelines. The primary target of toxicity following repeated administration of pyroxasulfone in these species was mainly the muscular system and the nervous system. In rats, incidences of myocardiac degeneration/necrosis (and to a lesser extent, skeletal muscle degeneration) were recorded in most of the repeat dose studies. In addition, a recurring incidence of axonal/myelin degeneration in the sciatic nerve was also noted in many studies. In beagle dogs, incidence of minimal to mild subacute inflammation of the skeletal muscles (with attendant impaired limb function) as well as axonal/myelin degeneration in the sciatic nerve, further strengthened the observation that the muscular and nervous systems were mostly at risk of pyroxasulfone toxicity. The data available also suggests that both dogs and rats were equally sensitive to the effects of pyroxasulfone since the one year studies in dogs and rats as well as the 2-year carcinogenicity study in rats all yielded a NOAEL of approximately 2 mg/kg bw/d. While the critical endpoint in dogs was muscular and sciatic nerve degeneration, the critical effect in rats included bladder mucosa hyperplasia and bladder transition cells papillomas in addition to cardiomyopathy and sciatic nerve effects.

Other effects produced by pyroxasulfone include cardiac toxicity (increased cardiomyopathy in mice and rats), liver toxicity (centrilobular hepatocellular hypertrophy) and kidney toxicity (an increased incidence of chronic progressive nephropathy in dogs).

While pyroxasulfone was not toxic following acute dermal exposure in rats, it was moderately toxic in the same species following a 4-week dermal exposure producing local inflammation and systemic effects of minimal to mild cardiac myofiber degeneration at the limit dose of 1000 mg/kg/day with a NOAEL of 100 mg/kg/day. Pyroxasulfone was not toxic by the inhalation route following short term exposure in a 28-day study.

Carcinogenicity & Genotoxicity

In a carcinogenicity study in mice renal tubular adenomas were observed in male mice at a dietary dose of 228 mg/kg bw/day (equivalent to 2000 ppm, the top dose tested in the study). The applicant provided OCS with a re-analysis of the kidney slides used as the basis for the histopathological reporting in the pyroxasulfone 14-day, 90-day and 18-month studies in mice, in an attempt to provide a mode-of-action explanation for the presence of kidney adenomas observed in male mice in the 18-month study at the top dose.

The re-analysis of the histopathological data has indicated that the 'renal tubular hyperplasia' originally observed are more accurately defined as dilated proximal tubules with simple hyperplastic lining (i.e. simple tubular hyperplasia). While the observed simple tubular hyperplasia is considered treatment-related, this finding is not generally considered a precursor to renal tubule neoplasia. Additionally, a number of these hyperplastic observations could be attributed to tangential sectioning through the periphery of altered tubules, which may have given a false impression of hyperplastic in-growth into the tubule lumen in the original report and interpreted as a precursor to a carcinogenic response. Additionally, the lack of cell necrosis and regeneration which are known to lead to precursor lesions such as atypical tubular hyperplasia, which are also known to precede neoplastic events, suggests that the observed simple tubular hyperplasia is unlikely to be a precursor to a carcinogenic event in this case.

Additionally, it was indicated that the reported severity in chronic progressive nephropathy (CPN) in the 2-year study was due to an incorrect attribution of all recorded non-neoplastic fibrotic scarring as part of a CPN response, and that a significant proportion of the observed scarring was in fact due to a retrograde nephropathy (RGN) response. After revised interpretation of renal histopathology slides, differentiating between CPN and RGN, it was concluded that at the top dose in males the frequency and severity of CPN was not increased with administration of pyroxasulfone, though an increased frequency and severity of RGN was observed with treatment. Although CPN is known to be related to tumour formation in rodent species, the similarity of control and 2000 ppm animals in this case supports the hypothesis that pyroxasulfone does not lead to oncogenic events through an induction of CPN.

However, though the study authors have postulated that the increased frequency and severity of RGN observed was possibly associated with urinary solids in the bladder, no evidence of urinary calculi, crystals or solids were reported in the bladder or urinary tract of the mice in this carcinogenicity study. Thus, based on available evidence, the mode of action for the observed RGN in this study remains uncertain and the direct relevance of RGN to the development of cancer is unknown. Though, since the top dose of 2000 ppm was decreased to 1000 ppm after approximately 14 months to insure a satisfactory survival rate in rats, it is considered that the top dose was close to the maximum tolerated dose (MTD), even though the overall decrease in bodyweight was < 10%. Furthermore, the reported incidence of renal tubular adenoma in male mice (6%) did not reach statistical significance when compared with concurrent control data and were only slightly outside the maximum historical range (0-4%). Consequently, when the absence of statistical significance is considered in conjunction with the revised histopathological interpretation and the lack of pre-cursor cytotoxicity or hyperplastic events, it is considered that the three renal adenomas observed in males only at the top dose, which is considered likely to be close to the MTD, are likely incidental to treatment. Thus, pyroxasulfone was not considered to be carcinogenic in male or female mice.

In rats, urinary bladder transitional cell papillomas and a single bladder carcinoma were observed in males only at ≥46 mg/kg/day. The applicant provided OCS with a re-analysis of the bladder slides used as the basis for the histopathological reporting in the pyroxasulfone 2-year study in rats, and provided a 7-day oral study in rats undertaken to detect evidence of cytotoxicity and necrosis. The reanalysis indicated that the diagnosis of a carcinoma was likely made incorrectly due to an apparent invasion of the lesion into the muscle wall of the bladder. It was noted that the epithelium is clearly benign in appearance throughout the bladder in the animal this lesion was observed, which is in contrast to what would be expected if it were truly a carcinoma. This finding was re-diagnosed as a diverticulum of the bladder instead of a malignant tumour.

The applicant has postulated that the mode of action for carcinogenicity in rodents involves a non-genotoxic response leading to increased cell proliferation resulting from site-specific cytotoxicity/irritation, followed by compensatory regenerative cell proliferation, leading to hyperplasia and subsequent benign lesions (in this case, papillomas in urinary bladder), though the carcinogenic effects only occurred at very high threshold doses relative to expected human exposures. This non-genotoxic mode of action possibly involved urinary microcrystals. Evidence to support this hypothesis, a two-week toxicity study did not present evidence of treatment-related urinary microcrystals in the bladder, and no reliable evidence was presented to show that cytotoxicity, increased cell death and regenerative cell proliferation occurred in the report. Furthermore, an additional one-week toxicity study (0, 50, 1000 or 2000 ppm dose groups), with particular attention given to histopathological examination of the bladder, reported limited evidence of cellular necrosis. However, clear cellular hyperplasia was observed at study day 7 though no urinary solids were present in day 7 urine samples. The study authors attributed this to either insufficiently sensitive detection methods, or a lack of urinary solids at the sampling time points attributable to the variance in urinary composition in rodents depending on sampling time, the transient insolubility of urinary solids in general and their overall tendency to be voided in urine. Secondary evidence regarding the presence of urinary solids was presented, relying on the presence of treatment-related precipitate or insoluble material in renal tubules of mice administered pyroxasulfone at 2000 ppm in the 18-month carcinogenicity study in mice but not the rat carcinogenicity study, and the high correlation of calcified or eosinophilic-staining materials in bladder slides from animals with papillomas in the two-year carcinogenicity study. However, although the study authors have provided literature evidence that urinary solids can be cytotoxic to the urothelium (e.g. uric acid, calcium oxalate, implanted silica), the lack of primary evidence in pyroxasulfone studies directly linking the presence of urinary solids to urothelial irritation, and the uncertain identity of the urinary solids (which were seen infrequently including in control animals) remain data gaps which adversely affect the certainty of the proposed mode of action. The limited strength of evidence for cellular necrosis (based on scanning electron microscope classifications) also diminishes the weight of evidence for the proposed mode of action, though this is countered somewhat by the increased BrdU labelling index values observed with pyroxasulfone treatment at 2000 ppm at day 7 of the study.

Additionally, it was proposed a non-genotoxic mechanism (i.e. tumour formation due to treatment-related urinary solid/calculi formation leading to hyperplasia and papilloma) is considered relevant to humans, though humans are less susceptible to the carcinogenic effects of calculi than rodents so risk is dependent on exposure. Consequently, scientific arguments were presented by the study authors asserting that pyroxasulfone is not carcinogenic to humans at expected human exposure levels based on the following assumptions:

- urinary calculi formation is a high-dose effect requiring large amounts of pyroxasulfone to be excreted through the urine;
- urinary calculi are considered toxic in humans due to their propensity to cause urinary obstruction, and would be addressed before any resulting long term exposure associated with urinary calculi could occur;
- in rare cases where calculi are formed (e.g. in cases of diverticuli or neurogenic bladder), the current medical and epidemiological evidence in the literature for increased bladder cancer is equivocal and confounded in part by the association of urinary calculi with bacterial cystitis, which is also known to increase the risk of bladder cancer; and

- the exposure to humans associated with the use of pyroxasulfone in products is low, and will be at doses which are not expected to cause cytotoxicity and regenerative cell proliferation.

However, these arguments do not address the uncertainties and data gaps for the proposed mode of action described above and thus establish that the observed urinary bladder transitional cell papillomas in male rats treated with pyroxasulfone would not be relevant to humans.

Consequently, from a toxicological hazard perspective it is considered there is still insufficient evidence proving that the observed urinary bladder transitional cell papillomas in male rats at doses of ≥ 46 mg/kg bw/d would not be relevant to humans. Thus the mode of action for the observed tumours has not been established and it has not been demonstrated that the observed bladder tumours in male rats would not be applicable to humans.

A battery of standard genotoxicity tests showed that pyroxasulfone was negative *in vitro* in an Ames, a mammalian gene cell mutation and a chromosomal aberration assay with and without metabolic activation. Pyroxasulfone was also negative in a standard *in vivo* mouse micronucleus assay. In non-standard studies, *in vivo* comet assays in the rat and mouse, an increase in tail intensity (indicating DNA strand breaks) was seen in rat bladder at ≥ 1000 mg/kg bw, rat liver at 2000 mg/kg bw and mouse kidney at ≥1000 mg/kg bw/d. However, the comet assay is not a recognised regulatory test guideline and no OECD Test Guideline is currently available. Furthermore, the assay was performed using the entire bladder while methodology guidelines for this assay recommend the preparation of single cells from epithelia from tissues in which the epithelium is a small percentage of the total organ (as in the bladder) should be used to avoid confounding factors. Additionally, there is concern that this non-standard study can produce false positives. Thus, noting no mutagenicity or genotoxicity were seen in robust *in vitro* studies with and without metabolic activation and no genotoxicity was seen in a robust *in vivo* mouse micronucleus assay, only limited confidence can be placed in these findings from a non-standard study. Thus, on the weight of evidence it is considered that pyroxasulfone is not an *in vivo* genotoxicant.

