Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active Fluxapyroxad in the Product MBREX Fungicide (Earlier named as BAS 700 01 F Fungicide)

APVMA Product Number P64104

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This publication is available from the APVMA website: www.apvma.gov.au.

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PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator 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 Ageing, 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 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 consistent with accepted scientific principles and processes. 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 conducted by the APVMA and of the specialist advice received from 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
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop or animal safety.

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

Any advice the APVMA receives through this consultation, which relies on to grant this application will be noted in a subsequent Advice Summary. Advice Summaries can be found on the APVMA website: http://www.apvma.gov.au

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 **BAS 700 01 F Fungicide now known as MBREX Fungicide** 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 matters include aspects of **public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade,** and **efficacy and target crop or animal safety**. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **12 September 2012** 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)
- Email or postal address (if available)
- The date you made the submission.

All personal information, and confidential information judged by the APVMA to be ***confidential commercial information (CCI)***[1] 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
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Symonston ACT 2609
Phone: 02 6210 4748
Fax: 02 6210 4776
Email: pesticides@apvma.gov.au

[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: www.apvma.gov.au

1 INTRODUCTION

Applicant

BASF Australia Ltd.

Details of Product

It is proposed to register MBREX Fungicide (known during assessments as BAS 700 01 F Fungicide) containing the new active constituent fluxapyroxad (62.5 g/L) as an emulsifiable concentrate formulation. The product is intended for control of Net form of net blotch (*Pyrenophora teres* f *teres*), Spot form of net blotch (*Pyrenophora teres* f *maculata*), leaf scald (*Rhynchosporium secalis*), leaf rust (*Puccinia hordei*) and powdery mildew (*Blumeria graminis* f. sp.*hordei*) of barley. BAS 700 01 F Fungicide is intended to be used at a rate of 250 mL – 1L product/ha.

Fluxapyroxad is a new active constituent to the Australian market. It is a fungicide which belongs to the fungicides group of succinate dehydrogenase inhibitors (SDHI). The Mode of Action of fluxapyroxad at the molecular level is the inhibition of the enzyme succinate dehydrogenase (SDH), also known as complex II in the mitochondrial electron transport chain. Through its inhibition of complex II, fluxapyroxad disrupts fungal growth by preventing energy production and also by eliminating the availability of the chemical building blocks for the synthesis of other essential cellular components. Current research by BASF indicates that fluxapyroxad inhibits spore germination, germ tube and appresoria formation, and the growth of mycelia. Fluxapyroxad is in Group 7 for fungicides resistance management. BAS 700 01 F Fungicide is a new fungicidal product with a new active ingredient proposed to complement current fungal control programs in barley.

Fluxapyroxad is currently registered for use in USA.

BAS 700 01 F Fungicide is new to the Australian market. The active fluxapyroxad as well as the end-use product will be manufactured overseas and imported into Australia.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of BAS 700 01 F Fungicide, and approval of the new active constituent, fluxapyroxad.

This submission has been assessed under a Global Joint Review (GJR) workshare arrangement where applications for registration for the same formulation and end-use have been submitted concurrently in Australia, Canada and USA.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

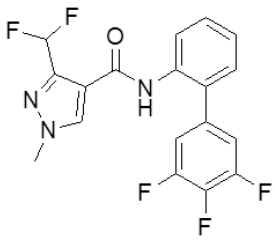
Fluxapyroxad is a new active constituent to be used as a fungicide in barley.

Manufacturing site

The active constituent fluxapyroxad is manufactured by BASF Corporation at its manufacturing site in Ludwigshafen, Germany.

Chemical Characteristics of the Active Constituent

The chemical active constituent fluxapyroxad has the following properties:

COMMON NAME (ISO):	Fluxapyroxad
IUPAC NAME:	3-(Difluoromethyl)-1-methyl-*N*-(3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1*H*-pyrazole-4-carboxamide
CAS NAME:	3-(Difluoromethyl)-1-methyl-*N*-(3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)- 1*H*-pyrazole-4-carboxamide
CAS REGISTRY NUMBER:	907204-31-3
MANUFACTURER'S CODE:	BAS Reg. No. 5094351; BAS 700F
MOLECULAR FORMULA:	$C_{18}H_{12}F_5N_3$
MOLECULAR WEIGHT:	381.31
STRUCTURE:	
CHEMICAL FAMILY:	Pyrazolecarboxamide

APVMA Active Constituent Standard for FLUXAPYROXAD

Constituent	Specification	Level
Fluxapyroxad	White to beige solid	970 g/kg minimum

Physical and Chemical Properties of Pure Active Constituent

PHYSICAL FORM:	Solid
COLOUR:	White to beige
ODOUR:	odourless
MELTING POINT:	156.8 °C (decomposition temp. *ca.* 230 °C)
DENSITY:	1.47 g/cm^3 (at 20 ºC)
UV ABSORPTION:	ε (L mol^{-1} cm^{-1}]) at pH 5.9: 44100 at 193 nm; 24010 at 230 nm; 978 at 290 nm.
PARTITION COEFFICIENT:	Log K_{OW}: 3.08 (deionized water); 3.09 at pH 4; 3.13 at pH 7; 3.09 at pH 9
VAPOUR PRESSURE:	2.7 x 10^{-9} Pa at 20°C and 8.1 x 10^{-9} Pa at 25°C
SOLUBILITY IN WATER:	At 20°C: 3.78 mg/L at pH 4.01; 3.88 mg/L at pH 5.84 (not buffered); 3.44 mg/L at pH 7.00 and 3.84 mg/L at pH 9.00.
SOLUBILITY IN ORGANIC SOLVENTS:	At 20 °C in g/L: acetone > 250; acetonitrile 167.6; dichloromethane 146.1; ethylacetate 123.3; methanol 53.4; toluene 20.0; octanol 4.69; heptane 0.106
STABILITY (TEMPERATURE, METALS AND METAL IONS):	Stable in the presence of metal and metal ions at normal and elevated temperature
STORAGE STABILITY:	Stable at ambient temperature

2.2 End use product

DISTINGUISHING NAME:	BAS 700 01F Fungicide
FORMULATION TYPE:	Emulsifiable Concentrate (EC)
ACTIVE CONSTITUENT CONCENTRATION:	Fluxapyroxad (62.5 g/L)

Physical and Chemical Properties of the Product

PHYSICAL FORM:	Liquid
COLOUR:	Red-brown
ODOUR:	Faint aromatic
SPECIFIC GRAVITY:	1.048 g/mL
PH (1% SOLUTION):	5.6 – 5.8
KINEMATIC VISCOSITY:	At 40 ^{o}C, 8.0x10^{-6} m^{2}s^{-1}
EXPLOSIVITY:	Not explosive
OXIDISING PROPERTIES:	Not oxidising
FLAMMABILITY:	Not highly flammable
STORAGE STABILITY:	Stability data provided by the applicant indicates that the product is expected to remain within specification for at least two years when stored under normal conditions in HDPE containers.
LOW TEMPERATURE STABILITY:	No visible separation in the product was observed after 7 days storage at 0°C.

Recommendation

Based on a review of the chemistry and manufacturing details provided by the applicant, registration of BAS 700 01F Fungicide is supported.

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

Public Health Aspects & Toxicology

BASF Australia Ltd along with their parent company BASF international have submitted a comprehensive toxicology and public health dataset for registration of the active constituent fluxapyroxad and associated product in the United States of America, Canada and Australia as part of a Global Joint Review. The toxicology assessment of fluxapyroxad was conducted jointly by scientists from Canada (PMRA), the United States (EPA) and Australia (OCS). The EPA was the primary reviewer with the PMRA and OCS as secondary reviewers.

Fluxapyroxad is a second generation carboxamide fungicide. The product, BAS 700 01 F fungicide an emulsifiable concentrate formulation containing 62.5 g/L fluxapyroxad), is a fungicidal agent that aids in the control of fungal diseases in barley. The product will be available in 5 L, 10 L and 20 L high-density polyethylene (HDPE) containers with a twist cap. Application rates are 250 - 1000 mL/ha in water to a spray volume of 50 to 100 L/ha for conventional ground boom operations and a minimum of 20 L/ha for aerial application (fixed of rotary winged aircraft). It is applied to crops up to twice per crop at an early growth stage (tilling) to no later than the emergence of the seed head.

The submitted studies on the active constituent in rats showed that it is rapidly and highly absorbed (approximately 80 %) by the oral route and excreted predominantly within three days after dosing. Fluxapyroxad is of low acute oral, dermal and inhalational toxicity in rats and is a slight skin irritant but not an eye irritant in rabbits, and is not a skin sensitiser in guinea pigs. The short-term toxicology studies showed effects on the liver in rats, mice and dogs leading to effects on thyroid hormone levels in rats. Long-term effects were similar to those of the short-term studies, with changes in liver enzymes leading to downstream effects on thyroid hormone balance. In addition to liver and thyroid effects, exposure to fluxapyroxad exposure also results in non-adverse changes in bone thickness and teeth coloration in rats and mice. These effects in the teeth and long bones (not the skull) suggested treatment-related changes in iron storage, but were not considered adverse because there was no evidence of microscopic damage to these tissues or clinical evidence of compromised tissue function.

There was no evidence of carcinogenic potential in male or female mice. In contrast, chronic exposure to fluxapyroxad in rats resulted in an increased incidence of hepatocellular adenomas, and adenomas and carcinomas combined in both sexes, and thyroid adenomas and carcinomas in males only. However, OCS considers that the observed liver and thyroid tumours in rats are of limited relevance to humans. Consequently, OCS considers that fluxapyroxad is not a hazard for carcinogenicity in humans.

Fluxapyroxad was not mutagenic and/or genotoxic *in vitro* and *in vivo*, not a reproductive toxicant in rats or teratogenic in rats and rabbits. OCS considers that the observed transient clinical effects of fluxapyroxad in an acute neurotoxicity rat study are an indication of a neuropharmacology effect rather than an indication of neuronal damage. Thus, fluxapyroxad is not considered to be a neurotoxicant. Furthermore, fluxapyroxad did not produce immunotoxic effects in mice.

The product BASF 700 01F fungicide is of low acute oral, dermal and inhalational toxicity in rats, is a slight skin irritant and a severe eye irritant in rabbits and is not a skin sensitiser in guinea pigs.

Occupational Health and Safety

The main occupational use of the imported product will be by farmers and their workers. 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 will be dermal with inhalation exposure from the spray 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. Exposure to the product during ground boom spray and aerial applications were at an acceptable level when a single layer of clothing (cotton overalls or equivalent clothing) was worn for application and chemical resistant gloves are additionally worn during mixing and loading.

Based on the risk assessment, a First Aid Instruction, a Warning Statement, Safety Directions and a Re-entry statement have been recommended for the product label.

Conclusion

Based on an assessment of the toxicology, it was considered that there should be no adverse effects on human health from the use of BASF 700 01F fungicide when used in accordance with the label directions.

3.2 Evaluation of toxicology

The toxicological database for fluxapyroxad, which consists primarily of toxicity studies conducted in rats, mice, rabbits and dogs, is considered sufficient to determine the toxicology profile of fluxapyroxad 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-Adverse-Effect-Level (NOAEL) 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 fluxapyroxad 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 international assessment collaboration between the agency partners, the OCS has adopted the no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) approach with scientific justification for the adoption of these NOAEL/LOAEL positions.

Chemical class

Fluxapyroxad is a second generation carboxamide fungicide. The mode of pesticidal action is inhibition of succinate dehydrogenase in complex II of the mitochondrial respiratory chain, resulting in inhibition of spore germination, germ tubes, and mycelial growth. Fluxapyroxad is taken up by plants, where it is widely distributed and metabolised.

Toxicokinetics/metabolism

Pharmacokinetic and metabolism studies with radiolabeled fluxapyroxad in rats show that plasma levels of radiolabel scaled with dose, indicating that uptake was not saturated up to dose levels of 500 mg/kg. There were no sex differences observed in the rate or extent of absorption in rats. The time to maximum plasma levels was dependent upon on dose, and ranged from 1 hour (at 5 mg/kg bw) to 24 hours (at 500 mg/kg bw). Radioactivity was widely distributed in both sexes with a similar pattern: the highest concentrations were found in the gut contents and stomach contents. However, lower concentrations were found in numerous other organs/tissues, including the liver, thyroid, adrenal glands, kidney, pancreas, testes/uterus, and brain. For both male and female rats, radioactivity declined in all tissues over time. The time course of the amount of radioactivity found in urine and faeces indicated the excretion occurred predominantly within three days after dosing. Bile duct cannulation experiments in the rat showed that the bile was a major route of excretion. The main biotransformation steps of fluxapyroxad in rats are hydroxylation at the biphenyl ring system, N-demethylation at the pyrazole ring system, loss of a fluorine atom at the biphenyl ring system, and conjugation with glucuronic acid or with glutathione derivatives.

A dermal absorption factor of 8.4% from an *in vivo* rat study was identified for use for the exposure estimation in the Occupational Health & Safety assessment.

Acute toxicity studies

Fluxapyroxad is of low acute toxicity by the oral (LD_{50} > 2000 mg/kg bw), dermal (LD_{50} > 2000 mg/kg bw) and inhalational route (4-h LC_{50} > 5100 mg/m^3) in rats, is a slight skin irritant but not an eye irritant in rabbits, and is not a skin sensitiser in guinea pigs.

The formulated product BASF 700 01F is of low acute oral (LD_{50} > 2000 mg/kg bw), dermal (LD_{50} > 5000 mg/kg bw) and inhalational toxicity (4-h LC_{50} > 5070 mg/m^3) in rats, is a slight skin irritant and severe eye irritant in rabbits, and is not a skin sensitiser in guinea pigs.

Systemic effects

The primary target organ for fluxapyroxad exposure via the oral route is the liver. Liver toxicity in response to fluxapyroxad was observed in several species with species differences in the sensitivity, development, and manifestations of liver toxicity. In rats only, changes in liver metabolism resulted in secondary toxicity in the thyroid. This toxicity was thyroid hormone dysregulation leading to thyroid follicular hypertrophy and hyperplasia.

The sensitivity to liver toxicity and the development and manifestations of liver toxicity over time varied with species. In rats, adaptive effects of hepatocellular hypertrophy and increased liver weights and changes in liver metabolism were first observed. As the dose or duration of exposure to fluxapyroxad increased, clinical chemistry changes related to liver function were observed, followed by hepatocellular necrosis, which was considered a clearly adverse effect. Liver toxicity was also observed in mice and dogs. In subchronic studies in mice, increased liver weights were observed along with fatty changes in the liver, with few observations of hepatocellular hypertrophy. At higher doses, liver necrosis was also observed. Higher

doses were required to achieve adverse liver effects in the mouse than in the rat. Liver effects in subchronic studies in dogs were limited to increased liver weight at high doses. However, in chronic studies, increased liver weights were observed in conjunction with fibrosis and cirrhosis at doses greater than those that caused adverse liver effects in rats and mice.

Fluxapyroxad administration via the oral route results in toxic effects in the thyroid. These thyroid effects occur secondary to the effects on the liver and are observed only in rats. Thyroid effects in rats were observed throughout the toxicity database and included changes in serum thyroid hormone levels, enlarged thyroid, increased thyroid weights, and/or microscopic effects of thyroid follicular hypertrophy and hyperplasia,. These effects showed a clear threshold, were evident within weeks and were observed out to two years. Although these effects were observed in male and female rats, males were usually more sensitive. Threshold doses at which thyroid effects occurred in the rat were accompanied by changes in the liver that were considered adaptive or potentially adverse. These changes included increased liver weights, hepatocellular hypertrophy, and changes in liver-associated clinical chemistry parameters. These results suggested that the effects in the thyroid were secondary to fluxapyroxad-induced changes in thyroid hormone metabolism by the liver and are not due to direct action of fluxapyroxad on the thyroid.