Reproductive & Developmental toxicity

Pyroxasulfone produced no evidence of a reproductive toxicity potential in rat studies, including doses that produced pronounced parental toxicity (reduced body weight, body weight gain and food consumption and increased kidney weight, cardiomyopathy and urinary bladder mucosal hyperplasia with inflammation). Pyroxasulfone did not exhibit teratogenicity in the rat at the limit dose of 1000 mg/kg/day and though it exhibited slight developmental toxicity in rabbits (reduced foetal weight and resorptions) at 1000 mg/kg/day the severity of these effects at the limit dose are not considered sufficient that pyroxasulfone be considered a hazard for teratogenicity.

Neurotoxicity

In neurotoxicity studies pyroxasulfone was not neurotoxic in rats following an acute oral dose of 2000 mg/kg or subchronic dietary administration of up to 2500 ppm (equivalent to 161/200 mg/kg/day in males/females, the highest dose tested). In repeat-dose toxicity studies pyroxasulfone produced neurotoxic effects in dogs (impaired hind limb function, and ataxia, tremors, and axonal/myelin degeneration of the sciatic nerve), mice and rats (sciatic nerve lesions). Thus, while neurotoxicity was seen in repeat-dose studies, specific

neurotoxicity tests did not reveal neurotoxic effects. However, developmental neurotoxicity was observed in offspring in a rat developmental neurotoxicity study.

In a rat (delayed) developmental neurotoxicity study, at ≥ 300 mg/kg bw/d a dose related decrease in absolute brain weight accompanied with a decrease in the thickness of the hippocampus, corpus callosum and cerebellum was seen in female offspring on postnatal day 21, with a decrease in absolute brain weight seen in males at 900 mg/kg bw/d. These findings were seen in the absence of maternal toxicity. Dosing was ceased at day 20 or 21, however, on postnatal day 66 a decrease was still observed in absolute brain weight in male and female offspring from the 900 mg/kg bw/d dose group, along with a decrease in the thickness of the hippocampus in females. Although no clear effect of treatment was seen on functional observational battery performance including all activity measures, auditory startle response habituation, pre-pulse inhibition, or on the learning and memory of the offspring, it is noted that neurotoxic effects have been observed in dogs, rats and mice in chronic studies. Therefore, the available evidence indicates that the nervous system is a target organ for pyroxasulfone activity. Consequently, the findings of decreased absolute brain weight and morphological changes present a neurological concern for the developing foetus, baby and child which would likely be more susceptible to the developmental neurotoxicity potential of pyroxasulfone.

Other information

Pyroxasulfone did not produce immunotoxic effects in mice following dietary feeding for 28 days up to 4000 ppm (633/791 mg/kg/day in males/females) or rats at dietary concentrations of 7500 ppm (529/570 mg/kg/day in males/females).

3.3 Public Health Standards

Poisons Scheduling

The delegate to the Secretary of the Department of Health and Ageing sought advice from the Advisory Committee on Chemical Scheduling (ACCS) on the scheduling of pyroxasulfone. Pyroxasulfone was discussed at the June 2011 meeting of the ACCS. The delegate to the Secretary of the Department of Health and Ageing noted and agreed with the ACCS recommendation, and in August 2011 the delegate to the Secretary of the Department of Health and Ageing announced an interim decision that a new Schedule 7 entry be created for pyroxasulfone with a cut-off to Schedule 6 for water dispersible granule preparations when used as a pre-emergence herbicide. The delegate to the Secretary of the Department of Health and Ageing also announced an interim implementation date of 1 January 2012.

NOAEL/ADI /ARfD

The Acceptable Daily Intake (ADI) is that quantity of an agricultural or veterinary chemical which can safely be consumed on a daily basis for a lifetime and is based on the lowest NOAEL obtained in the most sensitive species. This NAOEL 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 critical effect of pyroxasulfone identified based on chronic toxicity studies is effects on the muscular tissues and nerve fibres, which were observed in rats and dogs with both studies identifying a NOAEL of 2 mg/kg bw/d for these health effects. In addition to this, pyroxasulfone administration also resulted in increased incidence of urinary bladder papilloma in rats with the NOAEL for carcinogenicity identified at 2 mg/kg bw/d in a chronic study. These potential health effects are considered of sufficient toxicological significance to warrant the application of an additional 10-fold safety factor. Thus, applying a safety factor of 10 for potential interspecies difference, 10 for potential intra species differences and 10 to account for the seriousness of the observed health effects to the NOAEL of 2 mg/kg bw/d results in an ADI of 0.002mg/kg bw/d.

The acute reference dose (ARfD) is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated event. The ARfD is derived from the lowest NOAEL as a single or short-term dose which causes no adverse 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.

For setting an ARfD the most appropriate study to use is the rat developmental neurotoxicity study. In this study, a dose related decrease in absolute brain weight accompanied by a dose related decrease in the thickness of the hippocampus, corpus callosum and cerebellum in female offspring at ≥ 300 mg/kg bw/d on postnatal day 21. These findings, for which a NOAEL of 100 mg/kg bw/d was identified, were seen in the absence of maternal toxicity. As the observed effects are considered likely to have serious implication for growth and development of foetuses, babies and children, it is considered appropriate to justify the application of an additional 10-fold safety factor to protect this sensitive group in the population. Thus, applying a safety factor of 10 for potential interspecies difference, 10 for potential intra species differences and 10 to account for the seriousness of the observed health effects to the NOAEL of 100 mg/kg bw results in an ARfD of 0.1 mg/kg bw.

4 RESIDUES ASSESSMENT

4.1 Introduction

Sakura 850 WG Herbicide is a water-dispersible granule formulation and contains the new active constituent pyroxasulfone and is intended for control of annual ryegrass and other weeds in wheat, barley and triticale. As part of the residues assessment for pyroxasulfone, plant and animal metabolism studies, supervised residue trials, crop rotation studies, and trade aspects were considered and details are provided below.

4.2 Metabolism

Metabolism studies were conducted in corn, soybean, radish, wheat and soybean as confined rotational crops, lactating goats and laying hens. [Pyrazole-5-^{14}C] and [isoxazoline-3-^{14}C] labels were tested for all species.

A single application was made to corn and soybeans, both post-planting soil application and early post-emergence. Forage, roots and kernels/seeds were collected at various stages. Parent was a major component in post-emergence corn foliage but was not present in pre-emergence corn foliage. Parent was not found in corn kernels following pre-emergence application; post-emergence extracts were not analyzed. The pyrazolyl methyl sulfonic acid cleavage product M-1 and M-25 (desmethyl M-1) were the main identified residues in mature corn foliage while the pyrazolyl carboxylic acid metabolite M-3, M-1 and M-25 were the main residues in corn kernels. Limited amounts of parent were present in soybean foliage and in seeds following pre- and post-emergence application. In immature soybean foliage, M-1 and M-25 were major metabolites. In mature soybean foliage, M-1 was the main metabolite, with M-25 a minor metabolite. M-1 and M-25 were not detected in soybean seed. M-28, a malonic acid conjugate of pyrazolyl ring cleavage product, was a major metabolite in soybean foliage and seed. M-29 (a hydrolysis product of M-28) was a significant metabolite in soybean foliage. Unidentified metabolites were not significant in either crop.

The two main metabolic pathways for pyroxasulfone in corn and soybean are:

- Cleavage at the sulfur-isoxazoline bond to yield the sulfinic acid metabolite M-7, followed by oxidation to M-1 and demethylation to give M-25.
- Cleavage and oxidation at the pyrazolylmethyl-sulfone linking, yielding M-3, with subsequent demethylation yielding M-9.

For the confined crop rotation study, radiolabeled pyroxasulfone was applied to soil and aged for 30, 120, 365, or 490 days prior to sowing soybean, radish and wheat.

HPLC and TLC confirmed parent and two main metabolites (M-1 and M-25) as well as lesser amounts of M-3, M-6 (isoxazoline-4-OH-pyroxasulfone) and M-9 in the pyrazole experiments. Parent was found at low levels in 30-day wheat straw and radish, and 120-day radish, but not later. M-1 was a major residue (>10% TRR) in most matrices at all intervals. M-25 was a major residue in 30-day wheat, and soybean hay; and in 120- and 365-day wheat grain and radish foliage. M-3 was a major metabolite in 30-365-day wheat grain, and in 120- and 365-day radish tops. M-9 was present at ≤8% TRR, except in 120-day soybean hay and 365-day soybean forage where it was found at 11% TRR. M-9 malonyl glucoside was a major residue in

30-day soybean forage and hay, and radish root; 120-day soybean; and 365-day soybean forage and hay. An unknown (RT24) was a major residue in 30-day radish roots, 120-day wheat forage, radish roots, and radish foliage, and 365-day radish roots. For isoxazoline samples, several cysteine conjugates and derivatives (mostly of isoxazoline moiety metabolites) were found. M-28 and four other components were major residues (>10% TRR) at all intervals, mostly in wheat and radish matrices. M-28 was found in 30-365/490-day wheat and soybean.

Parent was a minor component in plant matrices, and was often absent; only in post-emergence corn foliage was it >10% TRR. M-1 was a major residue in many matrices, including corn and soybean foliage and roots, and rotational wheat forage, hay and straw, soybean forage and hay, and radish roots and leaves and was found in rotational wheat and soybean seed. M-3 was a major residue in rotational wheat grain and radish leaves and was present in corn kernels and soybean seeds. M-25 was a major residue in corn and roots, and soybean foliage, as well as rotational wheat forage, hay and straw and soybean hay and was present in rotational wheat grain, soybean forage and seed and radish root and leaves. M-29 was a major residue in corn foliage and roots, and soybean foliage and was present in corn kernels. M-28 was a major metabolite in soybean foliage, seeds, and roots, as well as rotational wheat grain, and soybean forage, hay and seed. M-9 was significant only in rotational soybean forage. M-1 is a major metabolite in the largest number of matrices, followed by M-25 and M-28. M-1 was found in a number of human foods, particularly in the rotational study. M-3 is present in fewer matrices, though it was a significant residue in rotational wheat grain.

M-1, M-3, M-9 and parent compound were found in rat tissues and excreta during the rat metabolism studies considered as part of the toxicological evaluation. M-25, M-28 and M-29 were not identified during the rat studies. However, only M-28 was a major metabolite in a human food matrix (soybean seed, and wheat grain during the rotational cropping metabolism study).

In Australian residue and rotational studies, parent, M-1, M-3 or M-25 were not found above LOQ in cereal or field pea grain. Parent was a minor component in forage and fodder. More significant amounts of M-1, M-3 and M-25 were found; maximum dry weight residues in wheat forage were 0.04, 0.36, 0.40, and 0.16 mg/kg for parent, M-1, M-3 and M-25 at 1.25x the proposed rate.

M-1 is detected more often than other analytes and is generally found at higher levels. Parent was occasionally present without M-1, while M-3 and M-25 were not found without M-1. To reduce the cost and complexity of analysis, while maximising the probability of detecting misuse, it is proposed to establish a plant commodity residue definition for MRL compliance of parent and M-1. It is proposed that the residue definition in plant commodities for dietary risk assessment be the sum of pyroxasulfone, M-1 and M-3, expressed as pyroxasulfone.