Supplementary, mechanistic studies were provided to characterize the effects of fluxapyroxad on the thyroid. A perchlorate discharge assay showed that fluxapyroxad treatment resulted in increased uptake of radiolabeled iodine by the thyroid similar to that observed with phenobarbital. (Phenobarbital is a hepatic enzyme inducer that is known to increase thyroid hormone clearance by the liver, resulting in indirect stimulation of thyroid hormone synthesis via a compensatory stimulation of the thyroid gland). Other mechanistic studies showed that fluxapyroxad caused increased liver weights and induction of Phase I and Phase II metabolizing enzymes similar to phenobarbital. T_4-metaboilizing Phase II enzymes in particular were induced by fluxapyroxad at doses lower than those that cause increased serum levels of TSH, decreased serum levels of T_4 and thyroid follicular hypertrophy and hyperplasia. The effects of fluxapyroxad on the thyroid were also shown to be reversible following discontinuation of treatment with fluxapyroxad. The OCS considers these supplementary studies sufficient to conclude that the thyroid effects observed in rats after treatment with fluxapyroxad are secondary to fluxapyroxad-induced increases in metabolizing enzymes. This increased metabolic activity of the liver resulted in increased metabolism of T_4. The decrease in circulating levels of T_4 leading to a compensatory increase in TSH, which leads to increased thyroid hormone synthesis and thyroid follicular hypertrophy and hyperplasia.

Although the effects of fluxapyroxad on the thyroid were demonstratively reversible and are secondary to changes in the liver, the OCS considers them adverse. The most sensitive of these thyroid effects are perturbations in thyroid hormone levels, which occur temporally before histopathological alternations in the thyroid. The OCS considers thyroid hormone perturbations adverse due to the important role of thyroid hormone in regulating cellular growth and metabolism, and the known disease states (hyper- and hypo-thyroidism) that result from these perturbations.

In addition to liver and thyroid effects, fluxapyroxad exposure also results in non-adverse changes in bone thickness and teeth coloration. This unusual effect of tooth whitening was observed in rats and mice in several studies. This effect was observed with increasing oral doses of fluxapyroxad. This was likely due to decreased deposition of a yellow iron-containing pigment in the "outer outer enamel” layer of the teeth. Bone thickening and white discoloration of the skull bones were also observed, as was increased deposition of Perl’s Prussian Blue stain (indicative of iron) in other bone tissues. These effects in the teeth and long bones (not the skull) suggested treatment-related changes in iron storage, but were not considered adverse because there was no evidence of microscopic damage to these tissues or clinical evidence of compromised

tissue function.
No toxic effects of fluxapyroxad were observed at doses up to and including the limit dose in a rat dermal 28-day study.

Carcinogenicity & Genotoxicity

Chronic exposure to fluxapyroxad in rats resulted in an increased incidence of hepatocellular adenomas, and adenomas and carcinomas combined in both sexes and thyroid carcinomas in males only. There was no evidence of carcinogenic potential in male or female mice. Additionally, no evidence of mutations or chromosomal damage were observed in a panel of guideline *in vitro* assays, and no evidence of chromosomal damage was observed in a guideline mouse erythrocyte micronucleus study *in vivo*. Together, these data indicated that the thyroid and liver tumours observed in rats were due to non-genotoxic and/or species-related factors and not due to genotoxic effects.

The liver tumours caused in both sexes by fluxapyroxad were adenomas with an increase in the incidence of carcinomas seen in high dose males, and the combined incidence of adenomas and carcinomas was also higher. These tumours were observed after two years of fluxapyroxad administration only, and were not observed in the interim (one year) sacrifice animals. A supplemental study investigating DNA repair showed no evidence of increased DNA repair, which was measured as unscheduled DNA synthesis in the liver after oral administration to rats, providing further evidence that fluxapyroxad caused liver tumours by a non-genotoxic mode of action. Additional, supplemental studies showed increased cell proliferation in the liver within one week of administration to rats, followed by increased liver weights and hepatocellular hypertrophy over time. These effects displayed a clear threshold and were reversible.

Mechanistic studies demonstrated a non-genotoxic mitogenic mode of action for liver tumour formation is operative in rats, whereby fluxapyroxad causes increased cell proliferation leading to adenoma formation with a clear threshold for these effects. Furthermore, key events in the fluxapyroxad liver tumour formation (e.g. enzyme induction, hepatocellular hypertrophy, increased liver weight and non-neoplastic alterations) were similar to those for phenobarbital for which no clear relationship between phenobarbital exposure and hepatotumourgenesis in humans has been established. Consequently, taking a conservative approach the relevance of these tumours to humans is equivocal at best. Therefore, OCS considers that the observed liver tumours in rats are of limited relevance to humans.

Thyroid tumours were observed in male rats only after two years of fluxapyroxad administration. Thyroid tumours were characterised as thyroid follicular adenomas and carcinomas, with a higher incidence of adenomas. These tumours were accompanied by an increased incidence of thyroid follicular hypertrophy and hyperplasia in males. Interim sacrifice data at one year also showed increased thyroid follicular hypertrophy and hyperplasia in males only with no increased incidence of thyroid tumours, indicating that sustained hypertrophy and hyperplasia are required for the development of thyroid adenomas and carcinomas. This information, together with other mechanistic studies showing that perturbations in thyroid hormone levels (e.g. increased TSH and decreased T4 levels) and thyroid follicular hypertrophy and hyperplasia were reversible following discontinuation of fluxapyroxad treatment, support a non-genotoxic mode of action. On the basis of this information, the OCS concludes that these thyroid effects in males are non-genotoxic with a clear threshold. The MOA is consistent with the known increased susceptibility of the male rat to sustained alterations in thyroid hormone homeostasis and resulting tumourgenesis which is of limited relevance to humans. Consequently, OCS considers that the observed thyroid tumours in male rats are of limited relevance to humans.

Therefore, OCS considers that fluxapyroxad is not a hazard for carcinogenicity in humans.

Reproductive & Developmental toxicity

Oral administration of fluxapyroxad did not cause reproductive effects in rats or malformations or variations in rats or rabbits. Toxic effects in offspring in response to fluxapyroxad were limited to decreased pup body weights and body weight development in rats at doses that caused maternal thyroid effects and are considered a secondary non-specific consequence of such. Therefore, the available data indicates fluxapyroxad is not a reproductive or developmental toxicant.

Neurotoxicity

Decreased rearing (in males only) and decreased motor activity were observed in both sexes after bolus dosing via oral gavage in the acute neurotoxicity study. However, there was no evidence of histopathological effects or alterations in brain weights. These effects were observed on the day of dosing only and no evidence of neurotoxicity was observed in the short-term dietary neurotoxicity study or elsewhere in the toxicity database. Therefore, OCS considers that the observed transient clinical effects of fluxapyroxad are an indication of a neuropharmacology effect rather than an indication of neuronal damage.

Immunotoxicity

Immunotoxicity was investigated via the oral route in male mice. No immunotoxic effects of fluxapyroxad were observed at doses up to and including the limit dose.

Studies on impurities

The production of fluxapyroxad results in three impurities. *In vitro* mutagenicity and genotoxicity studies with and without metabolic activation and an *in vivo* genotoxicity study were submitted for each of these impurities. No evidence of mutagenicity and/or genotoxicity was observed in these studies.

Studies on metabolites

There are three metabolites of fluxapyroxad: two soil metabolites (M700F001 and M700F002) and a metabolite found on food crops (M700F048). There was no evidence of mutagenicity and/or genotoxicity *in vitro* (with and without metabolic activation) and *in vivo* in response to M700F001 or M700F002, and no adverse responses to either of these metabolites were observed in sub-chronic dietary studies at doses up to the limit dose. Additionally, prenatal development studies in rabbits showed no maternal or offspring toxicity with M700F001 up to and including the highest dose of 250 mg/kg bw/day. While for M700F002, maternal toxicity was manifested as increased mortality and abortions at the limit dose, with no toxic effects seen in offspring.

No evidence of mutagenicity was observed *in vitro* for the food crop metabolite, M700F048, with and without metabolic activation. A single positive response in an *in vitro* chromosomal aberration study was seen with metabolic activation only but was not expressed in the follow-up mouse *in vivo* micronucleus study. Additionally, no unscheduled DNA synthesis was seen *in vivo* with M700F048. Toxic effects in a 28-day dietary study were limited to decreased absolute and relative monocyte counts in males only which was considered potentially adverse. A prenatal developmental toxicity study in rabbits showed maternal toxicity at the high dose of 100 mg/kg bw/day, which was manifested as mortality, abortions, and resorptions, with no toxic effects in offspring up to and including the highest dose tested. Metabolism and pharmacokinetic studies indicated that M700F048 was rapidly absorbed and excreted, primarily via the faeces.

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 fluxapyroxad. Fluxapyroxad was discussed at the October 2011 meeting of the ACCS. The delegate noted and agreed with the ACCS recommendation that fluxapyroxad be included in Schedule 5 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) with no cut-off. This was the interim decision of the delegate. The delegate's finals decision made on 1st February 2012 confirmed that fluxapyroxad be included in Schedule 5 of the SUSMP with no cut-off, along with an implementation date of 1 May 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 NOAEL 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 fluxapyroxad based on chronic toxicity studies in rats and mice is liver and thyroid toxicity. Rats appeared to be the most sensitive species for fluxapyroxad with an increase in non-neoplastic changes in the liver (both sexes), along with an increased incidence in hepatocellular adenomas (males) that are considered of limited relevance to humans, observed at 11and 14 mg/kg bw/d (M/F). The corresponding NOAEL was 2.1 and 2.7 mg/kg bw/d (M/F).

A 100-fold safety factor, consisting of factors of 10 for intraspecies and interspecies variation, was considered appropriate for fluxapyroxad. The toxicological database for fluxapyroxad included several long-term oral studies and carcinogenicity studies in the mouse and rat, and was considered complete. Additionally, since no sensitive population groups were identified during the course of this evaluation no additional safety factor is required for such at this time. Therefore, a safety factor of 100-fold was applied to the most sensitive NOAEL for the determination of an ADI value.

Thus, considering the observed effects of fluxapyroxad on the liver (the most sensitive end-point), an ADI value of 0.02 mg/kg bw/d is recommended, based on a NOAEL of 2.1 mg/kg bw/d in a 2-year oral study in rats and using a 100-fold safety factor.

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 NOEL as a single or short-term dose which causes no effect in the most sensitive species of experimental animal tested, together with a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

An acute reference dose (ARfD) has not been established for fluxapyroxad since no significant treatment related findings have been observed in the experimental animal database evaluated following a single dose administration of fluxapyroxad, which would be likely to present an acute hazard to humans.

4 RESIDUES ASSESSMENT

4.1 Introduction

BAS 700 01 F Fungicide contains the new active constituent fluxapyroxad (figure 1) and is proposed for use to control various fungal diseases in barley. As part of the residues assessment for fluxapyroxad, plant and animal metabolism studies, supervised residue trials and trade aspects were considered.

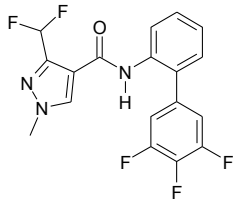


Figure 1: Fluxapyroxad

4.2 Metabolism

Plants

The metabolism of fluxapyroxad was investigated in soybean, tomato and wheat.

Soybean

Aniline or pyrazole labelled fluxapyroxad was applied foliarly to soybeans 3 times at a rate of 60 g ai/ha. Applications were made at BBCH 16/17, 51-59 and 71-75. Samples of soybean forage were taken after the first application (0 days after treatment; DAT) and immediately before the third application (21 days after the first treatment; 14 days after the second treatment). Soybean hay, straw, hull and seed were harvested at BBCH 89, approximately a month after the third application.

The TRRs in forage sampled directly after the first treatment (0 DAT) were 6.413 mg equiv/kg and 4.368 mg equiv/kg (aniline and pyrazole label, respectively). Directly before the last application (21 DAT), the TRRs in forage were 5.091 mg equiv/kg and 4.665 mg equiv/kg. The highest levels of TRRs were found in soybean hay (22-34 DALA), amounting to 61.238 mg equiv/kg for the aniline label and 54.294 mg equiv/kg for the pyrazole label. In soybean straw (34 DALA), residue levels of 1.006 mg equiv/kg and 0.837 mg equiv/kg were found, and soybean hull contained 2.737 mg equiv/kg and 2.237 mg equiv/kg (aniline and pyrazole label, respectively). In soybean seed, the TRR was much lower, at 0.115 mg equiv/kg (aniline label) and 0.260 mg equiv/kg (pyrazole label), respectively.

In general, the extractability of the radioactive residues with methanol and water was high for soybean forage, hay and straw (>93% of the TRRs) and only slightly lower for hull and seed (>77% of the TRRs).

BAS 700 F (parent) represented the main component of the total residue in all soybean matrices (53.9-97.7% of the TRRs) except for seed (7.4-21.2% of the TRRs). The main transformation product in seed was the metabolite M700F002 (33.4% of the TRRs) resulting from cleavage of BAS 700 F and thus only detectable with the pyrazole label. This metabolite was also found in hulls (2.0% of the TRRs).

Tomatoes
Aniline or pyrazole labelled fluxapyroxad was applied foliarly to tomatoes 3 times at a rate of 100 g ai/ha. Applications took place 17, 10 and 3 days before harvest (55, 62 and 69 days after planting). Ripe tomato fruit were sampled 3 days after the last treatment. Other green parts of the plants (stem, panicles and leaves – referred to as tomato leaves) were also sampled.

TRRs of 6.703 mg equiv/kg (aniline label) and 4.456 mg equiv/kg (pyrazole label) were found in tomato leaves, and TRRs of 0.166 mg equiv/kg (aniline label) and 0.112 mg equiv/kg (pyrazole label) were found in tomato fruits.

The extractability of radioactive residues with methanol and water was >98% of the TRRs in tomato leaves and fruits.

BAS 700 F (parent) was the only compound observed at levels >10% of the TRRs in tomato matrices, amounting to >94% of the TRRs in tomato fruits and >90% of the TRRs in tomato leaves.

Wheat
Aniline or pyrazole labelled fluxapyroxad was applied foliarly to wheat twice at a rate of 125 g ai/ha. Applications were made at BBCH 30/35 and 69. Wheat forage samples were collected 36 days after the first application at BBCH 59. Wheat hay was sampled at 4 DALA (BBCH 73-75); straw, chaff and grain samples were collected at 34 and 35 DALA for the aniline and pyrazole label, respectively (BBCH 89).