[Pyrazole-5-^{14}C]-pyroxasulfone was orally administered to a lactating goat at a nominal dose of 10 mg/kg in the diet daily for 5 days. Milk residues were 0.003-0.03 mg/kg, with residues reaching a plateau in two days. Residues were found in all tissues: 0.23 mg/kg in liver, 0.017 mg/kg in kidney, 0.0034 mg/kg in muscle, 0.0015 mg/kg in omental fat, and <LOQ in renal fat. A large proportion of the residue was bound and required aggressive extraction methods; this may have altered the residues chemically. Parent was not identified. Only one identifiable metabolite exceeded 0.01 mg/kg, M-12 (1-desmethyl-pyrazolyl methyl alcohol) at 0.014 mg/kg (6.2% TRR) in liver and only one metabolite exceeded 10% of the TRR, M-13 (pyroxasulfone isoxazoline-5-carboxylic acid) at 25% TRR (0.0067 mg/kg) in milk. Other metabolites

identified were M-1, M-3, M-9, M-11 (pyroxasulfone isoxazolinyl-5-methyl-OH), and M-5 (pyrazolyl-1-desmethyl pyroxasulfone) and/or M-6 (pyroxasulfone isoxazoline-4-OH).

[Isoxazoline-3-^{14}C]-pyroxasulfone was orally administered to a lactating goat at a nominal dose of 10 mg/kg in the diet. Residues in milk were 0.03-0.09 mg/kg. Steady-state conditions were not achieved during the study. Residues were found in all tissues: 0.90 mg/kg in liver, 0.29 mg/kg in kidneys, 0.066 mg/kg in muscle, 0.040 mg/kg in renal fat and 0.039 mg/kg in omental fat. No identified metabolite exceeded 10% of TRR in any matrix, and only one metabolite exceeded 0.01 mg/kg, M-22 (5,5-dimethylisoxazoline) in liver (1.5% TRR/0.014 mg/kg). Other identified metabolites were parent, M-5, M-6, M-13, M-15 (an M-22 conjugate), and M-16 (a pyrazolyl ring cleavage product).

The main metabolic pathways for pyroxasulfone in goats are:

- Cleavage between the sulfone group and the pyrazole moiety, with subsequent demethylation and oxidation of the resulting pyrazolyl alcohols to carboxylic acids;
- Cleavage between the sulfone group and the isoxazolinyl moiety, yielding pyrazolyl methyl sulfonic acid metabolites; and
- Hydroxylation of the isoxazolinyl methyl groups and subsequent oxidation.

Laying hens were given [pyrazole-5-^{14}C]-pyroxasulfone at a nominal dose of 10 mg/kg in the diet for 10 days. Residues were found in yolks at 0.05-0.13 mg/kg and in whites at 0.03-0.08 mg/kg. Steady state residues were achieved in 3 days in white and in 10 days for yolk. Residues were found in all tissues: 0.50 mg/kg in liver, 0.11 mg/kg in muscle, 0.049 mg/kg in skin and 0.022 mg/kg in fat. Tissue residues were not easily extractable with organic or polar solvents; the aggressive extractions required may have converted residues to different components. Two metabolites exceeded 0.01 mg/kg: M-1 (7.8% TRR/0.039 mg/kg in liver), and M-12 (2.6% TRR/0.013 mg/kg in liver and 9.5% TRR/0.011 mg/kg in yolk). Only one metabolite exceeded 10% TRR: M-12 (10.9% TRR/0.003 mg/kg) in egg white. Other metabolites identified were parent, M-3, M-5, M-8 (pyrazolyl methyl alcohol), M-10 (M-8 tautomer), M-11, M-13, and possibly M-9.

Laying hens were given [isoxazoline-3-^{14}C]-pyroxasulfone at a nominal dose of 10 mg/kg in the diet daily for 3 days. Residues were found in yolks at 0.01-0.1 mg/kg and in whites at 0.03-0.1 mg/kg. Residues in egg whites may have reached steady state at the end of the study; however, those in yolks still appeared to be increasing. Residues were found in all tissues: 0.12 mg/kg in liver, 0.041 mg/kg in muscle, 0.033 mg/kg in skin and 0.009 mg/kg in fat. Some residues were released only following protease digestion; aggressive extractions may have converted the residues to different compounds. Very few residues showed similar properties to standards; parent was tentatively identified in liver, M-5 in yolk, M-11 in white and yolk, and M-13 in white, yolk, and skin. Only one identifiable metabolite exceeded 0.01 mg/kg or a TRR of 10% in any matrix: M-13 at 19.5% TRR/0.019 mg/kg in yolk.

The main metabolic pathways for pyroxasulfone in hens are:

- *N*-demethylation of the pyrazolyl moiety;
- Hydroxylation and subsequent oxidation of the isoxazoline methyl groups;

- Cleavage at the sulfone-isoxazoline linkage yielding pyrazolyl methyl sulfonic acid metabolites, or the sulfone-pyrazolyl linkage yielding pyrazolyl methyl alcohols that are subsequently oxidized to carboxylic acids.

Residues of parent or metabolites are not expected to be detectable in grain as a result of using pyroxasulfone in cereals. Residues in poultry feed will therefore be much lower than the feeding levels in the metabolism studies. In turn, metabolites in poultry tissues and eggs will be well below LOQ after poultry have consumed treated grain.

Residues of parent in forage or fodder are not expected to exceed 0.1 mg/kg dry weight, while those of metabolites M-1, M-3, and M-25 are not expected to exceed ~0.5 mg/kg each. Dietary burden of parent in mammalian livestock will therefore be at least 100 times less than in the goat metabolism studies. Residues from ingestion of parent will be well below the LOQ in milk, meat or offal. Plant metabolites were not subjected to an animal metabolism study, however a cattle feeding study was conducted for M-1 and M-3, with feeding levels of 1x, 3x and 10x the expected maximum feeding level. M-1 and M-3, and the desmethyl metabolites, M-25 and M-9, were analysed in milk and tissues. Up to 0.012 mg/kg M-3 was found in 3x kidney, and up to 0.048 mg/kg M-3 in 10x kidney. Up to 0.0018 and 0.0013 mg/kg of M-1 and M-3 were observed in 10x milk. Up to 0.033 and 0.15 mg/kg respectively were found in 10x fat and 0.09 mg/kg M-3 was found in the 3x fat; it is possible that the fat results are due to contamination. No residues were found in any 1x samples.

Residues of parent or metabolites are unlikely to be found above the LOQ in milk, eggs or meat of livestock given feed from treated cereal crops. Metabolites would be more likely to be detected than parent after misuse of the product. M-3 was generally found at higher levels, and more often than M-1.

It is proposed to establish an animal commodity residue definition for the purpose of MRL compliance of M-3 only, expressed as pyroxasulfone. This will reduce the cost and complexity of analyses, while maximising the probability of detecting misuse of the chemical. It is proposed that the residue definition in animal commodities for dietary risk assessment be the sum of pyroxasulfone, M-1 and M-3, expressed as pyroxasulfone.

4.3 Analytical methods

Determination of pyroxasulfone residues in plant commodities

A method was developed and validated for the analysis of pyroxasulfone and the metabolites M-1, M-3 and M-25 in cereal grains, forage and straw. Samples were extracted with water/acetonitrile, cleaned up by partition with hexane and analysed by LC/MS/MS. The method was validated with limits of quantitation (LOQs) of 0.01 mg/kg for each component. Recoveries were determined at 0.01 and 0.1 mg/kg, and were 73-112% for parent, 70-109% for M-1, 76-110% for M-3, and 70-104% for M-25.

Determination of residues of pyroxasulfone in animal tissues

Methods were developed and validated for analysis of pyroxasulfone and the metabolites M-1 and M-3 in bovine muscle, fat, liver, kidney and milk, and in eggs. Samples were extracted with acetonitrile/water and then cleaned up by various methods depending on the sample and target analytes, including partition with

hexane or ethyl acetate, and solid phase extraction. Analyses were conducted using LC/MS/MS. The method was validated with limits of quantitation of 0.001 mg/kg for each analyte in milk, and 0.01 mg/kg for each analyte in eggs and tissues. Recoveries were determined at 0.001 and 0.01 mg/kg for milk, and 0.01 and 0.1 mg/kg for tissues and eggs. Mean recoveries were 87-108% for parent, 71-117% for M-1 and 95-109% for M-3.

The methods are suitable for the proposed purposes and are acceptable.

4.4 Residue definition

The following residue definition is recommended for pyroxasulfone:

COMPOUND	RESIDUE DEFINITION
Pyroxasulfone	For enforcement for commodities of plant origin: Sum of pyroxasulfone and (5-difluoromethoxy-1-methyl-3-trifluoromethyl-1H-pyrazol-4-yl) methanesulfonic acid, expressed as pyroxasulfone For enforcement for commodities of animal origin: 5-Difluoromethoxy-1-methyl-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid, expressed as pyroxasulfone For dietary exposure assessment for commodities of plant and animal origin: Sum of pyroxasulfone, (5-difluoromethoxy-1-methyl-3-trifluoromethyl-1H-pyrazol-4-yl) methanesulfonic acid, and 5-difluoromethoxy-1-methyl-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid, expressed as pyroxasulfone

4.5 Storage stability

Fortified samples of corn grain and forage containing parent compound, M-1 and M-3 were stored for up to 13 months prior to analysis, while samples of corn stover containing these three analytes were stored for up to 12 months before analysis. Corn forage and grain containing M-25 were stored for up to 26 months before analysis, and corn stover samples containing M-25 were stored for up to 25 months. Soybean forage, seed and hay containing parent, M-1 and M-3 were stored for up to 17 months, with soybean matrices containing M-25 being stored for 12 months before the latest reported analysis. With the exception of M-1 in corn stover and soybean seed, and M-3 in soybean hay, mean aged recoveries for all of the above storage intervals and sample matrix/residue component combinations were within the generally acceptable range of 70-120%. Low recoveries (62% and 56% respectively) were noted for M-1 in corn stover and soybean seed, while a slightly elevated recovery (124%) was noted for M-3 in soybean hay. Given that samples have been stored frozen for a maximum of 14.5 months during the residues trials, residues of pyroxasulfone or its metabolites in cereal samples are not expected to have been adversely affected by storage.

4.6 Residue trials

A package of residue trials was presented for wheat (8 trials), barley (4 trials), and triticale (4 trials). Trials were conducted in cereal growing areas of southern New South Wales, South Australia and Western

Australia at 1.25-2.5x the proposed application rate. Forage was collected for analysis at various intervals from 4-14 weeks after application, while grain and straw were collected at harvest. Samples were analysed for parent and the metabolites M-1, M-3 and M-25.

Summary of residues of pyroxasulfone and its metabolites in cereal grain, forage and fodder following a single application at 125-150 g ai/ha

COMMODITY	RESIDUE (MG/KG, DRY WEIGHT BASIS, AS PARENT EQUIVALENTS)			
	PARENT	M-1	M-3	M-25
Cereal forage	<0.04 (28), 0.04 (3), 0.08	<0.05 (3), 0.05 (2), 0.10 (5), 0.15 (7), 0.20 (7), 0.25 (4), 0.30, 0.40 (2), 0.45	<0.06 (19), 0.06 (4), 0.12 (5), 0.18, 0.24, 0.36, 0.60	<0.053 (19), 0.053 (3), 0.11 (5), 0.16, 0.21, 0.32, 0.53
Cereal straw	<0.01 (27), 0.01	<0.013 (2), 0.013, 0.025 (2), 0.038 (5), 0.05 (3), 0.063 (4), 0.076, 0.088 (2), 0.10, 0.11 (2), 0.14 (2), 0.15, 0.16, 0.38	<0.015 (28)	<0.013 (28)
Cereal grain	<0.01 (44)	<0.013 (44)	<0.015 (44)	<0.013 (44)

M-1: (5-Difluoromethoxy-1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-yl)methanesulfonic acid.