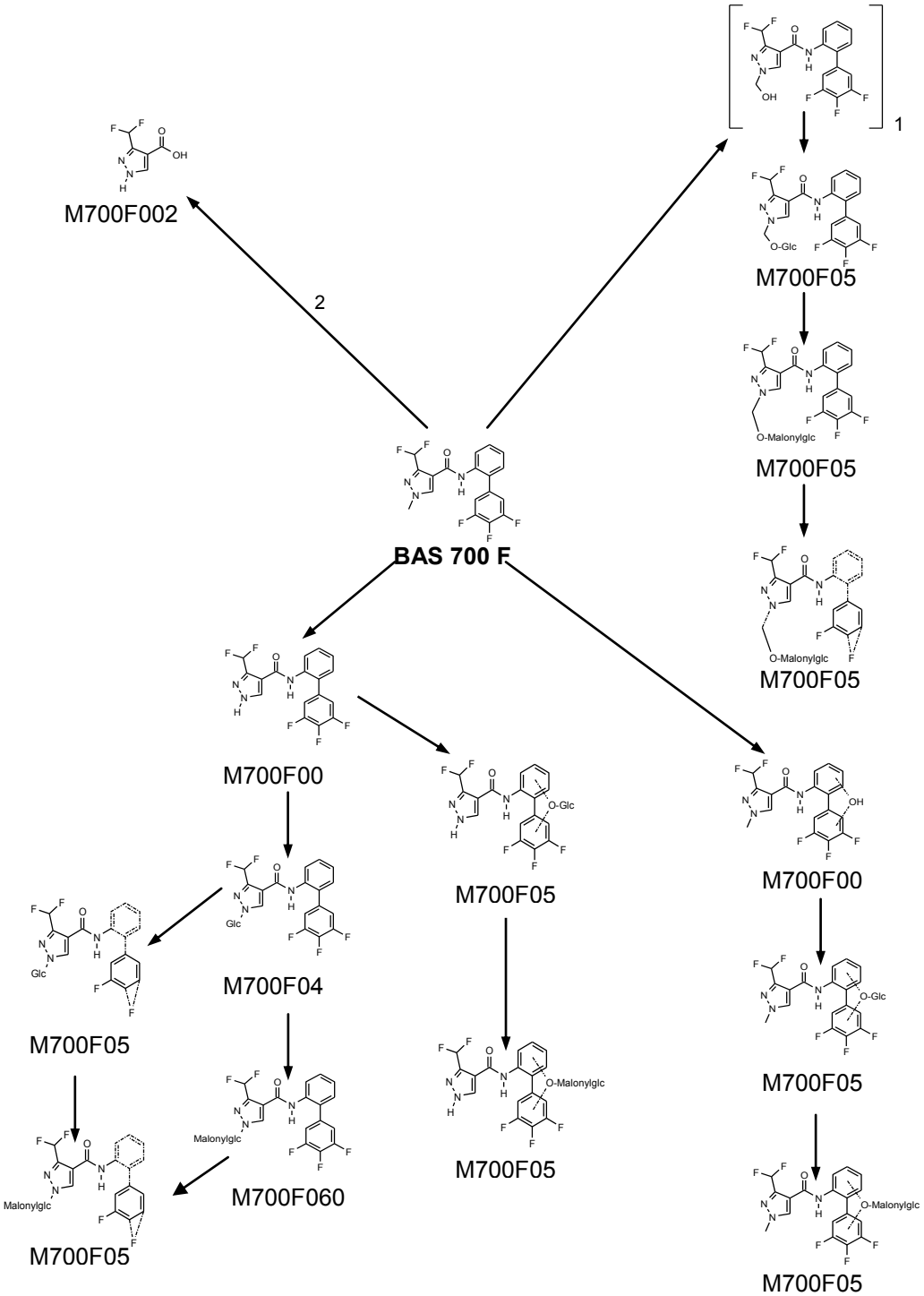
The TRRs in wheat forage (BBCH 59; 36 days after the first application) were 0.885 mg equiv/kg for the aniline label and 1.057 mg equiv/kg for the pyrazole label. In wheat hay (BBCH 73-75; 4 DALA), TRR levels of 10.211 mg equiv/kg for the aniline label and 10.318 mg equiv/kg for the pyrazole label were found. The TRRs in wheat straw at harvest (BBCH 89) were 19.291 mg equiv/kg for the aniline label (34 DALA) and 17.398 mg equiv/kg for the pyrazole label (35 DALA). In wheat chaff, TRRs of 6.733 mg equiv/kg for the aniline label (34 DALA) and 7.396 mg equiv/kg for the pyrazole label (35 DALA) were detected. The TRRs in wheat grain were 0.045 mg equiv/kg for the aniline label (34 DALA) and 0.057 mg equiv/kg for the pyrazole label (35 DALA).

The extractability of the radioactive residues with methanol and water was 87.7-97.7% for wheat forage, hay, straw and chaff, and 75.5-84.6% for wheat grain.

BAS 700 F (parent) was the only compound observed at levels >10% of the TRRs in wheat matrices, amounting to 60.2% to 91.3% of the TRRs.

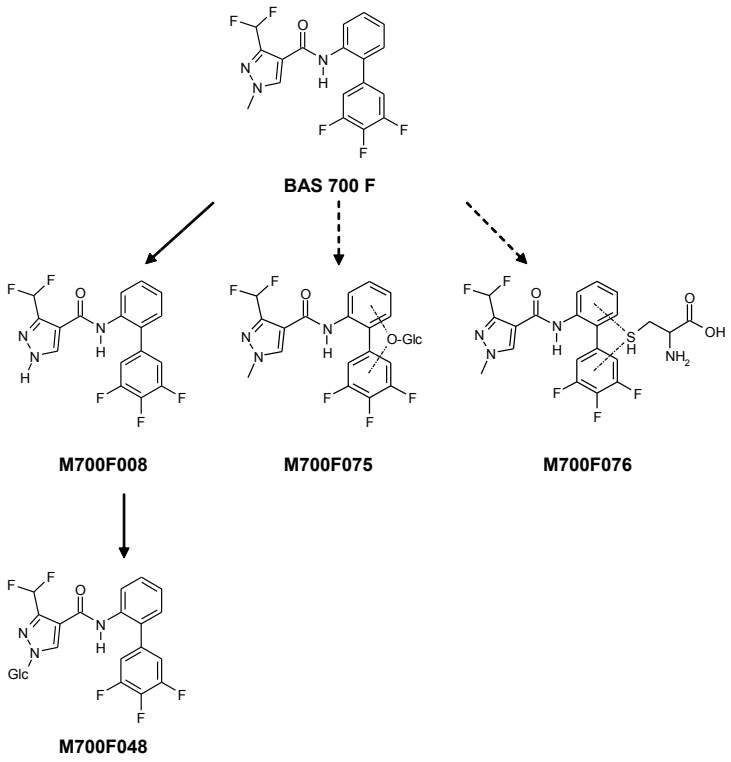
Summary of plant metabolism

In plants fluxapyroxad is metabolised mainly by N-demethylation of the pyrazole moiety, hydroxylation of the biphenyl moiety and subsequent O- and N-conjugation reactions (with glucose and/or malonic acid). Additional metabolites resulted from minor transformation reactions. Low amounts of cleavage products known to be formed in the soil were detected in some instances for the pyrazole label. As cleavage products were not detected for the aniline label it is possible these metabolites were formed in the soil and subsequently taken up by the plant. Proposed metabolic pathways for fluxapyroxad in soybeans, tomatoes and wheat are summarised in Figures 2, 3 and 4 respectively.



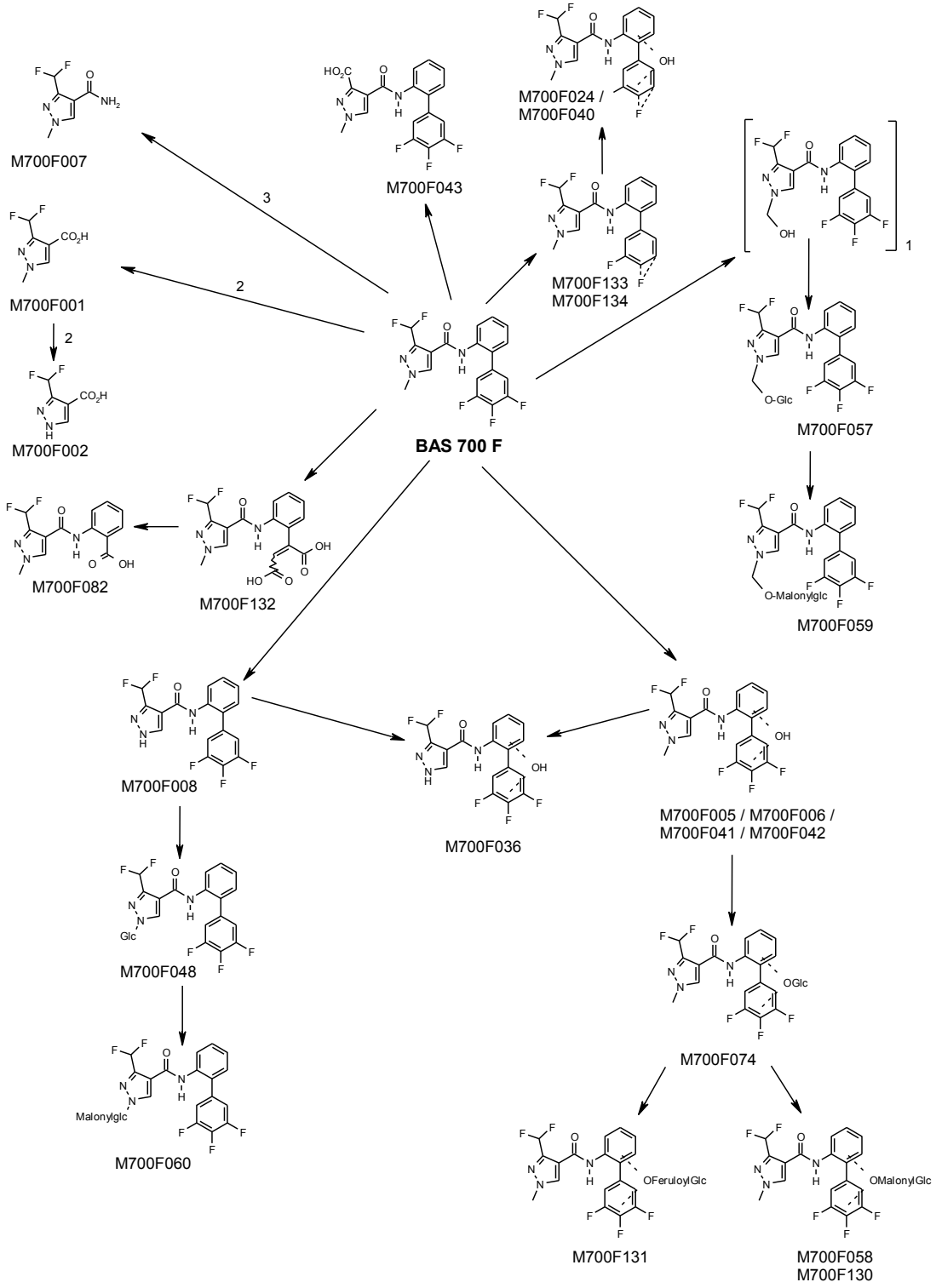
[1] Proposed intermediate
[2] Transformation steps proposed to occur in soil

Figure 2: Proposed metabolic pathways of BAS 700 F (fluxapyroxad) in soybeans.



Dotted arrows: putative routes

Figure 3: Proposed metabolic pathways of BAS 700 F (fluxapyroxad) in tomatoes



[1] Proposed intermediate
[2] Transformation steps proposed to occur in soil
[3] Known from irradiated water sediment study

Figure 4: Proposed metabolic pathways of BAS 700 F (fluxapyroxad) in wheat.

Confined rotational crops

Aniline label
Metabolism of BAS 700F was investigated in three representative succeeding crops, spinach (leafy vegetable), radish (root vegetable) and wheat (cereal grain). The study was performed with the test substance labelled in the aniline ring applied to bare soil, at a rate of 250 g a.i./ha, followed by soil aging intervals of 30, 120 and 365 days.

At all three replant intervals, significant translocation of radioactivity from soil into plant was observed, with radioactive residues in wheat straw up to 2.65 mg equiv/kg and in spinach up to 0.10 mg equiv/kg. Lower residues were observed in radish roots (maximum of 0.015 mg equiv/kg) and wheat grain (maximum of 0.020 mg equiv/kg).

The extractability of the radioactive residues with methanol and water was high for all matrices (77-98% of the TRRs), except for spring wheat grain (49-60% of the TRRs). In most cases, the major part of the radioactive residues was extracted with methanol.

No metabolites specific to rotational crops were found. As in foliar-treated plants, BAS 700F was the main component of the residue (8.5-85% of the TRR). The main metabolite in rotational immature spinach (30 DAT and 120 DAT) was the biphenyl-hydroxylated derivative M700F042 (15 and 25% of the TRR) which is conjugated to O-glucoside as M700F074 and the respective malonylglucoside as M700F058. The latter two conjugated metabolites are the main conversion products found in immature spinach (365 PBI, 10-13% TRR) and in mature spinach of all PBIs (11-18% TRR). The main metabolite in rotational immature white radish plant and mature white radish root was the demethylated derivative M700F008 (up to 38% TRR), accompanied by metabolites M700F048 (N-glucoside) and M700F057 (O-glucoside of the N-methyl group at the pyrazole ring) at lower concentrations. In mature white radish top, the metabolites M700F036 (demethylated and hydroxylated), M700F059 (malonylated derivative of M700F057) and M700F074 (biphenyl-O-glucoside) were additionally found in significant portions. The main biotransformation product in spring wheat was the demethylated metabolite M700F008 (up to 10% TRR).

Pyrazole label
Metabolism of BAS 700F labeled in the pyrazole ring was investigated in three representative succeeding crops: spinach (leafy vegetable), radish (root vegetable) and wheat (cereal grain). The test substance was applied to bare soil, at a rate of 250 g a.i./ha, followed by soil aging intervals of 30, 149 and 365 days.

At all three PBIs, significant translocation of radioactivity from soil into plant was observed, with radioactive residues in wheat straw up to 2.2 mg equiv/kg, and in spinach up to 0.18 mg equiv/kg. Lower residues were observed in radish roots (maximum of 0.014 mg equiv/kg) and wheat grain (maximum of 0.043 mg equiv/kg).

The main components in mature and immature spinach leaves were BAS 700 F (10-15% TRR) and the cleavage product M700F002 (23-62% TRR). In immature white radish plant and mature white radish tops, the most abundant components were BAS 700 F (13-31% TRR) and the metabolites M700F008 (7-18% TRR) and M700F002 (10-61% TRR). In mature white radish roots, BAS 700 F (39-69% TRR) and the metabolite M700F008 (12-29% TRR) were the main components. In wheat forage, straw, chaff and grain,

BAS 700 F was the most abundant component (6-76% TRR). The O-glucoside M700F074 was detected in wheat forage (149 PBI only, up to 21% TRR), and other components were present in wheat matrices in low amounts (≤10% of the TRRs).

As for the aniline labelled study, the metabolite pattern was similar to that identified for primary crops. No compounds specific for rotational crops were found. In contrast to the aniline study, two metabolites resulting from cleavage of the carboxamide bond of BAS 700 F were identified: the pyrazole acid M700F001 and its demethylation product M700F002. As both were identified as metabolites in soil metabolism studies with BAS 700 F, it is assumed they are generated by cleavage in the soil and subsequently taken up by the plant rather than being generated by cleavage within the plant.

Animals

The metabolism of fluxapyroxad (BAS 700 F) was investigated in lactating goats using BAS 700 F radiolabelled either in the aniline or the pyrazole ring, and in laying hens using BAS 700 F radiolabelled in the aniline ring only.

Lactating goats

Fluxapyroxad labelled in the aniline or pyrazole ring was orally administered by gavage to lactating goats at a level of 12 mg/kg feed for 8 consecutive days. Milk was sampled twice daily (in the morning before administration of the test substance and in the afternoon). Animals were sacrificed approximately 24 hours after the last dose. Samples of liver, kidney, leg-chest muscle and fat (kidney fat and intraperitoneal fat) were harvested.

Overall, ≥80% of the total administered dose was eliminated in excreta. In milk, 0.09-0.10% of the administered dose was detected (0.011-0.017 mg equiv/kg), with a plateau reached within 24 hours after administration. Tissues and organs retained <0.4% of the administered dose (0.007-0.009 mg equiv/kg in muscle, 0.021-0.025 mg equiv/kg in fat, 0.036-0.078 mg equiv/kg in kidney and 0.348-0.555 mg equiv/kg in liver). The extractability of the radioactive residues was ≥79% for all tissues other than liver. In liver, extractability was 30.3-34.2%. A major proportion of the residual radioactive residues (polar components) was released from extracted liver tissue after incubation with protease.

BAS 700 F (parent) represented one of the major residues in milk (13.0-19.8% of the TRRs), muscle (12.0%, aniline label only) and fat (34.1-43.6% of the TRRs), while accounting for minor proportions in liver and kidney (3.2-7.0% of the TRRs). The other predominant compound was the desmethyl metabolite M700F008, representing a main proportion in milk (23.9-25.4% of the TRRs), muscle (54.7-82.9% of the TRRs), fat (25.8-25.9% of the TRRs), liver (12.8-16.7% of the TRRs) and kidney (22.5-25.6% of the TRRs). Further metabolites at >10% of the TRRs were detected in milk, kidney and fat. In milk, the metabolite M700F010 was found at levels of 12.3-15.0% of the TRRs (≤0.0025 mg/kg). The metabolite M700F005 was present in fat at 13.7% of the TRRs (0.0034 mg/kg) and in kidney at 19.2% of the TRRs (0.015 mg/kg), with pyrazole label only. The metabolite M700F004 was present in kidney at levels of 12.3-13.1% of the TRRs (≤0.010 mg/kg).

BAS 700 F was metabolized *via* two main transformation reactions (Figure 5), N-demethylation of the pyrazole moiety and hydroxylation of the biphenyl moiety. These reactions, occuring also in combination, followed by conjugation with glucuronic acid, led to the main metabolites. Several minor metabolic routes, i.e. hydroxylation at the pyrazole ring, conversion of the pyrazole CHF_2 group into a carboxy group, N-glucuronidation of the desmethyl metabolite and removal of an aromatic fluorine substituent, led to a range of minor components.