M-3: 5-Difluoromethoxy-1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid

M-25: (5-Difluoromethoxy-3-trifluoromethyl-1*H*-pyrazol-4-yl)methanesulfonic acid

Parent and M-1 are to be included in the plant residue definition for MRL compliance. No residues were found above LOQ in grain (0.01 mg/kg of parent, and 0.013 mg/kg M-1 as parent equivalents). Therefore, an MRL of *0.02 mg/kg is proposed for pyroxasulfone in cereal grains.

Processing studies

Processing studies were not required for this application, given that residues were not found above the limit of quantitation in cereal grain from crops treated at up to 2.5x the proposed rate.

Animal feeds

On a dry weight basis, residues of M-1 as parent equivalents in forage were <0.05 (3), 0.05 (2), 0.10 (5), 0.15 (7), 0.20 (7), 0.25 (4), 0.30, 0.40 (2), 0.45 mg/kg (STMR = 0.15 mg/kg), while residues in straw were <0.013 (2), 0.013, 0.025 (2), 0.038 (5), 0.05 (3), 0.063 (4), 0.076, 0.088 (2), 0.10, 0.11 (2), 0.14 (2), 0.15, 0.16, 0.38 mg/kg (STMR = 0.063 mg/kg). Residues of parent were <0.04 (28), 0.04 (3), and 0.08 mg/kg in forage and <0.01 (27), and 0.01 mg/kg in straw.

The following entry in Table 4 of the MRL Standard is therefore recommended: Primary feed commodities: 0.7 mg/kg.

Crop rotation

Field dissipation studies were conducted for pyroxasulfone in the USA (4 sites) and in Australia (4 sites), with applications being made (using the formulated product) to bare soil at rates between 125 and 300 g ai/ha. At 12 months after application, residues of parent compound in the US studies were ≤2.5% of the initial levels, while in the Australian trials, between 84 and 100% of the applied amount of parent had degraded, indicating a DT90 value of ≤257 days. The DT50 values for pyroxasulfone in the US studies ranged from 10.3 to 35 days. Minor amounts of the metabolites M-1 and M-3 (only just above the detection limit) were found in the US studies at 12 months after application, while M-1 was found at termination (~8 months) in the Australian trials, at levels generally below those of parent compound.

Field rotational cropping trials were presented for field peas and wheat, with plant-back intervals simulating both replanting after a failed treated crop, and planting the following season. A single application at 125-250 g ai/ha was made by post-sowing pre-emergence spraying, or by incorporation by sowing, to a wheat or triticale crop. Wheat crops were then sown in the treated plots approximately 12 months after the first application. Field peas were planted either 1 month after the first application (where the initial crop had been destroyed by spraying with glyphosate) or 12 months later. Seed and straw samples were collected at maturity, while forage was sampled at intervals from 6 to 10 weeks after planting.

Rotational crop residues of pyroxasulfone and its metabolites in wheat and field pea matrices following a single application at 125-250 g ai/ha (1.25-2.5x the proposed application rate)

COMMODITY	PLANT-BACK INTERVAL (MONTHS)	RESIDUE (MG/KG, DRY WEIGHT BASIS, AS PARENT EQUIVALENTS)			
		PARENT	M-1	M-3	M-25
Wheat forage	12	<0.04 (4)	<0.05 (2), 0.10 (2)	<0.06 (4)	<0.05 (4)
Wheat grain	12	<0.01 (4)	<0.013 (4)	<0.015 (4)	<0.013 (4)
Wheat straw	12	<0.01 (4)	<0.013, 0.025, 0.038 (2)	<0.015 (4)	<0.013 (4)
Field pea forage	1	<0.04 (2)	<0.05, 0.10	<0.06 (2)	<0.05 (2)
	12	<0.04 (4)	<0.05 (4)	<0.06 (4)	<0.05 (4)
Field pea seed	1	<0.01 (2)	<0.013 (2)	<0.015 (2)	<0.013 (2)
	12	<0.01 (4)	<0.013 (4)	<0.015 (4)	<0.013 (4)
Field pea fodder	1	<0.01 (2)	0.063, 0.10	<0.015 (2)	<0.013 (2)
	12	<0.01 (4)	<0.013 (2), 0.025, 0.05	<0.015 (4)	<0.013 (4)

As no residues of parent or metabolites were found above the LOQ in rotational wheat field or pea grain, MRLs are not required for legumes/pulses to cover rotational crop residues.

No residues of parent, M-3 or M-25 were found above the LOQ in any rotational crop feed samples. Maximum residues of M-1 were 0.10 and 0.038 mg/kg in wheat forage and straw. The highest residue of M-

1 in field pea forage and fodder was 0.10 mg/kg in both cases. The proposed MRL for primary animal feed commodities (0.7 mg/kg) will cover potential residues in rotational cereal and legume crops as well as in cereal forage and fodder from crops to which the product was applied.

Residues of pyroxasulfone and its metabolites have limited potential for carry over to the following cropping season. A plantback interval is not required from a residues perspective for Sakura 850 WG Herbicide.

4.7 Animal commodity MRLs

The dietary intake of pyroxasulfone by cattle consuming treated cereal forage is estimated in the table below.

The highest residue of pyroxasulfone or its metabolites observed in cereal forage or fodder was 0.60 mg/kg M-3 (on a dry weight basis) in forage. This figure has been used as a worse case in the calculation of the dietary burden in cattle (see table below). By contrast, the highest residues of parent compound observed in cereal forage or fodder was 0.08 mg/kg on a dry weight basis.

Cattle - 500 kg bw, 20 kg DM/day

FEED GROUP	COMMODITY	% IN DIET	FEED INTAKE	RESIDUE, MG/KG	% DM	LIVESTOCK DIETARY EXPOSURE		
						MG/ANIMAL	PPM	MG/KG BW
Forages and fodders	Cereal forage	100	20	0.60 (dry weight basis)	100	12	0.6	0.024

In a lactating cattle feeding study, no residues of M-1, M-3, M-9 or M-25 were observed above the LOQ in the milk or tissues of animals given 0.6 mg/kg (0.02 mg/kg bw/day) in feed each of M-1 and M-3 daily for 28 days. No residues of parent or M-1 or M-3 were found above LOQ in the milk or tissues of cattle given 1.8 mg/kg in feed (0.07 mg/kg bw/day) of pyroxasulfone daily for 28 days.

Therefore, MRLs at the LOQ (0.002 (milk) or 0.02 (tissues) mg/kg of parent equivalents after adjustment of the LOQ of M-3 (0.001 or 0.01 mg/kg) for molecular weight differences) are proposed for pyroxasulfone in mammalian meat, offal and milk.

The only feed commodity of significance for poultry connected with the application is cereal grain, which will not have pyroxasulfone residues at levels above the limit of quantitation.

Poultry- 2 kg bw, 0.15 kg DM/day

FEED GROUP	COMMODITY	% IN DIET	FEED INTAKE	RESIDUE, MG/KG	% DM	LIVESTOCK DIETARY EXPOSURE		
						MG/ANIMAL	PPM	MG/KG BW
Cereal grain	Grain	100	2	0.01	100	0.0015	0.01	0.005

A poultry feeding study was not provided, however metabolism studies were conducted for pyroxasulfone in laying hens. Groups of five hens were administered pyroxasulfone labelled with carbon-14 in either the pyrazole or isoxazoline moiety at 10 or 12 mg/kg in feed. The highest observed total radioactive residue was 0.497 mg/kg (in liver of birds fed the pyrazole label). Scaling this residue for a feeding level of 0.01 mg/kg, the LOQ of pyroxasulfone and its metabolites in grain, shows that the highest total residue in poultry tissue or eggs would be 0.0005 mg/kg, well below the LOQ. It is therefore proposed to establish MRLs for pyroxasulfone in poultry meat, offal and eggs at the LOQ. Given that the proposed residue definition for animal commodities is M-3, expressed as equivalents of pyroxasulfone, the MRLs will be established at 0.02 mg/kg.

Based upon the metabolism studies, livestock dietary burden calculation, and the stockfeed residues data, the following animal commodity MRLs are recommended: edible offal [mammalian] (*0.02 mg/kg); eggs (*0.02 mg/kg); meat [mammalian] (*0.02 mg/kg); milks (*0.002 mg/kg); poultry, edible offal of (*0.02 mg/kg); and poultry meat (*0.02 mg/kg).

4.8 Spray drift

Application of Sakura 850 WG Herbicide using aircraft will not be permitted. Ground application of the product was modelled using AgDrift.

The animal commodity MRLs were based on a cattle feeding level of 0.6 mg/kg (dry weight basis). This corresponds to drift of 0.9 g ai/ha, assuming a worst case of 1500 kg of dry matter per hectare in a paddock being grazed by livestock. The application rate is 100 g ai/ha. The draft label instructions state that the product is to be applied using medium to coarse droplets. Modelling shows that drift will reach an acceptable level by 22 metres from the edge of the application area. To take account of the fact that livestock will graze across the entire paddock, averaging of the drift residues from 2 metres from the edge of the application area to 304 metres (the limit of the model) was conducted, giving a mean value of 0.35 g ai/ha, well below the maximum feeding level of 0.9 g ai/ha. Therefore, a buffer zone is not required for Sakura 850 WG Herbicide.

4.9 Bioaccumulation potential

The octanol-water partition coefficient ($\log_{10}K_{OW}$) for pyroxasulfone at 25 °C is 2.39. Where samples of whole milk during the lactating cattle feeding study were separated into skim milk and cream prior to analysis, neither parent compound nor the metabolites M-1 or M-3 were found above the LOQ in either sample type. This does not indicate high fat solubility for pyroxasulfone, therefore, residues of the parent compound or its metabolite will not be designated as fat soluble.

4.10 Estimated dietary intake

The chronic dietary intake risk for pyroxasulfone has been assessed. The ADI for pyroxasulfone is 0.002 mg/kg bw/day, based upon a NOEL of 2 mg/kg bw/day and a 1000-fold safety factor. The NEDI calculation is made in accordance with WHO Guidelines[2] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for pyroxasulfone is equivalent to 5.2% of the ADI. DIAMOND Modelling[3] of chronic dietary exposure is also performed on new chemicals. The DIAMOND model estimated the chronic dietary exposure of pyroxasulfone as 4.5% of the ADI for the general population.

The acute dietary intake risk for pyroxasulfone has been assessed. The ARfD for pyroxasulfone is 0.1 mg/kg bw, based on a NOEL of 100 mg/kg bw and a 1000-fold safety factor. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. The highest acute dietary intake was estimated at 0.8% of the ARfD.

It is concluded that the dietary exposure to pyroxasulfone is low and the risk from residues in food is acceptable when Sakura 850 WG Herbicide is used according to label directions.

Recommendations

The following amendments to the MRL Standard are recommended in relation to the proposed use of Sakura 850 WG Herbicide:

Table 1

COMPOUND	FOOD		MRL (MG/KG)
ADD:			
Pyroxasulfone	GC 0080	Cereal grains	*0.01
	MO 0105	Edible offal (mammalian)	*0.02
	PE 0112	Eggs	*0.02
	MM 0095	Meat (mammalian)	*0.02
	ML 0106	Milks	*0.002

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

3. DIAMOND: The Diamond Modelling Of Nutritional Data is a computer dietary modelling program based upon statistical software that is used by FSANZ.

COMPOUND	FOOD		MRL (MG/KG)
	PO 0111	Poultry, edible offal of	*0.02
	PM 0110	Poultry meat	*0.02

*MRL set at the limit of quantitation.

Table 3

COMPOUND	RESIDUE DEFINITION
ADD:	
Pyroxasulfone	*For enforcement for commodities of plant origin:* Sum of pyroxasulfone and (5-difluoromethoxy-1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-yl)methanesulfonic acid, expressed as pyroxasulfone *For enforcement for commodities of animal origin:* 5-Difluoromethoxy-1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid, expressed as pyroxasulfone *For dietary exposure assessment for commodities of plant and animal origin:* Sum of pyroxasulfone, (5-difluoromethoxy-1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-yl)methanesulfonic acid, and 5-difluoromethoxy-1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid, expressed as pyroxasulfone

Table 4

COMPOUND	ANIMAL FEED COMMODITY	MRL (MG/KG)
ADD:		
Pyroxasulfone	Primary animal feed commodities	0.7

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

HARVEST WITHHOLDING PERIOD

Wheat, barley and triticale: Withholding period not required when used as directed.

GRAZING WITHHOLDING PERIOD

Do not graze or cut for stock food for 6 weeks after application.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Commodities exported and main destinations

Some of the commodities of interest in connection with the proposed products, namely wheat and barley, mammalian and poultry meat and offal, eggs, and dairy produce are considered to be major Australian export commodities.

In 2009/10, 13705 kilotonnes of wheat were exported, at a value of $3.686 billion. Key wheat export destinations are Indonesia, Japan, Korea, Malaysia, China and the Middle East. Australian barley (including malt) exports in 2009/10 were 4256 kilotonnes, worth $1.098 billion. Triticale is not currently exported. Total exports of dairy products in 2009/10 were worth $2.0342 billion, with key export destinations being Japan, Singapore, China, the Philippines, Thailand and the USA. Total exports of beef and veal were worth $4.144 billion in 2009/10, with the major destinations being Japan, the USA, Korea, Indonesia and Taiwan. Total exports of lamb and mutton were worth $1.4555 billion in 2009/10, with the top destinations being the USA, the European Union, Japan, and the Middle East.

Overseas registration status

Codex MRLs have not been determined for pyroxasulfone.

Applications have been made for registration of products containing pyroxasulfone in the USA and Canada. MRLs have not yet been finalised.

Potential risk to trade

MRLs are proposed at the limit of quantitation for pyroxasulfone in cereal grains, mammalian meat and offal, milk, eggs, and poultry meat and offal.

Therefore, there is not expected to be any significant risk to overseas trade as a result of granting this application.

Conclusions

Cereals*:** The available residues trial data show that cereal grains from crops treated with pyroxasulfone are unlikely to contain quantifiable residues. ***The proposed Australian MRL at the limit of quantitation of *0.01 mg/kg is not expected to pose any significant risk to Australian trade in cereals, however the APVMA welcomes comment on the risk to trade associated with the proposed use.

Animal commodities*:** Metabolism data in lactating goats and modelling of the expected dietary burden in poultry and mammals feeding on commodities from crops treated with pyroxasulfone show that quantifiable residues are unlikely to be found in mammalian and poultry meat and offal, milk or eggs. MRLs are proposed for these commodities at the limit of quantitation. ***There is not expected to be any significant

risk to Australian trade in meat, milk and eggs, however the APVMA welcomes comment on the risk to trade associated with the proposed use.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Health hazards

Pyroxasulfone is not listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2011). With the available toxicology information, OCS has determined that pyroxasulfone is classified as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrases:

T: R61 (Repr. Cat. 2)	May cause harm to the unborn child
Xn; R40 (Carc. Cat. 3)	Limited evidence of a carcinogenic effect
Xn; R48/22	Danger of serious damage to health by prolonged exposure if swallowed

Based on the product toxicology information and limited practical experience reports, Sakura 850 WG Herbicide is classified as a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrases:

R61 (Repr. Cat. 2)	May cause harm to the unborn child
R40 (Carc. Cat. 3)	Limited evidence of a carcinogenic effect
R48/22	Danger of serious damage to health by prolonged exposure if swallowed
R43	May cause sensitisation by skin contact

Formulation, packaging, transport, storage and retailing

The active ingredient, pyroxasulfone and the accompanying product (Sakura 850 WG Herbicide, which contains 850 g/kg pyroxasulfone as water dispersible granules) will be manufactured overseas and imported into Australia as a solid in high-density polyethylene (HDPE) bottle or aluminium-foil lined polyethylene bag or polyethylene bag with outer fibre-board box. It will be available in the following pack sizes: 1.18 kg, 5 kg, 10 kg.

Use pattern

Sakura 850 WG Herbicide is designed for the control of annual ryegrass and other weeds in certain cereal crops. The use rate on cereals (triticale, barley and wheat) is 118 g product/ha (100 g pyroxasulfone/ha). It is expected that only one application is required per season by ground boom spray application.

Exposure during use

Farmers and their employees will be the main users of Sakura 850 WG Herbicide. Workers may be exposed to the product when opening containers, mixing/loading, application, and cleaning up spills and equipment. The main route of exposure to the product/spray will be dermal and inhalation, although ocular exposure is also possible.

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide was used to estimate exposure. The toxic endpoint of concern and identified NOAEL is derived from repeat dose study in animals, and in this instance a margin of exposure (MOE) of 1000 or above is acceptable.

The MOE takes into account both interspecies extrapolation and intraspecies variability. The MOE for ground boom spray application is at an acceptable level when a single layer of clothing (cotton overalls or equivalent clothing) are worn during mixing/loading and application.

Exposure during re-entry

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

Recommendations for safe use

Users should follow the First Aid Instructions, Warning Statements and Safety Directions on the product label.

Conclusion

The registration of Sakura 850 WG Herbicide, containing 850 g/kg pyroxasulfone for the control of annual ryegrass and other weeds in certain cereal crops is supported.

Sakura 850 WG Herbicide can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product Material Safety Data Sheet.

7 ENVIRONMENTAL ASSESSMENT

Introduction

Bayer CropScience Pty Ltd. has applied for registration of the herbicide product Sakura 850 WG Herbicide containing pyroxasulfone in conjunction with approval of the associated active constituent (ac) by Kumiai Chemical Industry Co. Ltd. This is the first time approval for pyroxasulfone has been sought in Australia. The registration and approval is being conducted as an OECD Global Joint Review, with simultaneous submission to the USEPA and Canadian PMRA. The proposed end use product Sakura 850 WG Herbicide will contain 85% (w/w) pyroxasulfone as a water dispersible granule. The product will be marketed for the pre-emergent control of ryegrass and certain other weeds in wheat, barley and triticale and will be applied at a rate of up to 118 g/ha (100 g ac/ha) once per season usually in Autumn. The product will be incorporated into soil by sowing, as soon as practicable after application.

7.1 Environmental Fate

Hydrolysis

Pyroxasulfone is stable in acidic and neutral conditions and slightly degradable in alkaline conditions (pH 9). Only one minor degradation product (not definitively identified) was detected in alkaline conditions.

Photolysis

Pyroxasulfone has limited absorption of UV/VIS light in the environmentally significant wavelength range of 290-800 nm. In standard soil photolysis and aqueous photolysis studies only slight degradation was shown. Photolysis is only expected to be a minor degradation pathway for pyroxasulfone.

Pyroxasulfone is unlikely to remain stable in the atmosphere, due to reactions with photo-chemically produced hydroxyl radicals with an estimated half-life of 2.9 hours.

Biodegradation

Aerobic

The metabolism of pyroxasulfone in aerobic soil was studied in five soils under laboratory conditions. Pyroxasulfone was found to be slightly to very slightly degradable with half-life values between 142 and 506 days. The major metabolite observed in soil was M-1 with M-3 also being prevalent. Other minor metabolites identified were M-6, M-9 and M-25. The primary aerobic degradation pathway of pyroxasulfone (KIH-485) is the cleavage of the methyl-sulfone bridge of the parent. This degradation produces the intermediate M-7 (only ever tentatively identified), which is then oxidized to form the sulfonic acid metabolite M-1. Non-extractable residues, in all studies were between 7 and 26% of applied radioactivity at the end of the incubation period. The metabolites M-1 and M-3 accounted for up to 50 and 10%, respectively of the applied radioactivity, at study termination. No other metabolites accounted for more than 10% of the applied radioactivity. Extensive mineralisation also occurred. Under field conditions pyroxasulfone was degradable with half-lives of between 10 and 35 days. The metabolite M-1 is very slightly degradable with an estimated

DT50 in soil of between 3 000 and 24 000 days. However, under field conditions it was never found in concentrations greater than the parent. It is concluded that under field conditions there is limited potential for residue carry over to the following cropping season if application is performed annually for either pyroxasulfone or its metabolites.

In aerobic aquatic conditions (water/sediment systems) pyroxasulfone dissipates by a combination of partitioning to the sediment from the water phase and also degradation in water and sediment. Degradation of pyroxasulfone proceeds via the same pathway as that for aerobic soil, excepting that the intermediate metabolite M-11 was detected. The half-life for degradation of pyroxasulfone in the complete system (sediment plus water) was similar to that of aerobic soil and ranged from 108 to 127 days. The DT50 for dissipation from the water phase ranged from 50 to 54 days. However, under field conditions in summer pyroxasulfone rapidly degraded in both water and sediment, with half-lives being less than 16 and 77 hours, respectively.

Anaerobic

Pyroxasulfone is degraded marginally faster under anaerobic conditions than aerobic conditions, but is still regarded as slightly degradable based on the treatment of a single soil under anaerobic conditions.
The DT50 values for soil and the total system are 99 days and 145 to 156 days, respectively. The route of degradation under anaerobic conditions was similar to that under aerobic conditions, with cleavage of the methyl-sulfone bridge of the parent, being the major route of degradation. Consequently, as with the aerobic studies, M-1 was the major metabolite. The carboxylic acid metabolite M-3 was also formed, but unlike the aerobic studies the intermediates M-8 (alcohol) and M-10 (aldehyde) were isolated in minor amounts. Further minor metabolites were also formed by hydroxylation. The amount of non-extractable residues (up to 20% of applied radioactivity) was similar to that found in the aerobic studies. Extensive mineralisation also occurred.