Goat metabolism studies were also conducted with plant metabolites M700F002 (observed in soybean seed and confined rotational crop study) and M700F048. For the first study, M700F002 was the only radioactive component detected in the matrices analyzed, indicating that M700F002 is not significantly transformed in goats. M700F048 follows the same route of metabolism as fluxapyroxad. Both fluxapyroxad and M700F048 are degraded to the common metabolite M700F008 followed by hydroxylation of the biphenyl moiety and conjugation steps.

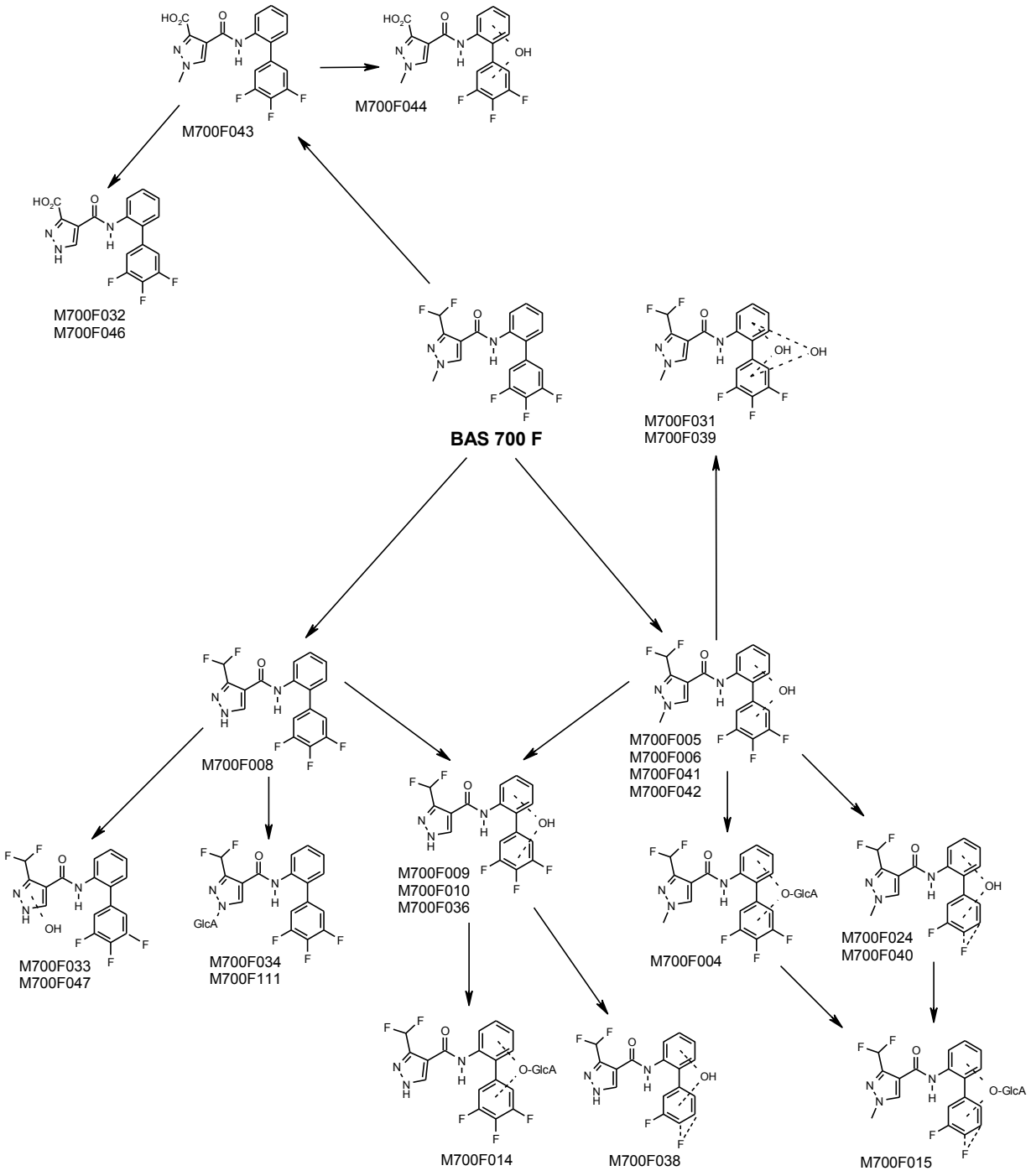


Figure 5: Proposed metabolic pathways for BAS 700 (fluxapyroxad) in lactating goats.

Laying hens

The poultry metabolism study was only conducted with BAS 700 F labelled in the aniline ring. Guidelines state that separate studies reflecting labelling of each ring or sidechain are usually required. The current approach was deemed acceptable given that goat and rat metabolism studies carried out separately with two labels (U-^{14}C-aniline and 4-^{14}C-pyrazole) were provided, which demonstrated that the metabolic pathways of

BAS 700 F in rat and livestock were similar and there was no cleavage of the carboxamide bond in the goat and no significant cleavage in the rat.

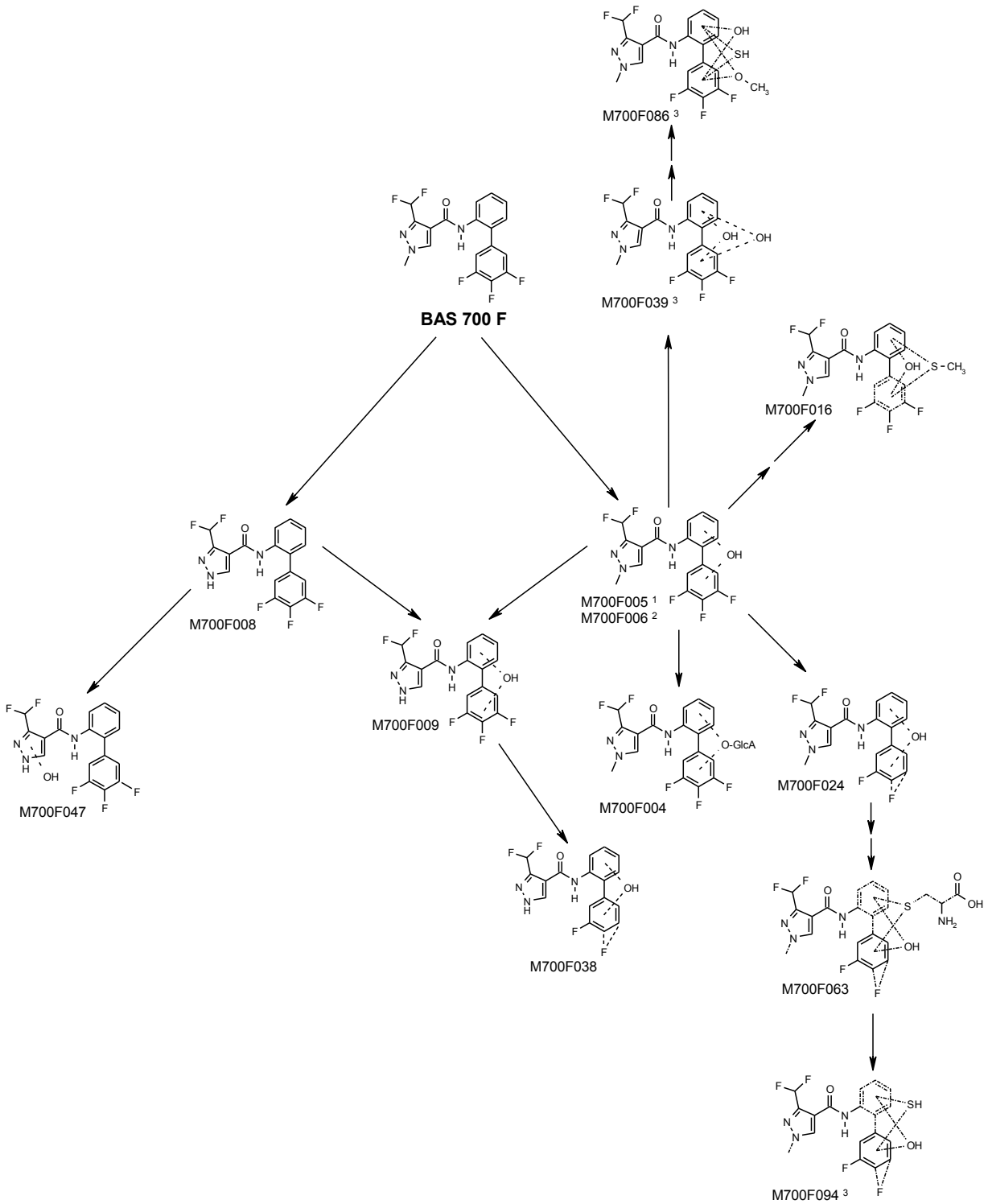
Fluxapyroxad labelled in the aniline ring was orally administered by gavage to 12 laying hens at a level of 12 mg/kg feed for 12 consecutive days. Eggs were collected twice daily (in the afternoon after administration of the test substance and the morning before subsequent administration). Animals were sacrificed approximately 23 hours after the last dose. Samples of liver, muscle (leg) and fat were collected.

Overall, ≥86% of the total administered dose was eliminated in excreta. In eggs, 0.18% of the administered dose was detected (0.004-0.079 mg equiv/kg), with a plateau reached at Day 9 of the application period. Tissues and organs (with the exception of the GI tract) retained <0.5% of the administered dose (0.010 mg equiv/kg in leg muscle, 0.059 mg equiv/kg in fat and 0.210 mg equiv/kg in liver). The extractability of the radioactive residues was ≥79% for all tissues other than liver. In liver, extractability was 68%. A significant proportion of the residual radioactive residues were released from extracted liver tissue after incubation with protease.

BAS 700 F represented one of the major residues in excreta (7.5% of the TRRs, 0.271 mg/kg), egg (13.5% of the TRRs, 0.009 mg/kg), leg muscle (17.6% of the TRRs, 0.0011 mg/kg), fat (63.3% of the TRRs, 0.023 mg/kg), and was observed in minor amounts in liver (1.0% of the TRRs, 0.002 mg/kg). The other predominant compound was the desmethyl metabolite M700F008, representing a main proportion in egg (49.9% of the TRRs, 0.033 mg/kg), leg muscle (together with M700F016 amounting to 25.7% of the TRRs, 0.0016 mg/kg), and fat (25.3% of the TRRs, 0.009 mg/kg). M700F008 was detected at minor amounts (<7%) in excreta (0.228 mg/kg) and liver (0.009 mg/kg).

The metabolism of BAS 700 F in laying hens (Figure 6) mainly proceeds via hydroxylation at the biphenyl moiety, loss of a fluorine atom at the biphenyl ring (presumably by substitution with a hydroxyl-group), conjugation of the hydroxyl groups with glucuronic acid, and demethylation at the pyrazole ring. Additionally, conjugates with glutathione derivatives were identified.

Hen metabolism studies were also conducted with plant metabolites M700F002 and M700F048. For the first study, M700F002 was the only radioactive component detected in the matrices analyzed, indicating that M700F002 is not significantly transformed in hens. M700F048 follows the same route of metabolism as fluxapyroxad. Both fluxapyroxad and M700F048 are degraded to the common metabolite M700F008 followed by hydroxylation of the biphenyl moiety and conjugation steps.



[1] M700F005 is hydroxylated in para-position to the amide group, established by ^{1}H NMR spectroscopy
[2] Proposed intermediate, not identified in the current study

Figure 6: Proposed metabolic pathways of BAS 700 F (fluxapyroxad) in laying hens.

4.3 Analytical methods

Plant matrices

A validated method (L0137/01) has been provided for the determination of BAS 700 F in plant matrices and processed commodities. The analyte is extracted from the plant matrices (except oils) into methanol water. An aliquot of the extract is diluted with saturated sodium chloride, acidified with hydrochloric acid and subsequently partitioned with water saturated ethyl acetate. An aliquot of the organic phase is evaporated to dryness and dissolved in methanol water prior to analysis by HPLC-MS/MS.

A similar method was used in the Australian barley and wheat trials provided in support of this application. Procedural recoveries of the target analytes from fortified samples of barley and wheat forage, grain and straw were within acceptable limits for the Australian trials as summarised below in Table 1.

Table 1: Recoveries of BAS700F residues from fortified untreated control samples from Australian barley and wheat residue trials.

ANALYTE	PORTION FORTIFIED	FORTIFICATION RANGE	AVERAGE RECOVERY	COEFFICIENT OF VARIATION
BAS 700 F	Wheat forage	0.01 – 5.0 mg/kg as BAS 700 F	97.5%, n = 9	15.8%
	Wheat grain	0.01 – 5.0 mg/kg as BAS 700 F	96.9%, n = 9	15.5%
	Wheat straw	0.01 – 5.0 mg/kg as BAS 700 F	94.7%, n = 9	14.1%
	Barley forage	0.01 – 5.0 mg/kg as BAS 700 F	97.2%, n = 9	16.8%
	Barley grain	0.01 – 5.0 mg/kg as BAS 700 F	95.4%, n = 9	15.1%
	Barley straw	0.01 – 5.0 mg/kg as BAS 700 F	95.0%, n = 9	13.8%

Animal commodities

In the dairy cattle feeding study samples were analysed for BAS 700 F, M700F002 and M700F008 using method L0140/01. After extraction with acetonitrile with homogenisation, a portion of the extract was reduced to dryness before being reconstituted with water and 2 N HCl. The reconstituted extract was partitioned against ethyl acetate before a portion of the ethyl acetate was then reduced to dryness. The sample was then reconstituted in methanol/water and quantified by HPLC-MS/MS. The LOQ was 0.01 mg/kg for tissues (liver, muscle, kidney and fat) and 0.001 mg/kg for milk and milk products. Concurrent recoveries from control samples fortified with BAS 700 F and M700F008 are summarised below in Table 2.

Table 2: Mean procedural recovery data for Method L0140/01 in dairy cattle feeding study.

MATRIX	SPIKING LEVEL (MG/KG)	RECOVERIES FOR BAS 700 F			RECOVERIES FOR M700F008		
		N	RANGE [%]	MEAN (RSD) [%]	N	RANGE [%]	MEAN (RSD) [%]
Milk	0.001	40	80 – 133[a]	101 (13.3)	40	95 – 126[b]	107 (7.40)
	0.01	40	73 – 117	101 (7.98)	40	88 - 118	104 (6.77)
Cream	0.001	2	82 – 106	94	2	98 - 110	104
	0.01	2	88 – 96	92	2	89 – 98	94
Skimmed milk	0.001	2	72 – 85	79	2	93 – 96	94
	0.01	2	93 – 98	95	2	83 - 86	85
Muscle	0.01	3	97 – 99	98 (1.02)	3	93 – 119	106 (12.3)
	0.1	3	101 – 106	103 (2.81)	3	97 – 105	102 (4.16)
Liver	0.01	5	78 – 114	99 (13.3)	5	83 – 108	98 (11.2)
	0.1	5	95 – 115	104 (7.16)	5	90 – 106	98 (6.55)
Kidney	0.01	3	101 – 109	104 (3.99)	3	93 – 110	101 (8.36)
	0.1	3	110 – 119	113 (4.60)	3	107 – 115	111 (3.65)
Fat	0.01	5	86 – 107	99 (8.34)	5	89 – 124	105 (11.9)
	0.1	5	96 – 109	101 (5.44)	5	98 - 105	103 (2.47)

RSD = relative standard deviation
[a] outliers 38% and 191% excluded from mean calculation
[b] outliers 21% and 168% excluded from mean calculation

Although there were some procedural recoveries outside the acceptable range of 70-120% for BAS 700 F and M700F008, the method is considered acceptable for the determination of these two analytes in milk and tissues given that mean recoveries were 70-120%, with RSD below 20%.

Similar methods were used in the laying hen feeding study. Procedural recovery data for method L0140/01 in the poultry feeding study are summarised below in Table 3.

Table 3: Mean procedural recovery data for Method L0140/01 from laying hen feeding study.

MATRIX	FORTIFICATION LEVEL (MG/KG)	MEAN RECOVERY FOR BAS 700 F [%]	BAS 700 F RSD [%]	MEAN RECOVERY FOR M700F008 [%]	M700F008 RSD [%]
Egg	0.001	98	13.0 (n=37)	96	22.4 (n=38)
	0.01	95	12.8 (n=38)	94	12.4 (n=38)
Muscle	0.01	93	4.24 (n=3)	100	4.95 (n=3)
	0.1	105	1.46 (n=3)	110	1.05 (n=3)
Liver	0.01	104	4.96 (n=3)	98	4.06 (n=3)
	0.1	111	2.89 (n=3)	104	4.51 (n=3)
Skin with fat	0.01	97	6.83 (n=4)	100	2.80 (n=3)
	0.1	103	2.75 (n=4)	108	6.07 (n=3)
Fat	0.01	105	10.7 (n=4)	110	9.40 (n=5)
	0.1	110	5.94 (n=4)	111	4.28 (n=5)

RSD = relative standard deviation

Stability of pesticide residues in stored analytical samples

A freezer storage stability study was carried out on plant samples fortified with BAS 700 F (fluxapyroxad) at 0.1 mg/kg and stored at -20°C. The results are summarised below in Table 4 and indicate that fluxapyroxad is stable for up to 24 months in apple, tomato, triticale, soybean seed, avocado, dried pea seed, cereal grain, potato tuber, grape, lemon and wheat straw.

Table 4: Storage stability of BAS 700 F in plant matrices.

MEAN RECOVERY (%)												
A: IN STORED SAMPLES, % OF NOMINAL					B: PROCEDURAL, IN FRESHLY SPIKED SAMPLE							
DAY	A	B	A	B	A	B	A	B	A	B	A	B
METHOD NO. L0076/3												
	Apple fruit		Tomato fruit		Triticale whole plant		Soybean seed		Avocado fruit		Dried pea seed	
0	89	91	87	83	84	87	78	86	94	84	93	88
28-31	78	79	78	78	84	81	79	82	83	81	83	81
244	93	94	90	93	88	94	85	91	87	92	93	95
365	90	97	92	95	96	97	89	94	100	106	99	93
539	84	92	84	87	78	85	81	82	82	94	83	87

MEAN RECOVERY (%)												
A: IN STORED SAMPLES, % OF NOMINAL					B: PROCEDURAL, IN FRESHLY SPIKED SAMPLE							
DAY	A	B	A	B	A	B	A	B	A	B	A	B
	Cereal grain		Potato tuber		Grape fruit		Lemon fruit		Wheat straw			
0	90	89	85	85	84	88	83	87	86	84		
28-31	80	80	71	75	78	75	77	80	82	81		
244	86	91	88	95	86	91	93	95	85	88		
365	104	104	97	96	92	103	99	94	99	104		
539	86	89	79	90	86	88	87	91	82	82		
Method No. L0137/01												
	Apple fruit		Tomato fruit		Triticale whole plant		Soybean seed		Avocado fruit		Dried pea seed	
0	97	95	96	94	106	101	93	94	96	97	100	99
28-31	104	98	105	109	100	104	98	93	104	101	93	102
85-88	93	100	96	98	87	100	82	74	95	95	90	91
548-554	83	104	96	103	97	104	87	80	89	96	97	100
734-737	77	95	79	90	75	100	77	91	77	95	85	92
	Cereal grain		Potato tuber		Grape fruit		Lemon fruit		Wheat straw			
0	99	99	97	95	98	99	102	102	94	98		
28-31	103	99	108	102	106	104	102	105	97	89		
85-88	90	90	103	97	96	98	97	104	89	84		
548-554	100	110	94	100	96	101	92	102	92	94		
734-737	85	94	82	95	92	97	87	98	78	83		

4.4 Residue definition

Plants

In the plant metabolism studies parent was generally the main component of the TRR. In the tomato and wheat studies parent was the only component observed at >10% of the TRR. In tomatoes parent accounted for >94% of the TRR in fruit and >90% TRR in leaves; in wheat parent accounted for 60.2-91.3% of the TRR. The group of metabolites M700F008, M700F043, M700F041 and M700F006 was found to occur in all wheat matrices as the second most abundant peak, representing 2.4-6.5% of the TRRs.

In the soybean studies, parent accounted for 53.9-97.7% of the TRR in all matrices except seed, where it accounted for 7.4-21% of the TRR. Another peak was assigned to metabolite M700F008/M700F006 (0.2-5.4% of the TRRs). The major metabolite in soybean seed was M700F002 at 33% of the TRR (0.087 mg/kg) which is specific for the pyrazole label only. As the corresponding cleavage product was not observed for the aniline label, and M700F002 is known to be formed in the soil, it is likely that this metabolite was not formed in the plant. An additional metabolite, M700F048 accounted for 8.8 – 19.9% (0.023 mg/kg) of the TRR in soybean seed.

The metabolite M700F002 was not detected (<0.002 mg/kg) in the Australian wheat and barley trials provided in support of this application. In US and European cereal trials M700F002 was generally not detected and always below the LOQ (0.01 mg/kg). In US and European rotational field trials M700F002 was generally found below or at the LOQ (0.01 mg/kg), the highest residue was 0.03 mg/kg in radish tops. It is therefore considered unnecessary to include M700F002 in the residue definition for plant commodities.

In the residue trials provided with the application, M700F048 was generally not detected, except at low levels in forage, hay and straw and only when parent was significantly higher. For example the highest M700F048 residue in barley hay was 0.07 mg/kg, when parent was 2.34 mg/kg. It is not considered necessary to include M700F048 in the residue definition for plant commodities.

It is considered that a residue definition of parent only is appropriate for fluxapyroxad on plant material for both dietary risk assessment and compliance with MRLs.

Animals

In the goat metabolism studies, BAS 700 F represented one of the major residues in milk (13.0-19.8% of the TRRs), muscle (12.0%, aniline label only) and fat (34.1-43.6% of the TRRs), while accounting for minor proportions in liver and kidney (3.2-7.0% of the TRRs). The other predominant compound was the desmethyl metabolite M700F008, representing a significant proportion in milk (23.9-25.4% of the TRRs), muscle (54.7-82.9% of the TRRs), fat (25.8-25.9% of the TRRs), liver (12.8-16.7% of the TRRs) and kidney (22.5-25.6% of the TRRs).

Further metabolites at >10% of the TRRs were detected in milk, kidney and fat. In milk, the metabolite M700F010 was found at levels of 12.3-15.0% of the TRRs (≤0.0025 mg/kg). The metabolite M700F005 was present in fat at 13.7% of the TRRs (0.0034 mg/kg) and in kidney at 19.2% of the TRRs (0.015 mg/kg), with pyrazole label only. The metabolite M700F004 was present in kidney at levels of 12.3-13.1% of the TRRs (≤0.010 mg/kg).

In the hen metabolism study, BAS 700 F represented one of the major residues in egg (13.5% of the TRRs, 0.009 mg/kg), leg muscle (17.6% of the TRRs, 0.0011 mg/kg), fat (63.3% of the TRRs, 0.023 mg/kg), and was observed in minor amounts in liver (1.0% of the TRRs, 0.002 mg/kg). The other predominant compound was the desmethyl metabolite M700F008, representing a significant proportion in egg (49.9% of the TRRs, 0.033 mg/kg), leg muscle (together with M700F016 amounting to 25.7% of the TRRs, 0.0016 mg/kg), and fat (25.3% of the TRRs, 0.009 mg/kg). M700F008 was detected at minor amounts (4%) in liver (0.009 mg/kg).

It is considered that a residue definition of parent plus M700F008 is appropriate for commodities of animal origin for dietary risk assessment. The metabolites M700F010, M700F005 and M700F004 were found at >10% of the TRR in only one or two matrices. It is therefore not considered necessary to include M700F010, M700F005 and M700F004 in the risk assessment residue definition for animal commodities.

The recommended residue definition for compliance with animal commodity MRLs is fluxapyroxad, in line with the established tolerance definitions in the EU and USA.

4.5 Residue trials

Details of 6 Australian trials conducted on wheat and barley in 2008 have been provided in support of the application. In addition details of twelve trials on barley and 25 trials on wheat conducted in the US during 2008/2009 and sixteen trials conducted on barley in 2007/2008 have been provided. An additional 16 residue trials were performed on wheat (12) and triticale (4) in the EU over 2 seasons (2007/2008).

In the Australian trials matching the proposed GAP, residues of parent in barley grain collected at harvest after 2 applications at 62.5 g ai/ha were 0.03 and 0.05 mg/kg. Residues in wheat grain in the Australian trials matching GAP were <0.01 (2) and 0.01 (2) mg/kg. In European barley trials involving 2 applications at 1.3× the proposed rate with the last application at BBCH 69 (proposed Z59), residues in grain were 0.02, 0.026, 0.05 (2), 0.056, 0.07 (3), 0.093, 0.10, 0.114, 0.130, 0.137, 0.140, 0.15 and 0.176 mg/kg. Residues in wheat and triticale grain in European trials involving 2 application at 2× the proposed rate with the last application at BBCH 69 were <0.01, 0.01 (4), 0.02 (4), 0.03 (3), 0.04 (2), 0.05 and 0.06 mg/kg. However, as barley is a naked grain, extrapolation from residue data for other cereals following treatment at these growth stages is not appropriate.

An MRL of 0.2 mg/kg is recommended for fluxapyroxad on GC 0640 Barley based on a HR of 0.05 mg/kg in the Australian trials and 0.176 mg/kg in European barley trials involving a higher rate and later application than proposed. The STMR is 0.07 mg/kg. The harvest withholding period is not required when used as directed.

In the Australian trials matching the proposed GAP residues of parent in wheat and barley straw collected at harvest after 2 applications at 62.5 g ai/ha were 0.43, 0.52, 0.58, 1.07, 2.57 and 4.53 mg/kg dry weight. In European barley trials involving 2 applications at 1.3× the proposed rate with the last application at BBCH 69 residues in straw were 0.07, 0.09, 0.115, 0.117, 0.19, 0.228, 0.30, 0.37, 0.430, 0.550, 0.64, 0.68, 0.84, 0.860, 1.12 and 1.19 mg/kg.

In the Australian trials, residues of parent in wheat and barley forage collected at 14 days after the first application at 62.5 g ai/ha (1× proposed) were 1.15, 1.66, 2.31 and 3.28 mg/kg on a dry weight basis. For 2 trials which did not determine residues in forage after a 14 day PHI residues were 0.63 and 2.47 mg/kg (dry weight) at 7 and 0 days respectively after application at 62.5 g ai/ha. For the Australian trials

involving application at 2× the proposed rate residues in forage at 14 days after application were 2.47, 3.65, 4.02 and 4.47 mg/kg (dry weight).

An MRL of 7 mg/kg is considered appropriate for fluxapyroxad on barley forage, fodder and straw in conjunction with a 14 day grazing withholding period.

Rotational crop field trials

European and North American rotational crop field trials were provided in support of the application. The North American studies involved 2 applications to bare soil at 100 g ai/ha per application. The European studies involved a single application to bare soil at 250 g ai/ha or 2 applications to a primary crop at 125 g ai/ha per application. Residues found are summarised in Table 5.

Table 5: Residues found in rotational crops after application of fluxapyroxad to bare soil or a primary crop.

ROTATIONAL CROP	NO.OF TRIALS	RESIDUE RANGE, MG/KG / AFTER APPLICATION TO BARE SOIL				
		30 day PBI	60 day PBI	90 day PBI	120 day PBI	365 day PBI
Cereal forage	10	0.02 - 0.12	<0.01 - 0.08	<0.01 - 0.03	<0.01 - 0.05	<0.01 – 0.03
Cereal grain	10	<0.01	<0.01	<0.01	<0.01	<0.01
Cereal straw	10	<0.01 - 0.42	0.04 - 0.54	0.04 - 0.16	0.03 – 0.31	0.02 – 0.08
Oilseed forage	4	<0.01 – 0.03				
Oilseed grain	6	<0.01				
Oilseed fodder	6	<0.01 – 0.038				
Root and tuber veg. (roots)	12	<0.01-0.08	<0.01 - 0.01	<0.01 - 0.01	<0.01 – 0.03	<0.01 – 0.02
Brassica veg.	5	<0.01			<0.01	<0.01
Leafy veg.	7	<0.01	<0.01 - 0.02	<0.01	<0.01 – 0.02	<0.01
		Residue range, mg/kg after application to primary cereal crop / Rotational crop planted within 2 months of harvest of primary crop				
Leafy veg.	2	0.01 – 0.02				
Root and tuber veg. (roots)	2	0.01 – 0.02				

PBI = plant back interval

While the field rotational crop studies involved higher application rates than proposed for Australia (maximum 2 applications per crop, each at 62.5 g ai/ha), they do suggest residues of fluxapyroxad may occur in succeeding crops, especially cereal straw (up to 0.54 mg/kg after application to bare soil at 1.6× rate). To cover this possibility it is recommended that an MRL be established at 1 mg/kg for fluxapyroxad

on Primary feed commodities (except barley forage and barley straw and fodder, dry). This would also cover residues found in corn, canola and sunflower plant material in the other rotational studies.

In the European study involving application to bare soil residues of fluxapyroxad and metabolites in cauliflower/broccoli and lettuce at harvest were below the LOQ for all re-planting intervals. Low residues of parent (up to 0.02 mg/kg) were observed in lettuce from the US study and also the European study involving application to a primary cereal crop. For other rotational crops, residues were below the LOQ in wheat grain, canola seed, corn cobs and grain and sunflower seed at harvest. In addition, residues above the LOQ were not found in potatoes or sugarbeet roots. However, in carrot/radish roots fluxapyroxad was found at up to 0.08 mg/kg. This suggests the possibility of low residues in root and tuber vegetables grown as rotational crops after application of fluxapyroxad to a primary crop.

To cover the possibility of residues in rotational crops it is recommended that an MRL of 0.1 mg/kg be established for fluxapyroxad in 'All other foods'.

Processing studies

A barley processing study indicates that residues of BAS 700 F concentrate in bran (1.3-2.5x, average processing factor 1.9x), but do not concentrate in any of the other processed commodities of barley.

Based on a highest residue of 0.176 mg/kg in barley grain, the highest predicted residue in bran is 0.33 mg/kg. It is recommended that an MRL of 0.5 mg/kg be established for fluxapyroxad on CM 0640 Barley bran, unprocessed.

4.6 Animal commodity MRLs

Cattle

A feeding study with fluxapyroxad was conducted in lactating cows. The animals received co-doses of fluxapyroxad at 3.19, 6.13, 18.22 and 60.31 mg/kg feed (dry matter), corresponding to 0.022, 0.047, 0.133 and 0.443 mg/kg bw/day, plus metabolite M700F002 at 0.10, 0.29, and 0.98 mg/kg feed (dry matter), corresponding to 0.003, 0.008 and 0.025 mg/kg bw/day, for a period of 28 days followed by a depuration period of 7 days.

The maximum dietary intake of fluxapyroxad for cattle is estimated assuming consumption of barley straw and fodder as 100% of the diet to give an intake of 4.53 ppm in the feed as calculated below.

Cattle- 500 kg bw, 20 kg DM/day

COMMODITY	% IN DIET	FEED INTAKE	RESIDUE, mg/kg	% DM	LIVESTOCK DIETARY EXPOSURE		
					mg/ANIMAL	ppm	mg/kg bw
Barley straw and fodder	100	20	4.53	100	90.6	4.53	0.181

Maximum residues in tissues and milk in the transfer study after dosing at 6 ppm are summarised in Table 6.

Table 6: Maximum residues in tissues and milk after dosing at 6 ppm.

MATIX	FLUXAPYROXAD (mg/kg)	M700F008 (mg/kg)	COMBINED RESIDUE FOR RISK ASSESSMENT (mg/kg)
Milk	0.00321	0.00268	0.0060
Cream	0.00541	0.00493	0.0105
Muscle	<0.01	<0.01	<0.020
Liver	0.0145	0.0513	0.0677
Kidney	<0.01	0.0114	0.0218
Fat	0.0241	<0.01	0.0345

Conversion factor for M700F008 to parent equivalents = 1.038.