In aquatic conditions, pyroxasulfone degrades slightly faster again than in anaerobic soil, but is still regarded as slightly degradable. It dissipated from the water column with a DT50 of between 50 and 54 days by a combination of degradation and partitioning to the sediment and it degraded from the system with a half-life of approximately 71 days. The proposed anaerobic water sediment pathway is the same as that for anaerobic soil. The major transformation product M-1 was found at its maximum value at the end of the study, indicating that it is more persistent than the parent molecule, under these conditions.

Mobility

Pyroxasulfone has high mobility in soils with Koc values of between 57 and 119 with a mean of 95. The K_{des} values are greater than the K_{ads} values suggesting that once pyroxasulfone is adsorbed on soil it is generally more difficult to desorb it. The adsorption behaviour was linear indicating that it was independent of the test item (in the range tested). There was some correlation between the organic carbon content of soil and Kd, suggesting that KIH-485 binds to organic carbon.

The major metabolite M-1 has similar properties to its parent with Koc values of 41 to 140.

Under field conditions pyroxasulfone was found to have limited potential to leach but M-1 had potential under some conditions.

Volatilisation is not expected to be a major route of dissipation of pyroxasulfone.

Accumulation

Pyroxasulfone is unlikely to bioaccumulate in organisms or accumulate in soil.

7.2 Environmental Effects

Avian

Birds were slightly sensitive to pyroxasulfone, with some effects being shown in the short term and reproductive studies, to Mallard duck. Effects to the Mallard duck were evident (body weight) at 1000 mg ac/kg-diet during short term exposure and 60 mg/kg-diet (reproduction) during sub-chronic exposure.

Fish

Fish were not acutely sensitive to pyroxasulfone to the limits of its water solubility in test conditions (2.2 to 2.8 mg/L). However, there was a reduction in the wet weight and length of fish, exposed to 3.9 mg pyroxasulfone/L during their early life stage.

Aquatic Invertebrates

Daphnia were not sensitive to pyroxasulfone to the limit of its water solubility (1.9 to 4.4 mg/L under test conditions) in acute and sub-chronic studies.

Algae and Aquatic Plants

As expected for a herbicide algae and aquatic plants were sensitive to pyroxasulfone. Green algae were by far the most sensitive and pyroxasulfone is regarded as very highly toxic to this species. It also showed inhibitory effects on blue-green algae and marine algae at levels above 0.14 and 0.8 mg/L but an EC50 based on growth rate could not be established to the limits of pyroxasulfone's water solubility (2.9 to 3.5 mg/L under the tested conditions). By contrast the freshwater diatom was insensitive to pyroxasulfone to the limits of its water solubility. Pyroxasulfone is algistatic and recovery occurred for green algae exposed to up to 2 µg pyroxasulfone/L for 72 hours. The major metabolites M-1 and M-3 are slightly toxic to algae and practically non-toxic to duckweed.

Terrestrial Invertebrates

Earthworms, and bees were not found to be sensitive to pyroxasulfone to the level tested. In the case of bees the LD50 is > 100 µg/bee for acute contact exposure. No effects were observed in earthworms for exposure levels of up to 997 mg/kg dry weight of soil. In laboratory tests on glass, the parasitic wasp and predatory mite showed some sensitivity to the formulation containing pyroxasulfone. At the highest tested rates both species showed approximately 50% reduction in beneficial effect when exposed to the formulation; however, for predatory mites the effect was not dose responsive. At the proposed Australian

rate applications of formulations containing pyroxasulfone are unlikely to affect the parasitic wasp but may cause a reduction in feucundity of predatory mite.

Micro-organisms

Exposure of pyroxasulfone to micro-organisms resulted in no significant toxic effects on glucose simulated respiration or microbial mineralisation up to 2 mg ac/kg.

Terrestrial Plants

The effects of the formulation containing nominally 85% (w/w) pyroxasulfone on terrestrial vascular plants were studied. As expected for a herbicide both seedling emergence and vegetative vigour were inhibited. The vegetative vigour of monocots was not affected to the levels tested (300 g ac/ha). However, for seedling emergence both monocots and dicots were affected. The most sensitive plants were onion and pumpkin for emergence and vegetative vigour respectively. Fifty percent inhibition (EC50) was not observed in any of the plants tested.

7.3 Risk Assessment

Sakura 850 WG Herbicide containing 85% (w/w) pyroxasulfone is intended to be applied once per season. The resulting estimated environmental concentration of pyroxasulfone and its formulation showed an acceptable risk to birds, bees, earthworms, fish, daphnia and soil microorganisms. For beneficial invertebrates there is a risk to some beneficial insects in the immediate vicinity of application, but there is unlikely to be any adverse effect beyond this area. The risk to algae and duckweed from spray drift was found to be unacceptable unless a downwind no spray zone was imposed. Standard APVMA modelling for low boom spraying with medium and coarse spray nozzles was used. This resulted in a downwind no spray zone of 160 and 80 m, respectively for the protection of the aquatic environment. There is also risk to non-target terrestrial plants, but provided precautions are taken to prevent spray drift a mandatory downwind no spray zone is not required.

Due to pyroxasulfone's high mobility, toxicity to algae and aquatic plants; and moderate persistence, contaminated run-off water posed a risk to algae and duckweed. The proposed incorporation of pyroxasulfone into soil shortly after application reduced the amount available for run-off. However, even with the reduced amount of pyroxasulfone available after incorporation into soil the risk was found to be unacceptable to algae and mitigable to duckweed. Consideration was given to pyroxasulfone's rapid degradation in water under field conditions, adjusted to lower temperatures, likely to be experienced in Australian waterways at the time of the proposed application. The risk to duckweed and algae was found to be on the margins of what is regarded as mitigable and acceptable in a realistic worst case, but that the effects were likely to be transient. Further due to the climatic conditions in the wheat belt, the realistic worst case scenario is likely to be a very rare event. Therefore provided that measures to prevent run-off including ensuring incorporation into soil before any likely run-off event are in place the risk to aquatic plants and algae is regarded as acceptable.

8 EFFICACY AND SAFETY ASSESSMENT

This application seeks to register Sakura 850 WG Herbicide for the pre-emergence control of annual ryegrass (*Lolium rigidum*), barley grass (*Hordeum leporinum*), annual phalaris (*Phalaris paradoxa*), silver grass (*Vulpia bromoides* and *Vulpia myuros*) and toad rush (*Juncus bufonius*) in wheat, barley and triticale.

The active constituent of Sakura is pyroxasulfone, a new active ingredient. Pyroxasulfone is absorbed by the roots and shoots of germinating weeds and works by inhibiting growth in meristematic tissue. The mode of action is inhibition of the biosynthesis of very long chained fatty acids (VLCFA) with subsequent build-up of fatty acid precursors. Pyroxasulfone has been classified as a Group K mode of action for weed resistance.

8.1 Proposed use pattern

Sakura 850 WG Herbicide is to be applied to soils pre-planting at a rate of 118 g/ha. It should be incorporated by sowing (IBS) wheat (not durum wheat), barley or triticale using knife points and press wheels or (excluding barley) by narrow points and harrows.

8.2 Summary of Evaluation of Efficacy and Crop Safety

Trial description

A total of 119 field trials and one laboratory trial, conducted over four seasons were relied on in support of this registration. Field trials were conducted in the cereal cropping regions of Western Australia, New South Wales, Victoria, South Australia and to a lesser extent Queensland.

All trials were small plot replicated trials, mostly as randomized complete blocks and were replicated three or four times. Untreated controls and appropriate commercial standards were included. The trials evaluated a range of Sakura rates from below the proposed label rate in efficacy trials, up to three times the proposed label rate in crop tolerance trials and up to four times the proposed label rate in plant-back recropping trials.

As appropriate, trials assessed both crop safety and weed control efficacy using 0 to 100 rating assessments and weed counts based on quadrat counts. Crop safety measurements included emergence counts (some trials), crop discolouration (phytotoxicity) and biomass reduction at one or more intervals after crop emergence through to maturity. The weed challenge for each weed species was specified for most of the efficacy trials. The majority of efficacy trials were not taken through to a harvested yield (drought impacted on many). Most of the crop tolerance and plant back trials were harvested for yield determination.

Both the raw assessment data and tables of data summaries were available in most reports. Appropriate statistical analysis and valid interpretation of the data was made.

Submitted trials covered the following areas of efficacy and crop safety:

1. Evaluation of Sakura for the control of annual ryegrass, barley grass, annual phalaris, silver grass and toad rush in wheat, barley and triticale.

2. The effect of application IBS and PSPE on the efficacy against the target weeds and on crop safety of wheat, barley and triticale
3. Evaluation of seeding systems, knife points and harrows, depth of seeding, surface trash levels, use of knockdowns, time between treatment application and sowing and Sakura rates and application methods on weed control efficacy and crop safety.
4. Varietal tolerance screens for wheat, including durum varieties, barley and triticale.
5. Rotational crop plant back recropping trials for winter and summer growing crops.
6. Physical and biological compatibility of Sakura with knockdown herbicides, knockdown spikes and residual pre-emergence herbicides.
7. Product efficacy and crop safety comparison in field trials with commercial standards.

All trials were considered to be appropriate given the purpose of evaluating a new active constituent in a range of environments, soil types and cropping systems including a wide range of seeding equipment. All of the trials were conducted in commercial cropping field environments under mostly commercial cultural and management practices. In this respect, the soil types, seasonal conditions and treatment application conditions reflected anticipated commercial conditions. In all instances, treatments were applied at or near to the targeted timing which was pre-emergent to the crop and weeds.

All of the trials were appropriate to demonstrate/test efficacy for control of target weed(s) and safety to the crop species at each site. Trial locations and all information relating to the conduct of all the trials appears to be appropriate and in order. The trials were conducted in the period 2006–09 inclusive by Bayer CropScience staff or reputable contract trials researchers.

Summary of trial results

Efficacy

Annual ryegrass: Over fifty trials evaluated the efficacy of pyroxasulfone for the control of ryegrass in wheat and barley crops over a three year period in the cereal growing areas of Australia. The majority of data, taking into consideration the level of weed challenge and the various cropping systems evaluated, demonstrated the reliable control of ryegrass when used at the proposed label rate and in accordance with label recommendations. Control was at least equivalent and mostly better than the available commercial standards.

Barley grass: Eight trials over a three year period evaluated the efficacy of pyroxasulfone for the control of barley grass in wheat. Not all trials gave commercially acceptable barley grass control, however when used in accordance with the proposed label recommendations in respect of no prior cultivation and the use of a knockdown herbicide, good and reliable barley grass control was achieved, even at high densities. No fully effective, commercial, pre-emergence standard exists.

Annual phalaris: Seven trials evaluated the efficacy of Sakura for the control of annual phalaris in wheat and barley over a three year period. All except one trial gave good to excellent control of phalaris at the proposed label rate of Sakura, the exception being a trashy site which was very dry for a long period after

seeding. In most trials, control was at least equivalent and mostly better than the available commercial standards.

Silver grass: Seven trials were conducted in the years 2007 and 2009 in wheat and barley. *Vulpia myuros* was only included in two trials with the remainder comprising *Vulpia bromoides*. One of the trials conducted in WA gave poor to fair silver grass control, with the failure to use a pre-sowing knockdown, 50% trash cover and very wet conditions post sowing in a sandy textured soil used to explain the poor control. The remaining trials, sometimes under a high weed challenge, gave excellent control of both Vulpia spp. Sakura at the proposed label rate gave better control of silver grass than the standard.

Toad rush: During 2009 four trials were conducted for the control of toad rush in wheat and barley; in two of these trials the weed density was very high. In three of the four trials the toad rush control was excellent and equivalent or better than the registered standards. Poorer control was achieved in a WA trial under high weed challenge in sandy soils with 420 mm of rainfall between seeding and the final weed count.

Crop safety/variety tolerance

Most of the efficacy trials reviewed also rated crop safety at various intervals after treatment application for phytotoxicity and biomass reductions. These trials identified the good safety of bread wheats to pyroxasulfone and increased sensitivity, but still generally good safety, of barley to this product.

The variety tolerance screens verified the safety to wheat and triticale, but highlighted the greater sensitivity of durum wheat to pyroxasulfone. Accordingly the label advises against its use on durum wheat varieties. Barley varieties exhibited greater biomass reductions more often than wheat and triticale and this sometimes was reflected in reduced yield of one or more varieties compared to the untreated control. There was no consistency between trials in demonstrating one variety to being more sensitive to Sakura than another.

Crop rotation and recropping interval

Trials commenced in 2007 and are ongoing evaluating the safe plant back period for both winter and summer crops. Below average and low rainfall was recorded at most sites in 2007 and 2008, and for the range of crop and pasture species tested the current label recommendations with respect to plant back periods are likely to be very robust. One of the original 2007 trials was sown to rotational crops in 2009 and four new trials treated in 2008 were sown to crop and pasture species in 2009. The more recent trial work has reinforced and confirmed previous data and allowed plant back recommendations to be extended to additional crops. At the same time it has confirmed the sensitivity of barley requiring a nine month plant back interval and highlighted the sensitivity of durum wheat and oats requiring a twenty one month plant back interval.

Compatibility

Sakura was compatible both physically and biologically with a range of knockdown herbicides such as glyphosate and Spray.Seed, a range of soil residual herbicides such as trifluralin, Logran and Monza and a range of common ‘spike’ herbicides commonly added to glyphosate to enhance weed knockdown such as Hammer, 2,4-D formulations, Striker, Goal, Cadence and Ally.

8.3 Conclusions

In a comprehensive series of trials conducted in the cereal cropping regions of Australia from 2006 to 2009 inclusive, Sakura 850 WG Herbicide was demonstrated to provide control of annual ryegrass (*Lolium rigidum*), barley grass (*Hordeum leporinum*), annual phalaris (*Phalaris paradoxa*), silver grass (*Vulpia bromoides* and *myuros*) and toad rush (*Juncus bufonius*) in wheat, triticale and barley. Sakura invariably performs at an equivalent but generally superior level to commercial standards in the control of these weeds.

Later trials were conducted in accordance with current label recommendations for the effective and safe use of Sakura. These recommendations include application to uncultivated ground with less than 50% soil surface trash cover, use of a pre-plant knockdown herbicide and using the product pre-planting and incorporating by seeding with knife points and press wheels. Some flexibility exists for applying pyroxasulfone days or even weeks in advance of the seeding operation however application at, or as near to, seeding as possible was advocated particularly when using on barley. Good moisture conditions around the time of seeding are also important to maximize weed control.

Good crop safety was demonstrated in the efficacy trials and backed up by cereal variety tolerance screening trials. While bread wheats and triticale demonstrated good tolerance, durum wheat varieties were clearly less tolerant of pyroxasulfone and are not recommended to be treated and indeed be planted on treated ground for at least 21 months after use. Barley varieties, while seemingly more sensitive to Sakura than wheat, demonstrated good tolerance however some trials identified variety sensitivity at label and particularly at above label rates and when used PSPE. Damage occurrence and variety sensitivity appeared to be unpredictable based on soil type, rainfall or region. Potential crop safety issues in respect of barley are adequately addressed on the product label in Restraints and crop safety information in General Instructions, and users are alerted to this crop safety information by Critical Comments in the Directions for Use table.

Rotational crop plant back re-cropping studies were conducted generally under dry conditions at and between treatment application and planting of the rotational crop, which was not conducive to breakdown of chemical residues. Proposed re-cropping intervals reflect current study findings.

Physical and chemical compatibility of Sakura with a range of knockdown, soil residual and knockdown spikes was demonstrated. Some of the residual herbicides are for wheat only, have some crop safety issues in their own right and have extended plant back intervals. Users need to be alerted to these issues in the Sakura label under compatibility.

Trials were conducted by qualified researchers who reported their work thoroughly and professionally. The overview and trials summary provided was also thorough and as concise as such a large amount of trial data would allow. It accurately reflected the findings of the trials in a very logical and easy to follow manner. The proposed label for Bayer CropScience Sakura 850 WG Herbicide provides clear and concise guidelines for effective weed control and crop safety based on the large body of trial work generated.

The application for registration of Sakura 850 WG Herbicide is accordingly supported.

9 LABELLING REQUIREMENTS

DIRECTIONS FOR USE (For use in all States)

RESTRAINTS
DO NOT apply with aircraft
DO NOT plant durum wheat (*Triticum durum*) after the application of Sakura 850 WG (refer to **Crop Rotation Recommendations** for further advice).
DO NOT plant barley with narrow points and harrows after the application of Sakura 850 WG
DO NOT apply if heavy rain has been forecast within 48 hours.
DO NOT apply unless incorporation by sowing (IBS) can be performed within 3 days of application.
DO NOT apply to waterlogged soil.
DO NOT irrigate to the point of run-off.

SPRAY DRIFT RESTRAINTS
DO NOT apply with spray droplets smaller than a **COARSE** spray droplet size category according to "APVMA Compliance Instructions for Mandatory COARSE or Larger Droplet Size Categories" located under this title in the GENERAL INSTRUCTIONS section of this label.

DO NOT apply when wind speed is less than 3 or more than 20 kilometres per hour as measured at the application site.

DO NOT apply during surface temperature inversion conditions at the application site.

Users of this product **MUST make an accurate written record** of the details of each spray application within 24 hours following application and **KEEP** this record for a minimum of 2 years. The spray application details that must be recorded are: **1**.date with start and finish times of application; **2**.location address and paddock/s sprayed; **3**.full name of this product; **4**.amount of product used per hectare and number of hectares applied to; **5**.crop/situation and weed/pest; **6**.wind speed and direction during application; **7**.air temperature and relative humidity during application; **8**.nozzle brand, type, spray angle, nozzle capacity and spray system pressure measured during application; **9**.name and address of person applying this product. (Additional record details may be required by the State or Territory where this product is used.)

MANDATORY NO-SPRAY ZONES
DO NOT apply if there are aquatic and wetland areas including aquacultural ponds, surface streams and rivers within **80 metres** downwind from the application area.

CROP	WEED	RATE (g/ha)	CRITICAL COMMENTS
Wheat (not durum wheat) and triticale (sow using knife points and press wheels OR narrow points and harrows). **Barley** (sow using knife points and press wheels ONLY)	Annual ryegrass (*Lolium rigidum*), annual phalaris or paradoxa grass (*Phalaris paradoxa* only), barley grass (*Hordeum leporinum*), silver grass (*Vulpia bromoides*, *Vulpia myuros*), toad rush (*Juncus bufonius*)	118	Apply pre-sowing and incorporate by sowing (IBS). For best results apply just before sowing (refer to **Interval between Application and Sowing** in **GENERAL INSTRUCTIONS**). Avoid throwing treated soil into adjacent crop rows when sowing with knife points and press wheels. To reduce the risk of crop effects refer to **Crop Safety** in **GENERAL INSTRUCTIONS.** To optimise weed control apply directly to uncultivated soil. Weed control may be greatly reduced where weed seeds have been buried by cultivation prior to sowing. Weed control may be adversely affected by; • uneven application, • application to ridged or cloddy soil, • stubble or trash cover particularly above 50%, • germinated and emerged weeds that are not controlled by a knockdown herbicide • insufficient rainfall within 7 to 10 days after application. • in soils prone to leaching, rainfall which is sufficiently heavy to cause movement of the herbicide out of the weed seed zone. These factors when combined may substantially reduce weed control.

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

WITHHOLDING PERIODS
Wheat, barley and triticale
Harvest: **NOT REQUIRED WHEN USED AS DIRECTED**
Grazing/Stockfood: **DO NOT GRAZE OR CUT FOR STOCKFOOD FOR 6 WEEKS AFTER APPLICATION**

GENERAL INSTRUCTIONS
Sakura® 850 WG Herbicide is a residual, soil applied, pre-emergent herbicide. It is absorbed by both the roots and to a lesser extent by the shoots of germinating weeds, and works by inhibiting growth in the meristematic area. Weed control is optimised when Sakura is applied evenly to moist soil just prior to incorporation by sowing and there is sufficient rainfall soon after sowing to ensure uptake of the herbicide by germinating weeds. Weed control may be greatly reduced where weed seeds have been buried by cultivation prior to application. Weed control may also be reduced

where there is insufficient soil moisture for herbicide uptake or in soils prone to leaching where rainfall is sufficiently heavy to cause movement of the herbicide out of the weed seed zone. Sakura will not reliably control emerged weeds. A knockdown herbicide should be used to control emerged weeds at sowing.

Crop Safety

Sakura generally shows good crop selectivity when used as directed. The following directions will help minimise the risk of crop effects.

- Do not plant durum wheat after the application of Sakura as it may be severely damaged. Refer to **Crop Rotation Recommendations** for further advice.
- When incorporation is by sowing with knife points and press wheels avoid throwing treated soil into adjacent crop rows.
- Do not use a combination of both press wheels and a covering device such as harrows or chains when sowing.

Situations which lead to concentration of herbicide in the planting row, or movement of herbicide to the depth of the crop seed, may increase the potential for crop damage. This includes the following scenarios;

- Where deep furrows are formed by the sowing operation, soil movement into the crop row may occur due to wind or heavy rainfall soon after sowing resulting in concentration of herbicide in the crop row.
- Where soil has a high potential for leaching, heavy rainfall between application and crop emergence may result in movement of herbicide into the crop seed zone.

The potential for crop damage may also be increased when Sakura is applied in tank mixes with other herbicides, and where crop vigour is reduced due to factors such as water logging, frosts, insect attack, crop disease, when weather damaged seed is used and/or with the use of some fungicide seed treatments especially in conjunction with crop varieties with short coleoptile length.

Additional Crop Safety Information Specific to Barley

Barley tends to be more sensitive than wheat or triticale to Sakura. Following the use of Sakura in barley reduced crop growth is more likely, it may be more pronounced and may persist for longer than would be expected following use in wheat or triticale. Further, in the absence of weed competition significant yield reductions have occasionally been measured in barley.