The following mammalian commodity MRLs are proposed for fluxapyroxad, based on the residues observed in a dairy cattle transfer study involving dosing at 6 ppm in the feed:

MO 0105 Edible offal (mammalian) 0.03 mg/kg
MM 0095 Meat [mammalian][in the fat] 0.05 mg/kg
ML 0106 Milks 0.005 mg/kg
Milk fats 0.02 mg/kg

(Based on the high residue of 0.0054 mg/kg in cream and an assumed fat content of 40% the high residue in milk fat is estimated to be (0.0054/0.4) 0.014 mg/kg)

Poultry

A feeding study with fluxapyroxad was conducted in laying hens. The animals received co-doses of fluxapyroxad at 0.3, 0.605, 1.828 or 6.037 mg/kg feed (dry matter), corresponding to 0.022, 0.047, 0.133 and 0.443 mg/kg bw/day, plus M700F002 at 0.025, 0.05, 0.152 or 0.503 mg/kg feed (dry matter), corresponding to 0.00185, 0.0039, 0.0111 and 0.037 mg/kg bw/day, for a period of 28 days followed by a depuration period of 14 days.

The maximum dietary intake of fluxapyroxad for poultry is estimated assuming consumption of barley grain as 100% of the diet to give an intake of 0.176 ppm in the feed as calculated below.

Poultry- 2 kg bw, 0.15 kg DM/day

COMMODITY	% IN DIET	FEED INTAKE	RESIDUE, mg/kg	% DM	LIVESTOCK DIETARY EXPOSURE		
					mg/ANIMAL	ppm	mg/kg bw
Barley grain	100	0.15	0.176	100	0.0264	0.176	0.0132

Maximum residues in tissues and eggs in the transfer study after dosing at 0.3 ppm are summarised in Table 7.

Table 7: Maximum residues in tissues and eggs after dosing at 0.3 ppm.

MATIX	FLUXAPYROXAD (mg/kg)	M700F008 (mg/kg)	COMBINED RESIDUE FOR RISK ASSESSMENT (mg/kg)
Eggs	0.00212	<0.001	0.0032
Liver	<0.01	<0.01	<0.02
Fat	<0.01	<0.01	<0.02
Muscle	<0.01	<0.01	<0.02
Skin with fat	<0.01	<0.01	<0.02

Conversion factor for M700F008 to parent equivalents = 1.038.

The following poultry commodity MRLs are recommended for fluxapyroxad based on the residues observed in a laying hen transfer study involving dosing at 0.3 ppm in the feed.

PE 0112 Eggs 0.005 mg/kg
PO 0111 Poultry, Edible offal of *0.01 mg/kg
PM 0110 Poultry meat [in the fat] *0.01 mg/kg

4.7 Estimated dietary intake

The chronic dietary exposure to fluxapyroxad is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines[2] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for fluxapyroxad is equivalent to 3% of the ADI.

It is concluded that the chronic dietary exposure to fluxapyroxad is acceptable.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR 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 Office of Chemical Safety recommended that an Acute Reference Dose is not necessary for fluxapyroxad. It is therefore not necessary to undertake NESTI calculations.

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

4.8 Bioaccumulation potential

The partition coefficient (Log P_{ow}) for fluxapyroxad is 3.10 suggesting moderate fat solubility. In the animal metabolism studies residues of fluxapyroxad were higher in fat than in muscle, however in the animal transfer studies fluxapyroxad residues in tissues, including fat, rapidly declined to below the LOQ following a period on clean feed. The potential for bioaccumulation is considered to be low.

4.9 Spray drift

In the dairy cattle animal transfer study provided in support of the application, dosing with fluxapyroxad at 3.19 ppm gave highest residues of parent of 0.0108 mg/kg in fat. For residues of parent to be at the LOQ (0.01 mg/kg) the maximum feeding level is 2.95 ppm. Assuming pasture consists of 1500 kg DM/ha this corresponds to a maximum permitted drift of 4.43 g ai/ha.

Calculations of the average deposition over a 300 metre field using the standard scenarios for ground and aerial application available on the APVMA web site indicate that no spray zones are not required for protection of international trade;

Recommendations

The following MRLs will be established:

Table 1

COMPOUND	FOOD	MRL (mg/kg)
FLUXAPYROXAD		
ADD:		
	All other foods	0.1
GC 0640	Barley	0.2
CM 0640	Barley bran, unprocessed	0.5
MO 0105	Edible offal (mammalian)	0.03
PE 0112	Eggs	0.005
MM 0095	Meat [mammalian][in the fat]	0.05
ML 0106	Milks	0.005
	Milk fats	0.02
PO 0111	Poultry, Edible offal of	*0.01
PM 0110	Poultry meat [in the fat]	*0.01

Table 3

COMPOUND	RESIDUE
ADD:	
Fluxapyroxad	Commodities of plant origin: Fluxapyroxad
	Commodities of animal origin for enforcement: Fluxapyroxad
	Commodities of animal origin for dietary exposure assessment: Sum of fluxapyroxad and 3-(difluoromethyl-N-(3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide (M700F008)

Table 4

COMPOUND		ANIMAL FEED COMMODITY	MRL (mg/kg)
Fluxapyroxad			
ADD:			
		Barley forage	7
AS	0640	Barley straw and fodder, dry	7
		Primary feed commodities (except barley forage and barley straw and fodder, dry)	1

The following withholding periods are required in relation to the above MRLs:

Harvest: Not required when used as directed.
Grazing: Do not graze or cut for stock food for 14 days after application.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Commodities exported

Barley is a major export commodity along with animals that have been fed feeds containing residues arising from the proposed use. Of the possible rotational crops which are major export commodities residues are not expected to occur in the seed/grain of cereals, oilseeds and pulses. The risk to trade in oaten hay from rotational crops must also be considered.

Destination and Value of Exports

In 2009-10 Australia exported 4256 kt of barley, valued at $1098 million (source ABARES). Information provided by the applicant indicated that approximately 65% of the total Australian barley crop is exported annually, which equates to about 2.1 million tonnes of feed barley.

Information on the destination of Australian exports of barley is not readily available. Information on the ABARES website indicates that the major world importers of barley are China, European Union, Japan, Russian Federation and Saudi Arabia. The barley industry has indicated that the major export markets for Australian feed barley are Japan, Saudi Arabia and Kuwait.

The significant export markets for animal commodities are defined in Part 5B of MORAG.

Proposed Australian use-pattern

BAS 700 01F Fungicide (62.5 g/L fluxapyroxad)

CROP	PEST	RATE PER HA	CRITICAL COMMENTS
Barley	Net form of net blotch (*Pyrenophora teres* f *teres*) Spot form of net blotch (*Pyrenophora teres* f *maculate*)	250 mL (15.6 g ai/ha)	Apply when conditions favour disease development and prior to development of disease in the crop. Two applications at this rate are required for adequate disease control. Apply once at around stem elongation (Z32) and again before ear emergence (Z59). DO NOT apply later than Z59.
	Leaf scald (*Rhynchosporium secalis*) Leaf Rust (*Puccinia hordei*	500 mL to 1 L (31.3 – 62.5 g ai/ha)	Apply when conditions favour disease development and prior to development of disease in the crop. A repeat application may be required if infection pressure persists. Regularly monitor the crop from 3-4 weeks after the first application for signs of reinfection. Apply the higher rate when the disease is present on the upper leaves or when conditions are favourable for disease development. DO NOT apply later than Z59.

CROP	PEST	RATE PER HA	CRITICAL COMMENTS
	Powdery mildew (*Blumeria graminis* f. sp. *hordei*	500 mL to 1 L (31.3 – 62.5 g ai/ha)	Apply when conditions favour disease development and prior to development of disease in the crop. A repeat application may be required if infection pressure persists. Regularly monitor the crop from 3-4 weeks after the first application for signs of reinfection. Apply the higher rate when the disease is present on the upper leaves or when conditions are favourable for disease development. DO NOT apply later than Z59.

Withholding periods:
Harvest: Not required when used as directed.
Grazing: Do not graze or cut for stock food for 14 days after application.

Export of treated cereals
Growers should note that Maximum Residue Limits (MRLs) or import tolerances do not exist in all markets for cereals treated with BAS 700 01F Fungicide. Additionally, some export markets have established MRLs different to those in Australia. If you are growing cereals for export, please check with BASF Australia Ltd or your grain exporter for the latest information on MRLs and import tolerances BEFORE using BAS 700 01F Fungicide.

LIVESTOCK DESTINED FOR EXPORT MARKETS
The grazing withholding period only applies to stock slaughtered for the domestic market. Some export markets apply different standards. To meet these standards, ensure that in addition to complying with the grazing withholding period, the Export Slaughter Interval is observed before stock are sold or slaughtered.

EXPORT SLAUGHTER INTERVAL (ESI)
After observing the withholding period for grazing or cutting for stockfood, livestock that have been grazed on or fed treated crops should be placed on clean feed for 2 days prior to slaughter.

Overseas registration and approved label instructions

The applicant indicated that registration applications for BAS 700 01 EC have been lodged in the USA, Canada, New Zealand and the EU for control of fungal diseases in various crops.

Comparison of Australian MRLs with Codex and overseas MRLs.

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods. Fluxapyroxad has not been considered by Codex. Fluxapyroxad is being considered by the JMPR in 2012 and MRLs may be established in 2013.

The following overseas residues MRLs/tolerances have been established for fluxapyroxad.

COUNTRY	COMMODITY	MRL (mg/kg)
EU	Barley	2
	Bovine and sheep meat	*0.01
	Bovine and sheep fat	0.05
	Bovine and sheep liver	0.03
	Bovine and sheep kidney	*0.01
	Bovine and sheep edible offal	*0.01
	Milk	0.005
USA	Grain, cereal, group 15 (except corn, field, grain; except corn, pop, grain; except corn kernels plus cobs with husks removed; except wheat)	3
	Cattle, fat	0.05
	Cattle, meat	0.01
	Cattle, meat byproducts	0.03
	Milk	0.005
	Sheep, fat	0.05
	Sheep, meat	0.01
	Sheep, meat byproducts	0.03
Canada (Proposed)	Cereal grains (Crop Group 15, except wheat and corn)	3
	Fat of cattle, goats, horses and sheep	0.05
	Meat byproducts (except kidney) of cattle goats, horses and sheep	0.03
	Kidney of cattle goats, horses and sheep	0.01
	Milk	0.005

Residue definition for compliance with MRLs is fluxapyroxad in both the EU, USA and Canada (proposed).

Potential risk to trade

Export of treated produce containing finite (measurable) residues of fluxapyroxad may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country or (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country.

The draft label includes the following advice regarding export of treated cereals:

Growers should note that Maximum Residue Limits (MRLs) or import tolerances do not exist in all markets for cereals treated with BAS 700 01F Fungicide. Additionally, some export markets have established MRLs different to those in Australia. If you are growing cereals for export, please check with BASF Australia Ltd or your grain exporter for the latest information on MRLs and import tolerances BEFORE using BAS 700 01F Fungicide.

Appropriate MRLs have not been established by Codex or by Japan. The EU has established a relevant MRL at 2 mg/kg for barley. The US has established a cereal grains MRL at 3 mg/kg and a similar MRL has been proposed for Canada. The applicant has indicated their intention to apply for import tolerances in Japan using data from the US, Canada and the EU. The earliest expected decision by Japan would be in the second quarter of 2015. Codex MRLs may be established in 2013 (JMPR evaluation in 2012). The Australian National Residue Survey is expected to include fluxapyroxad in its cereals grains screen prior to the end of 2012 with an LOQ at or below the Japanese uniform limit of 0.01 mg/kg.

Finite animal commodity MRLs are proposed at 0.03 mg/kg for edible offal (mammalian) and 0.05 mg/kg for meat [mammalian][in the fat], which represents a possible risk to trade as overseas tolerances are established in the EU and USA only. However, in the dairy cattle transfer study after dosing with fluxapyroxad for 28 days at 60.3 ppm in the feed, residues of parent in all tissues fell to below the LOQ after a further 2 days on clean feed. A 2 day export slaughter interval is proposed and would ensure no quantifiable residues in animal commodities for export and ensure that the risk to trade is negligible.

Low residues may be expected in milk (0.003 mg/kg parent, assuming consumption of barley forage/fodder as 100% of the diet with maximum residue of 6 mg/kg for 28 days). However, given milk products will be subjected to bulking and blending before export, it is considered that the risk to trade in dairy produce is low.

The risk to trade in livestock that have been fed on rotational crops grown after an initial crop has been treated with fluxapyroxad was also considered. The highest residue in cereal straw in the field rotational studies was 0.54 mg/kg (after application at 1.6× maximum overall rate and a 60 day PBI). Assuming a dry matter content of 88% this converts to 0.61 mg/kg on a dry weight basis. In the animal transfer study dosing with fluxapyroxad at 3.19 ppm gave highest residues of parent in fat of 0.0108 mg/kg. The estimated parent residue in fat after a maximum fluxapyroxad intake of 0.61 ppm from rotational crops is 0.002 mg/kg which is below the LOQ. The feeding level for residues of parent in fat to be at the LOQ is 2.95 ppm. The conservatively modelled peak concentration in soil (as modelled by DSEWPaC) is not expected to produce residues above this level after continuous annual application.

In addition:

- Not all of an aged residue in soil is expected to be bioavailable.
- Estimates of rotational residues in animal feed commodities are based on application to bare soil. Residues following application to crops are expected to be lower.
- Barley is not grown in a continuous rotation.
- Application is not always expected according to maximum GAP.
- Half lives of the target residue in animal tissue are short (<0.4 days).

the risk to trade in animal commodities associated with rotational residues arising from the proposed use is considered to be very low.

There is also a potential risk to trade in rotational crops, noting the proposed establishment of an 'All other foods' MRL at 0.1 mg/kg. However, residues were not observed in grains of rotational cereals or oilseeds. The trade risk for grains, oilseeds and pulses grown in rotation with treated crops is considered to be low.

For oaten hay, standards for fluxapyroxad are not established in *The Ordinance of the Standards of Feed Additives* (to May 2010[3]). The trade risk for oaten hay grown in rotation with treated crops is considered to be low.

[3] www.famic.go.jp/ffis/feed/obj/shore_eng.pdf

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Health hazards

Fluxapyroxad (CAS: 907204-31-3) is not listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2011). With the available toxicology information, OCS has not classified fluxapyroxad as a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). No human health risk phrases will be required for this new active constituent.

Based on the product toxicology information, BAS 700 01 F Fungicide is classified as a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). The product will require the following risk phrase.

R41	Risk of serious damage to eyes

Formulation, packaging, transport, storage and retailing

The active constituent fluxapyroxad will be manufactured overseas. The product BAS700 01 F Fungicide will be manufactured and packaged overseas and be imported into Australia in 5, 10 and 20 L high-density polyethylene (HDPE) containers with a twist cap.

Use pattern

The product, BAS 700 01 F Fungicide an emulsifiable concentrate formulation containing 62.5 g/L fluxapyroxad), is a fungicidal agent that aids in the control of fungal diseases in barley through a process of succinate dehydrogenase inhibition. This prevents fungal growth, spore germination, germ tube and appresoria formation and growth of mycelia.

It is proposed to be used at a rate of 250 - 1000 mL/ha in water to a spray volume of 50 to 100 L/ha for ground boom operations and a minimum of 20 L/ha for aerial application. It is applied to crops up to twice per crop at an early growth stage (tilling) to no later than the emergence of the seed head. It is recommended to apply BAS 700 01F as a broadcast application using a conventional boom sprayer with either mechanical or by-pass agitation or by aerial application using either fixed or rotary winged aircraft.

Exposure during use

Farmers and their employees will be the main users of BAS 700 01 F Fungicide. 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 will be dermal with 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 (1998) 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 100 or above is acceptable.

The MOE takes into account both interspecies extrapolation, intraspecies variability and the seriousness of the critical health effect of concern. The MOE for both ground boom spray and aerial applications are at an acceptable level when a single layer of clothing (cotton overalls or equivalent clothing) are worn for application and chemical resistant gloves are additionally worn during mixing and loading.

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.

Recommendations for safe use

Users should follow the First Aid Instruction, Warning Statement and Safety Directions on the product label.