- To reduce the risk of crop damage from the movement of the product into the crop seed zone, sow barley as soon as practicable after the application of Sakura.
- When sowing barley incorporation should only be by knife points and press wheels; do not use harrows or other covering devices e.g. chains when sowing barley.

Incorporation by Sowing

Sakura should be applied prior to sowing, and incorporated by sowing using knife points and press wheels or (excluding barley) narrow points and harrows. When incorporation is by knife points and press wheels, weeds germinating in the seed row may not be controlled. Weeds germinating from depth, weeds just about to emerge, or weeds that have emerged which are not controlled by a knockdown herbicide at sowing may not be controlled by Sakura.

Interval between Application and Sowing

Incorporate by sowing as soon as practicable after the application of Sakura, but no later than 3 days after application. To reduce the risk of crop damage sow barley as soon as practicable after the application of Sakura.

Sandy soils
Weed control may be reduced in soil prone to leaching where rainfall after application and sowing is sufficiently heavy to cause movement of the herbicide out of the weed seed zone.

Mixing
Ensure sprayer and nozzle filters are clean before preparing the spray mixture. Half fill the spray tank with water and, with the agitators in motion, add the correct amount of Sakura directly to the spray tank. Complete filling the tank with agitators in motion. Agitation must continue before and during spraying. When other products are to be applied in addition to Sakura, always add Sakura to the spray tank first and ensure it is fully dispersed in the spray tank before adding other products.

Application
Ensure complete and even spray coverage of the soil is achieved. Poor spray coverage may result from application to ridged or excessively cloddy soil or in situations of high stubble or trash cover. A significant reduction in weed control may result where stubble, trash or other ground cover exceeds 50%, and in situations where a 'cold' or incomplete burn of stubble results in a mass of material which can act as a physical barrier between the herbicide and germinating weeds; this can be exacerbated in header trails where there may be greater weed seed numbers and higher levels of trash. Weed control can be particularly affected where Sakura is applied to a barrier of stubble, trash or other ground cover, and there is insufficient following rainfall to transfer Sakura to the soil surface and the germinating weed seeds.

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 100 L water/ha is applied with spray droplets of a COARSE droplet size category. In some situations (e.g. high stubble loads) high water volumes may give higher levels of weed control.

Aircraft – DO NOT apply Sakura 850 WG by aircraft.

APVMA Compliance Instructions for Mandatory COARSE or Larger Droplet Size Categories

Important Information

These instructions inform users of this chemical product how to lawfully comply with the requirement of a COARSE or larger spray droplet size category for spray application.

Spray droplet size categories are defined in the ASAE S572 Standard (newer name may also be shown as ASABE) or the BCPC guideline. Nozzle manufacturers may refer to one or both to identify droplet size categories, but for a nozzle to comply with this requirement, the manufacturer must refer to at least one.

In the following instructions, Section 1 is for ground application and Sections 2 and 3 are for aerial application.

Complying with the label requirement to use a specific droplet size category means using the correct nozzle that will deliver that droplet size category under the spray operation conditions being used. The APVMA has approved only the following specific methods for choosing the correct nozzle. Use one of the methods specified in these instructions to select a correct nozzle to deliver a COARSE or larger droplet size category.

SECTION 1 Instructions for **Ground Application – for COARSE droplet size or larger categories**

Mandatory Instructions for Ground Applications

USE ONLY nozzles that the nozzles' manufacturer has rated to deliver a COARSE, a VERY COARSE or an EXTREMELY COARSE droplet size category as referenced to ASAE S572 or BCPC. Choose a nozzle specified to provide the droplet size category required in the label Spray Drift Restraints.

DO NOT use a higher spray system pressure than the maximum the manufacturer specifies for the selected nozzle to deliver the droplet size category required in the label Spray Drift Restraint.

SECTIONS 2 and 3 are not applicable to this label.

Compatibility

Sakura 850 WG is compatible with any one of the following herbicides; Ally®, Avadex® Xtra, Cadence® WG, Diuron 900WG, Dual® Gold, Estercide® Xtra 680, Glean®, glyphosate (Glyphosate CT, Roundup PowerMax®), Goal® EC, Gramoxone® 250, Hammer®, Logran®, Logran B-Power®, Monza®, Spray.Seed®, Striker®, Surpass® 475, Trifluralin 480 and Triflur X®

Sakura 850 WG is compatible with mixtures of glyphosate (Glyphosate CT, Roundup PowerMax) with any one of the following herbicides; Ally, Cadence WG, Estercide Xtra 680, Goal EC, Hammer, Logran B-Power, Monza and Striker.

Sakura 850 WG is compatible with any one of the following insecticides; Endosulfan, Fastac® and Le-mat®.

Always refer to the crop tolerance and plant back restrictions and other directions for use on the label of the tank mix partner.

Refer to **Mixing** section above for advice on preparing tank mixtures with Sakura. Mixtures with products containing paraquat (e.g. Gramoxone and Spray.Seed) require particular attention to these instructions, including ongoing agitation to ensure Sakura remains in suspension in the spray tank.

For advice on compatibilities not listed above, contact Bayer CropScience.

Crop Rotation Recommendations

Sakura breaks down by microbial degradation, which is favoured by warm, moist aerobic soil.

Minimum recropping intervals (months after Sakura application) have been established for Sakura to minimise the risk of damage to following crops (see table below). However, environmental and agronomic factors make it impossible to eliminate all risk and therefore the potential for damage to following crops exists.

Rainfall of less than the minimum interim rainfall required (see table below) may result in extended recropping intervals. Interim rainfall is the total rainfall between the application of Sakura and planting of the particular following crop. For recropping with winter crops, where a minimum of 250 mm of interim rainfall is required, if rain from application to the end of spring is less than 125 mm and isolated heavy summer and autumn falls and break rains are required to achieve the 250 mm interim rainfall, then extended recropping intervals may apply.

Crops	Recropping recommendation	
	Minimum recropping interval	Minimum interim rainfall
Wheat (not durum wheat) and triticale	0 months	0 mm
Cotton, maize, mung beans, sorghum, soybeans and sunflowers	5 months	150 mm
Barley*, canola**, chickpeas, faba beans, field peas, lentils, lupins, vetch and subterranean clover	9 months	250 mm
Durum wheat, oats, lucerne and medic	21 months	550 mm

* Barley can be sown immediately after the application of Sakura where Sakura has not already been incorporated. However, where Sakura has been incorporated into the soil by, for example, a previous sowing operation, barley should not be sown for at least 9 months after the application of Sakura.

**For canola sown the year after the application of Sakura there may occasionally be some crop stunting but no yield reductions have been measured.

For advice on crops and situations not listed above, contact Bayer CropScience.

Resistant Weeds Warning **GROUP K HERBICIDE**

Sakura 850 WG Herbicide is a member of the isoxazoline group of herbicides and has the inhibitor of very long chain fatty acids (VLCFA inhibitors) mode of action. For weed resistance management Sakura is a Group **K** herbicide. Some naturally-occurring weed biotypes resistant to Sakura, and other Group **K** 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 Sakura or other Group **K** herbicides.

Do not rely exclusively on Sakura for weed control. Use as part of an integrated weed management program involving herbicides with other modes of action and non-chemical methods of control. CropLife Australia resistance management strategies are available from your local agricultural chemical supplier or at the CropLife Australia website (www.croplifeaustralia.org.au). 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 Sakura to control resistant weeds.

PRECAUTIONS

Re-entry Period

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

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product or used containers.
DO NOT apply if heavy rain has been forecast within 48 hours.
DO NOT apply unless incorporation by sowing (IBS) can be performed within 3 days of application.
DO NOT apply to waterlogged soil.
DO NOT irrigate to the point of run-off.

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 non-target plants, cropping lands or pastures.
Undersown Pasture Species
DO NOT undersow with pasture species (legumes or grasses) following the application of Sakura.

STORAGE AND DISPOSAL
Store in the closed, original container in a dry, cool, well-ventilated area out of direct sunlight.
(HDPE containers only)
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 deliver empty packaging to an approved waste management facility. If an approved waste management facility is not available bury the empty container 500 mm below the surface in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots, in compliance with relevant Local, State or Territory government regulations. Do not burn empty containers or product. Do not re-use container for any other purpose.

(Bag-in-a-box containers only)
Single rinse before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. Puncture and deliver empty packaging to an approved waste management facility. If an approved waste management facility is not available bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots, in compliance with relevant Local, State or Territory government regulations. Do not burn empty containers or product. Do not re-use container for any other purpose.

SAFETY DIRECTIONS
Repeated exposure may cause allergic disorders. Sensitive workers should use protective clothing. When using the product wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical-resistant gloves. Wash hands after use.

FIRST AID
If poisoning occurs contact a doctor or Poisons Information Centre (telephone 13 11 26).

ADDITIONAL USER SAFETY INFORMATION
WARNING: Children and pregnant women should not come into contact with this product.

Limited evidence of a carcinogenic effect.

MATERIAL SAFETY DATA SHEET
Additional information is listed in the Material Safety Data Sheet, which can be obtained from

www.bayercropscience.com.au.

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

APVMA Approval No.: 63998/47161

Sakura® is a registered trademark of **Kumiai Chemical Industry Co. Ltd**

Sakura is a Pyroxasulfone product

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

drumMUSTER eligible container

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Bayer CropScience

Batch no.:
Date of manufacture:

DrumMUSTER logo only required for HDPE containers

ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ARfD	Acute Reference Dose (for humans)
bw	bodyweight
C_{max}	the maximum concentration of an administered chemical
d	day
DM	dry matter
DT_{50}	Time taken for 50% of the concentration to dissipate
EC_{50}	concentration at which 50% of the test population are immobilised
g	gram
h	hour
ha	hectare
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
IBS	Incorporated by sowing
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
JMPR	Joint FAO/WHO meetings on pesticide residues
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LC/MS/MS	Liquid chromatography–mass spectrometry
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOQ	Limit of Quantitation – level at which residues can be quantified

mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
NEDI	National estimated daily intake
NESTI	National estimated short term intake
NOAEL	No observable adverse effect level
NOEL	No Observable Effect Level
Pa	Pascal
PSPE	Post-sowing pre-emergence
ppm	parts per million
TLC	Thin layer chromatography
T_{max}	The time from dosing when the maximum concentration of an administered chemical is reached
TRR	Total radio-active residue
µg	microgram
WG	Water Dispersible Granule
WHP	Withholding Period
w/w	weight/weight

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.
Biodegradation	Breakdown of a chemical in the presence of micro-organisms
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
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
Hydrolysis	Breakdown of chemicals in the presence of water
Immunotoxic	Toxic or damaging to the immune system
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octonol water partitioning co-efficient
Metabolism	The conversion of food into energy
Metabolites	Breakdown products following metabolism
Parent	The original chemical as applied, i.e. prior to breakdown by metabolism
Photolysis	Breakdown of chemicals due to the action of light
Sensitiser	A substance that causes a proportion of exposed people or animals to develop an allergic reaction in normal tissue after repeated exposure
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

Australian Pesticides and Veterinary Medicines Authority 2008, *Ag MORAG: Manual of Requirements and Guidelines*, APVMA, Canberra.