Conclusion

The registration of BAS 700 01F fungicide containing fluxapyroxad at 62.5 g/L for the control of fungal diseases in barley is supported.

BAS 700 01F fungicide 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

BASF Australia Ltd. has applied for the approval of a new active constituent fluxapyroxad in conjunction with registration of the end use product BAS 700 01 F fungicide containing that active constituent. This is the first time approval for fluxapyroxad has been sought in Australia. The proposed end use product BAS 700 01 F will contain 62.5 g ac/L. The product will be marketed for the control of certain fungal diseases in barley and will be applied at a rate of up to 1 L/ha (62.5 g ac/ha) twice per season with a minimum interval between treatments of approximately 21 days.

7.1 Environmental Fate

Hydrolysis

Hydrolysis is unlikely to be a major route of degradation for fluxapyroxad (BAS 700 F) in the environment. Under sterile conditions, it is hydrolytically stable in the environmentally relevant pH range (4-9) and no degradation products were identified. The aqueous metabolite M700F007 found under irradiated conditions in aerobic water/sediment systems was also investigated. It was similarly found to be hydrolytically stable in the environmentally relevant pH range, with no degradation products identified.

Photolysis

Fluxapyroxad does not significantly absorb UV/VIS light in the environmentally significant wavelength range of 290-800 nm. In standard soil photolysis and aqueous photolysis studies the degradation rates were not significantly different from the dark controls. Photolysis is not expected to be a significant degradation pathway for fluxapyroxad. Fluxapyroxad is unlikely to remain stable in the atmosphere, due to reactions with photo-chemically produced hydroxyl radicals with an estimated half-life of 0.69 days.

Biodegradation

Aerobic

The metabolism of fluxapyroxad in aerobic soil was studied in several soils at a range of temperatures between 10 and 27°C. Fluxapyroxad is slightly or very slightly degradable with half-life values between 70 and 2850 days. As expected the half-life was longer at 10°C than at 20°C and shorter at 27°C. Major metabolites observed in the soil were M700F001 and M700F002, with M700F008 also occasionally present in minor amounts. The conjectured metabolite M700F003 was never indentified in any study and is believed to rapidly and irreversibly bind to soil. The primary aerobic degradation pathway of fluxapyroxad (BAS700F) is the cleavage of the carboxamide bridge of the parent. This degradation produces the carboxylic acid intermediate M700F001, which is de-methylated to form M700F002. Some direct adsorption of BAS 700 F to soil, without transformation may also occur. Non-extractable residues in all studies were between 8 and 55% of applied radioactivity at the end of the incubation period. The metabolites M700F001 and M700F002 were present at levels up to 33% and 39% of the applied radioactivity, respectively. In the studies where the greatest amounts of metabolites were found both peaked at day around 120 but for M700F002 this was study termination. The metabolite M700F001 is rapidly transformed in soil, with DT50 values in the range of

2.7 to 9.3 days. However, the other major metabolite M700F002 was found to have similar persistence to the parent with half-lives of between 82 and 159 days. Some mineralisation also occurred with CO2 accounting for up to 13% of applied radioactivity.

Under field conditions studied in several North American and European locations, fluxapyroxad generally dissipated more rapidly than under laboratory conditions. Fluxapyroxad dissipated with DT50 values of 9.9 to 436 days. However, some of half-life values need to be considered in context as the data did not fit any of the models describing dissipation very well. In many cases there was considerable slowing of the degradation of fluxapyroxad and regardless of the DT50 value all of the test sites had DT90 values over 1 year with considerable carryover of fluxapyroxad after that period.

In aerobic aquatic conditions (two water/sediment systems) fluxapyroxad dissipates by a combination of partitioning to the sediment from the water phase and also degradation in water and sediment. The major route of degradation is the same as for aerobic soil (cleavage of the carboxamide bridge); however, as the two metabolites are highly water soluble they are only detected in this compartment. In a test under irradiated conditions an additional metabolite M700F007 was also detected in the aquatic compartment. Although dissipation of fluxapyroxad from water to sediment is rapid (DT50 = 4.8 to 6.4 days), fluxapyroxad is still regarded as very slightly degradable with half-lives in the whole system (sediment and water) ranging from 420 to 701 days. Under irradiated conditions fluxapyroxad degraded faster but is still regarded as slightly degradable with half-lives ranging between 116 and 145 days.

Anaerobic

Fluxapyroxad is very slightly degradable based on the treatment of a single soil under anaerobic conditions, with a DT50 value of 591 days. Although a further study was conducted where fluxapyroxad degraded more quickly, it is likely that the aerobic pathway was not completely excluded in this study. Regardless of this, fluxapyroxad was still found to be very slightly degradable. Levels of radioactivity in the surface water for the pyrazole labelled test substance increased slightly with time from 18% of applied radioactivity at flooding (Day 30), to a maximum value of 22% at DAT 123. There was little change in the levels of radioactivity in the water for the trifluorophenyl label. Non-extractable residues rose before falling again for the pyrazole label with a final amount representing 29% TAR. For the trifluorophenyl label the non extractable residue rose steadily to reach a maximum of 37% TAR at study termination. Only minimal amount of CO2 and volatile organics were evolved. The route of degradation is similar to that of aerobic degradation excepting that the metabolite M700F001 did not de-methylate to form M700F002. Fluxapyroxad is very slightly degradable in anaerobic sediment-water systems with a DT50 value of 731 days. It dissipated slowly from the water column with a DT50 of 177 days mainly by partitioning to the sediment. Only minor amounts of the metabolites M700F001 and M700F002 were formed (4.4 and 2.0 % of applied radioactivity, respectively). These were only found in the aqueous phase. After 365 days approximately half of the radioactivity was found in the sediment. Of this between 10 and 14% was non-extractable residue.

Mobility

Fluxapyroxad has moderate to low mobility in soils with Koc values of between 320 and 1108 mL/g. The Kdes values are greater than the Kads values suggesting that once fluxapyroxad is adsorbed on soil it is generally more difficult to desorb it. The slope (1/n) was close to, but less than 1 suggesting that fluxapyroxad will partition slightly more to water as the concentration of fluxapyroxad increases. There was some correlation of adsorption (K) with organic carbon, suggesting that fluxapyroxad binds to organic carbon but other mechanisms of binding are likely to also be involved.

The two major metabolites M700F001 and M700F002 were found to be very highly or highly mobile with little affinity for organic carbon in the soil.

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

Accumulation

In spite of fluxapyroxad's persistence and relatively low water solubility, fluxapyroxad was found to be unlikely to bio-accumulate based on a whole fish bio-concentration factor of between 86 and 93. However, it is likely to accumulate in soil and this is the subject of ongoing studies by the applicant.

7.2 Environmental Effects

Avian

Fluxapyroxad is at most slightly toxic (LD50> 2000 mg/kg b.w.;LC > 2000 mg/kg diet) to birds, over the short term. Bobwhite quail showed the greatest sensitivity with an estimated LD50 of 2457 mg ac/kg-diet (≡ 561 mg ac/kg b.w.) based on short term dietary exposure. However, effects from high light intensity may have influenced this study. The exact effect of the light intensity is unknown and the findings of this study are inconsistent with other studies on the bobwhite quail including a repeat short term dietary study, with lower light intensity. Sub-chronic effects on mallard ducks included an increase in the number of dead birds in shells with a flow on effect on the number of survivors at day 14. The NOEL was established at 300^0 mg ac/kg-diet (≡ 31.9 mg ac/kg b.w.).

Fish

All of the toxicity values were established to be below the solubility of fluxapyroxad in water. However, due to fluxapyroxad's low water solubility some studies used a co-solvent. Fluxapyroxad is considered to be moderately or highly toxic on an acute basis and the toxicity of the formulation is considered to be largely from the active constituent. Chronic exposure to fluxapyroxad was found to cause a reduction of growth of fish and it is considered to be moderately toxic. The most sensitive species was carp with an LC50 of 0.29 mg/L. In chronic testing on fathead minnow over 33 days the NOEC was established at 0.039 mg/L. The metabolites of fluxapyroxad were practically non-toxic.

Aquatic Invertebrates

Fluxapyroxad is moderately acutely toxic to daphnia with an LC50 of 6.8 mg/L. This value is higher than the reported water solubility of fluxapyroxad and co-solvents were used in the study to aid dissolution. There may have been some physical effect from colloidal suspensions of fluxapyroxad, but this was not delineated from the chemical effects in the study presented. Chronic exposure to fluxapyroxad caused a reduction in reproduction and growth to daphnia. The 21 day NOEC for fluxapyroxad was established as 0.5 mg/L and it is considered to be slightly chronically toxic. The formulation in terms of active constituent is ten times more toxic, suggesting that other components in the formulation are contributing to the toxicity. As with fish the metabolites of fluxapyroxad were practically non-toxic to daphnia.

Algae and Aquatic Plants

Fluxapyroxad is highly or moderately toxic to algae and duckweed; although for the fresh water diatom, the marine alga and duckweed 50% inhibition based on growth rate did not occur to the limits of fluxapyroxad's water solubility. The ErC50 for green algae, which is the most sensitive species, is 0.66 mg/L. No morphological effects were observed, except for the marine algae and duckweed, where smaller cells or fronds were observed. The toxicity of the formulation is considered to be largely from the active constituent. The three major metabolites of fluxapyroxad (M700F001, M700F002 and M700F007) are at least an order of magnitude less toxic than the parent, and are considered slightly (10-100 mg/L) or practically non toxic (> 100 mg/L) to algae. Part of two of the metabolites' (M700F001 and M700F002) toxicity may be due to their acidity.

Terrestrial Invertebrates

Fluxapyroxad is very slightly toxic to bees on its own and is considered slightly toxic to bees when incorporated in the BAS 700 01 F formulation. The most sensitive endpoint is 15.7 µg/bee for contact with the formulation. In semi-field studies no adverse effects were found to brood feeding at treatment levels of up to 125 g ac/ha. All of the non-target beneficial insects showed some sensitivity to the formulation containing nominally 62.5 g ac/L with increased mortality and/or reduction in reproduction. The predatory mite (Typhlodromus pyri) was the most sensitive but in higher tier tests simulating more realistic exposure, the sensitivity was reduced to the point where no adverse effects were observed.

Earthworms and collembola were slightly sensitive to fluxapyroxad and its formulation. An acute NOEC for earthworms of 125 mg ac/kg dry weight of soil was established and the formulation was slightly more toxic with a NOEC of 39.7 mg ac/kg dry weight of soil. However, no acute EC50 could be established to the level tested. Chronic exposure to the highest concentration of the formulation containing fluxapyroxad appeared to have caused a reduction in the number of juveniles and biomass. The chronic NOEC was therefore determined to be 10.6 mg ac/kg. Chronic exposure of collembola to a formulation containing fluxapyroxad appeared to have caused higher mortality and a reduction in mortality at exposure levels greater than 1.5 mg ac/kg. The higher mortality and reduction was regarded as statistically significant at exposure levels above 3.0 mg/kg. Collembola and earthworms were not sensitive to the major soil metabolites M700F001 and M700F002 to the levels tested.

Micro-organisms

There were no short or long-term effects on soil micro-organisms to the exposure of fluxapyroxad, its formulation or its metabolites at the levels tested. This was 2.01 mg fluxapyroxad/kg, 0.37 mg M700F001/kg, 1 mg M700F002/L and 320 mg formulation/kg, respectively. Fluxapyroxad similarly had no effect to sewage micro-organisms, with a NOEC of 100 mg/L.

Sediment Dwelling Organisms

The fresh water amphipod was insensitive to fluxapyroxad to the level tested. However, the marine amphipod showed significant increase in mortality at exposure levels greater than 18 mg ac/kg, with a corresponding measured concentration of fluxapyroxad in overlying water of 1.11 mg ac/L. An LC50 of 142 mg ac/kg was established with the measured concentration in the overlying water of 2.42 mg ac/L. Chronic exposure of non-biting midge showed slight sensitivity of this species to fluxapyroxad. The emergence rate

was reduced at levels above 75 mg ac/kg. The measured concentration of fluxapyroxad in the overlying water was between 0.9 and 1.61 mg ac/L, whilst it was between 1.15 and 1.88 mg ac/L in the pore water.

Terrestrial Plants

Terrestrial plants showed slight sensitivity to fluxapyroxad. At the highest levels tested effects on growth, seedling emergence and survival were observed. There were also effects on the dry weight of carrots and lettuces in the seedling emergence study but this was not dose responsive. Fifty percent inhibition (EC50) on any parameter was not observed in any of the plants tested.

Marine & Other Organisms

Fluxapyroxad is moderately acutely toxic to mysid. The LC50 of 3.6 mg is approximately equal to the reported solubility of fluxapyroxad and a co-solvent was used to aid dissolution in the study. Oysters were also slightly sensitive to fluxapyroxad. Although no mortality occurred, shell growth was inhibited and an EC50 of 0.96 mg ac/L was established. Sheepshead minnow showed similar sensitivity to fluxapyroxad as freshwater species. Sewage sludge organisms were found to be insensitive to fluxapyroxad.

7.3 Risk Assessment

BAS 700 F 01 may be applied by ground or aerial methods as a broadcast application at a rate of 1 L formulation/ha (≡ 62.5 g ac/ha), up to twice per season, with an approximate minimum 21 day interval between applications.

The major potential risk to the environment was fluxapyroxad's potential to accumulate in soil and sediment from multiple applications. In spite of conservative modelling, likely to over predict the exposure, acceptable risk to aquatic organisms was found from run-off water entering environmental waters. Similarly the risk to sediment and soil dwelling organisms from spray drift and run-off was found to be acceptable in spite of the potential of fluxapyroxad to accumulate in these environmental compartments. However, this modelling of accumulation should be confirmed by the ongoing soil accumulation studies.

8 EFFICACY AND SAFETY ASSESSMENT

This application seeks to register a new product, BAS 700 01 F Fungicide containing a new active fluxapyroxad, for control of various fungal diseases of barley.
BAS 700 01F is a broad spectrum fungicide. It inhibits spore germination, mycelial growth and sporulation of the fungus on the leaf surface. The product can be applied in either pre-or post-infection situations. However, optimum disease control is achieved when the product is applied preventatively in a regular scheduled spray program and is used in a rotational program with other fungicides. Through coverage of the crop is necessary for best results. For fungicide resistance management the product is a Group 7 fungicide.

8.1 Proposed use pattern

The product BAS 700 01 F Fungicide is a new fungicide for the control of specified fungal diseases of barley. The product is intended for control of Net form of net blotch (*Pyrenophora teres* f *teres*), Spot form of net blotch (*Pyrenophora teres* f *maculata*), leaf scald (*Rhynchosporium secalis*), leaf rust (*Puccinia hordei*) and powdery mildew (*Blumeria graminis* f. sp.*hordei*) of barley. BAS 700 01 F Fungicide is intended to be used at a rate of 250 mL – 1L product/ha. It is proposed to complement current fungal programs in barley.

8.2 Assessment of study/trial data

Data are supplied from eleven field trials in four Australian states over two seasons. The candidate formulation proposed for registration was used in all trials at 4-5 rates, including all label rates. Four barley cultivars were utilized – Gairdner, Yagan, Maritime and Mundah. Results were compared with those from untreated plots and plots treated with a commercial fungicide, Opus (epoxiconazole) at its label rate. Trials were carried out by two agrisearch companies and utilized a common trial format : 4-8 reps. of 13-54 sq m plots in a randomized complete block design (RCB), sprayed either once at flag leaf emergence, or twice, at flag leaf emergence plus at early flowering. Application at the rate of 80-120L/ha was by either gas pressurized backpack plus hand held boom or by a quadbike sprayer. Disease assessments were carried out at 2-4 times for incidence and severity on each of the top four leaves on 10-20 tillers per plot and results analysed by analysis of variance and significant differences between treatment means shown.

Disease pressure was sufficient to provide useful supporting data in 10 of the 11 trials with 1-5 trials supporting each disease claim. As assessments were carried out at up to four dates, on each of four leaves, and for both disease incidence and severity, there were a number of data sets to permit comparisons of treatments. To indicate the effectiveness of the candidate against each disease one or two indicative trial results have been summarised in the following table, selecting where possible the incidence or severity ratings on flag (F) or F-1 leaf (as the more important leaves to the plant) at a critical evaluation time for a spray (14 days after application number two), for two or more of the label rates. In these tables the abbreviation BAS500(1) indicates the candidate BAS 700 01 F Fungicide at 500mL/ha, one spray application; the abbreviation 15DAA2 indicates an assessment date 15 days after the second spray application.

Control of Scald

TRIAL NO DATA NO	TRIAL LOCATION COMPANY DATE	ASSESSMENT (SEVERITY OR INCIDENCE AND TIMING)	RESULT (% SEVERITY OR % INCIDENCE)	CONCLUSION
7 48596	Toodyay, West Aust. Peracto 2009	Severity on F 12DAA2	BAS500(1) 2.7 % BAS250(2) 1.0 % Opus(2) 1.7 % Control 37.9 %	Good control by two label rates of BAS, both stat. equiv. to ind. std.
12 48595	Werribee, Vic. Peracto 2010	Severity on F 14DAA2	BAS500(1) 11.0 % BAS1L(1) 1.8 % BAS250(2) 1.6 % Opus(2) 9.2 % Control 63.4 %	Good control by three label rates of BAS, all stat. equiv. to ind. std.

Control of Rust

TRIAL NO DATA NO	TRIAL LOCATION COMPANY DATE	ASSESSMENT (SEVERITY OR INCIDENCE AND TIMING)	RESULT (% SEVERITY OR % INCIDENCE)	CONCLUSION
5 48593	Naracoorte, South Aust. Peracto 2009	Severity on F 14DAA2	BAS500(1) 2.3 % BAS1L(1) 1.2 % BAS250(2) 0.8 % Opus(2) 1.3 % Control 5.7 %	Good control by two label rates of BAS, both stat. equiv. to ind. std. Control by 500(1) rate less at 60 % and stat. inferior to ind. std.
12 48595	Werribee, Vic. Peracto 2010	Severity on F 14DAA2	BAS500(1) 2.6 % BAS250(2) 0.2 % Opus(2) 1.3 % Control 13.6 %	Good control by two label rates of BAS, both stat. equiv. to ind. std. (500(1) rate gave 81 % control this time)

Control of Spot Form of Net Blotch

TRIAL NO DATA NO	TRIAL LOCATION COMPANY DATE	ASSESSMENT (SEVERITY OR INCIDENCE AND TIMING)	RESULT (% SEVERITY OR % INCIDENCE)	CONCLUSION
5 48593	Naracoorte, South Aust. Peracto 2009	Severity on F 14DAA2	BAS500(1) 9.0 % BAS250(2) 3.0 % Opus(2) 41.0 % Control 73.0 %	Good control by two label rates of BAS, both stat. superior to ind. std.
8 48597	Arthurton, South Aust. Peracto 2010	Incidence on F-1 16DAA2	BAS(500) 5.0 % BAS250(2) 1.3 % Opus(2) 16.3 % Control 30.0 %	Good control by two label rates of BAS, both stat. superior to ind. std.

Control of Net Form of Net Blotch

TRIAL NO DATA NO	TRIAL LOCATION COMPANY DATE	ASSESSMENT (SEVERITY OR INCIDENCE AND TIMING)	RESULT (% SEVERITY OR % INCIDENCE)	CONCLUSION
7 48596	Toodyay, West Aust. Peracto 2009	Severity on F 12DAA2	BAS500(1) 2.4 % BAS250(2) 2.1.% Opus(2) 2.4 % Control 18.3 %	Good control by two label rates of BAS, both stat. equiv. to ind. std.
9 48598	Toodyay, West Aust. 2010	Severity on F-1 17DAA2	BAS500(1) 7.2 % BAS250(2) 10.1 % Opus(2) 15.9 % Control 37.7 %	Good control by two label rates of BAS, one stat. equiv. to ind. std., one stat. superior to ind. std.

Summary of efficacy against Rust, Scald, Net Form of Net Blotch and Spot Form of Net Blotch
The above tables show that for each of the four diseases the candidate fungicide in both single and double spray applications is demonstrated to give commercially acceptable levels of disease control and that these levels are equivalent to those obtained by using a fungicide currently registered for these uses.
In general control increased with increasing fungicide dose, and two sprays were superior to one where equivalent quantities of ai/ha were applied.

Control of Powdery Mildew

TRIAL NO DATA NO	TRIAL LOCATION COMPANY DATE	ASSESSMENT (SEVERITY OR INCIDENCE AND TIMING)	RESULT (% SEVERITY OR % INCIDENCE)	CONCLUSION
11 48589	Forth, Tas. Peracto 2010	Incidence on F 15DAA2	BAS500(1) 10.0 % BAS1L(1) 3.3 % BAS500(2) 3.3 % BAS1L(2) 1.7 % Opus(2) 0.0 % Control 21.7 %	Good control by three label rates of BAS, all stat. equiv. to ind. std. But BAS500(1) gave 54% control, stat. inferior to ind.std.
		Severity on F-1 15DAA2	BAS500(1) 5.1 % BAS1L(1) 2.3 % BAS500(2) 0.9 % BAS1L(2) 0.8 % Opus(2) 0.4 % Control 8.6 %	Good control by the two double applications of BAS, all stat. equiv. to ind. std. But BAS500(1) gave 41% control and BAS1L(1) gave 73% control, both stat. inferior to ind. std.

Summary of efficacy against Powdery Mildew

The single trial on this disease demonstrated that double applications of the candidate fungicide gave commercially acceptable levels of control, and this level was statistically equivalent to that obtained by using a commercial fungicide currently registered for this use.

Single applications were less effective, in particular the 500 mL/ha rate, whether assessed by incidence or disease severity, gave control levels inferior to that achieved with an industry standard.

Phytotoxicity

No symptoms of phytotoxicity were observed in 11 trials on four barley cultivars when application rates up to double the draft label rates were used.

8.3 General conclusions

The claims for control of Rust, Scald, Net Form of Net Blotch and Spot Form of Net Blotch are supported by the trial results. These trial data support the label directions to make two applications at the 250 mL/ha rate or one at 500mL – 1L/ha, repeating if infection persists.
The claim for control of Powdery Mildew is supported by results from a single trial. These trial data support the optional one application at 1L/ha, or repeat applications at 500 – 1L/ha. The data do not support the label recommendation for one application at 500 mL/ha as they demonstrate an inadequate level of reduction of disease incidence and severity, statistically less than that achieved with the industry standard. It is noted that in this one trial disease pressure was high and there was significant disease present before treatment commenced.

9 LABELLING REQUIREMENTS

CAUTION

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

MBREX FUNGICIDE

ACTIVE CONSTITUENT: 62.5 g/L FLUXAPYROXAD

GROUP	7	FUNGICIDE

For the control of specified fungal diseases of barley (except malting barley) as per the Directions for Use Table.

CONTENTS: 5, 10, 20 L

BASF Australia Ltd ABN 62 008 437 867
Level 12, 28 Freshwater Place Southbank VICTORIA 3006

® Registered trademark of BASF

APVMA Approval No.: 64104/49905

STORAGE AND DISPOSAL

Store in the closed, original container in a cool, well-ventilated area out of direct sunlight. Triple or preferably pressure rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on-site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and bury empty containers in a local authority landfill. Empty containers and product should NOT be burnt.

SAFETY DIRECTIONS

May irritate the skin. Will damage the eyes. When opening the container, mixing and loading and using the prepared spray, wear cotton overalls (or equivalent clothing) buttoned to the neck and wrists and elbow-length chemical resistant gloves and face shield or goggles. Wash hands after use. After each day's use wash gloves and face shield or goggles and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet.

CONDITIONS OF SALE

All conditions and warranties rights and remedies implied by law or arising in contract or tort whether due to the negligence of BASF Australia Ltd or otherwise are hereby expressly excluded so far as the same may legally be done provided however that any rights of the Buyer pursuant to non- excludable conditions or warranties of the Trade Practices Act 1974 or any relevant legislation of any State are expressly preserved but the liability of BASF Australia Ltd or any intermediate Seller pursuant thereto shall be limited if so permitted by the said legislation to the replacement of the goods sold or the supply of equivalent goods and all liability for indirect or consequential loss or damage of whatsoever nature is expressly excluded. This product must be used or applied strictly in accordance with the instructions appearing hereon. This product is solely sold for use in Australia and must not be exported without the prior written consent of BASF Australia Ltd.

APVMA Approval No: 64104/49905

Batch No:
Date of Manufacture:

BASF Australia Ltd
ABN 62 008 437 867
Level 12, 28 Freshwater Place
Southbank VICTORIA 3006

FOR SPECIALIST ADVICE IN AN EMERGENCY ONLY PHONE 1800 803 440 TOLL FREE-ALL HOURS-AUSTRALIA WIDE

CAUTION

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

MBREX FUNGICIDE

ACTIVE CONSTITUENT: 62.5 g/L FLUXAPYROXAD

GROUP	7	FUNGICIDE

For the control of specified fungal diseases of barley (except malting barley) as per the Directions for Use Table.

CONTENTS: 5, 10, 20 L

BASF Australia Ltd ABN 62 008 437 867
Level 12, 28 Freshwater Place Southbank VICTORIA 3006

APVMA Approval No.: 64104/49905

DIRECTIONS FOR USE

DO NOT apply more than 2 applications of MBREX Fungicide (or other Group 7 fungicide) in any one season on the same paddock with a minimum of 21 day interval between applications.

SPRAY DRIFT RESTRAINTS

DO NOT apply with spray droplets smaller than a MEDIUM spray droplet size category according to nozzle manufacturer specifications that refer to the ASAE S572 Standard or the BCPC Guideline.

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, 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 the product. (Additional record details may be required by the state or territory where this product is used.)

CROP	DISEASE	RATE	CRITICAL COMMENTS
Barley (except malting barley)	Net form of net blotch (*Pyrenophora teres* f *teres*) Spot form of net blotch (*Pyrenophora teres* f *maculata*) Leaf scald (*Rhynchosporium secalis*) Leaf Rust (*Puccinia hordei*)	250 mL/ha	Apply when conditions favour disease development and prior to development of disease in the crop. Two applications at this rate are required for adequate disease control. Apply once at around stem elongation (Z32) and again before ear emergence (Z59). DO NOT apply later than Z59.
		500 mL to 1 L/ha	Apply when conditions favour disease development and prior to development of disease in the crop. A repeat application may be required if infection pressure persists. Regularly monitor the crop from 3-4 weeks after the first application for signs of reinfection. Apply the higher rate when the disease is present on the upper leaves or when conditions are favourable for disease development. DO NOT apply later than Z59.
	Powdery mildew (*Blumeria graminis* f. sp. *hordei)*	500 mL to 1 L/ha	Apply when conditions favour disease development and prior to development of disease in the crop. Two applications at 500 mL are required for control. A repeat application of 1 L may be required if infection pressure persists. Regularly monitor the crop from 3-4 weeks after the first application for signs of reinfection. Apply the higher rate when the disease is present on the upper leaves or when conditions are favourable for disease development. DO NOT apply later than Z59.

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

WITHHOLDING PERIODS:

GRAZING: DO NOT GRAZE OR CUT FOR STOCK FOOD FOR 14 DAYS AFTER APPLICATION

HARVEST: NOT REQUIRED WHEN USED AS DIRECTED

GENERAL INSTRUCTIONS

MBREX is a broad spectrum fungicide. It inhibits spores germination, mycelial growth and sporulation of the fungus on the leaf surface. MBREX can be applied in either pre- or post- infection situations. However, optimum disease control is achieved when MBREX is applied preventatively in a regularly scheduled spray program and is used in a rotational program with other fungicides. Thorough coverage of the crop is necessary for best results.

FUNGICIDE RESISTANCE WARNING

GROUP	7	FUNIGICIDE

MBREX FUNGICIDE is a member of the succinate dehydrogenase inhibitor (SDHI) group of fungicides. For fungicide resistance management the product is a Group 7 fungicide. Some naturally occurring individual fungi resistant to Mbrex and other Group 7 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungal population if MBREX is used repeatedly. These resistant fungi may not be controlled by MBREX or other Group 7 fungicides, thus resulting in a reduction in efficacy and possible yield loss.
Since the occurrence of resistant fungi is difficult to detect prior to use, BASF Australia Ltd accepts no liability for any losses that may result from the failure of MBREX to control resistant fungi.

MIXING

MBREX is an emulsifiable concentrate formulation. The addition of a non-ionic surfactant is generally not required, although under certain environmental conditions and lower total application volumes, the addition of a non-ionic surfactant may assist in providing better coverage of sprayed surfaces. Add the product to the half filled spray tank while agitating. Continue to agitate while topping up the tank and during spraying.

APPLICATION

Ground application

Apply in a water volume of between 50 and 100 L/ha, using flat fan nozzles operating at around 50 cm above the top of the crop. Use the higher water volume in crops with heavier canopies.

Aerial application

Apply with suitable aircraft, set up and operated to apply fungicides to cereal crops in a minimum water volume of 20 L/ha.

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.

PRECAUTIONS

Avoid contact with eyes and skin. Protect eyes while using.

WARNING STATEMENT

Will damage eyes.

CAUTION

Export of treated cereals

Growers should note that Maximum Residue Limits (MRLs) or import tolerances do not exist in all markets for cereals treated with MBREX FUNGICIDE. Additionally, some export markets have established MRLs different to those in Australia. If you are growing cereals for export, please check with BASF Australia Ltd or your grain exporter for the latest information on MRLs and import tolerances BEFORE using MBREX FUNGICIDE.

LIVESTOCK DESTINED FOR EXPORT MARKETS

The grazing withholding period only applies to stock slaughtered for the domestic market. Some export markets apply different standards. To meet these standards, ensure that in addition to complying with the grazing withholding period, the Export Slaughter Interval is observed before stock are sold or slaughtered.

EXPORT SLAUGHTER INTERVAL (ESI):

AFTER OBSERVING THE WITHHOLDING PERIOD FOR GRAZING OR CUTTING FOR STOCKFOOD, LIVESTOCK THAT HAVE BEEN GRAZED ON OR FED TREATED CROPS SHOULD BE PLACED ON CLEAN FEED FOR 2 DAYS PRIOR TO SLAUGHTER.

PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET CROPS

DO NOT apply under weather conditions, or from spraying equipment, that may cause spray to drift onto nearby susceptible plants/crops, cropping lands or pastures.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product or used containers

STORAGE AND DISPOSAL

Store in the closed, original container in a cool, well-ventilated area out of direct sunlight. Triple or preferably pressure rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on-site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and bury empty containers in a local authority landfill. Empty containers and product should NOT be burnt.

SAFETY DIRECTIONS

May irritate the skin. Will damage the eyes. When opening the container, mixing and loading and using the prepared spray, wear cotton overalls (or equivalent clothing) buttoned to the neck and wrists and elbow-length chemical resistant gloves and face shield or goggles. Wash hands after use. After each day's use wash gloves and face shield or goggles and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet.

CONDITIONS OF SALE

All conditions and warranties rights and remedies implied by law or arising in contract or tort whether due to the negligence of BASF Australia Ltd or otherwise are hereby expressly excluded so far as the same may

legally be done provided however that any rights of the Buyer pursuant to non- excludable conditions or warranties of the Trade Practices Act 1974 or any relevant legislation of any State are expressly preserved but the liability of BASF Australia Ltd or any intermediate Seller pursuant thereto shall be limited if so permitted by the said legislation to the replacement of the goods sold or the supply of equivalent goods and all liability for indirect or consequential loss or damage of whatsoever nature is expressly excluded. This product must be used or applied strictly in accordance with the instructions appearing hereon. This product is solely sold for use in Australia and must not be exported without the prior written consent of BASF Australia Ltd.

APVMA Approval No: 64104/49905
Batch No:
Date of Manufacture:
® = Registered trademark of BASF

BASF

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ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
ESI	Export Slaughter Interval
EUP	End Use Product
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice

h	hour
ha	hectare
Hct	Heamatocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram

NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period
w/w	weight/weight

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product (also referred to as active ingredient (a.i.))
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrolysis	Breakdown of chemicals in the presence of water
Hydrophobic	Repels 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 octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
Metabolites	Breakdown products following metabolism
Parent	The original chemical as applied, i.e. prior to breakdown by metabolism
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

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