Public Release Summary
on

Evaluation of the new active

KRESOXIM-METHYL

in the product

STROBY WG FUNGICIDE

National Registration Authority
for Agricultural and Veterinary Chemicals

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FOREWORD

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

In undertaking this task, the NRA works in close cooperation with advisory agencies, including the Department of Health and Family Services (Chemicals and Non-prescription Medicines Branch), Environment Australia (Risk Assessment and Policy Section), the National Occupational Health and Safety Commission (NOHSC) and State departments of agriculture and environment.

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

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

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

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

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

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CONTENTS

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LIST OF ABBREVIATIONS AND ACRONYMS

ac	active constituent
ADI	acceptable daily intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
bw	bodyweight
d	Day
DAT	Days after treatment
DT_{50}	Time taken for 50% of the initial concentration to dissipate
DT_{90}	Time taken for 90% of the initial concentration to dissipate
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated environmental concentration
EUP	end use product
Fo	original parent generation
FAISD	First aid instructions and safety directions
GAP	Good agricultural practice
GC	Gas cromatography
GGT	γ-glutamyl transferase
h	Hour
HPLC	high pressure liquid chromatography *or* high performance liquid chromatography
id	Intradermal
im	Intramuscular
ip	Intraperitoneal
IPM	Integrated pest management
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
iv	Intravenous
kg	Kilogram
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOQ	Limit of quantitation
mg	Milligram
mL	Millilitre
MRL	maximum residue limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
ng	Nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	no observable effect concentration/level
po	Oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
s	Second

sc	Subcutaneous
SC	suspension concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
T-Value	a value used to determine the First Aid Instructions for chemical products that contain two or more poisons
TGAC	technical grade active constituent
WDG	water dispersible granule
WHP	withholding period

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SUMMARY

Kresoxim-methyl is a new fungicide from the strobilurin group of chemicals. The biochemical mode of action is by inhibition of electron transport in the mitochondria of fungal cells, thus preventing the formation of ATP which is necessary for the normal metabolic processes of the fungus.

BASF Australia Limited have applied for registration of the product Stroby WG Fungicide (Stroby), a water dispersible granule formulation containing 500g/kg kresoxim-methyl. The product will initially be marketed for the control of black spot or scab (*Venturia inaequalis)*and powdery mildew (*Podosphaera leucotricha)* on apples in all States.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Stroby WG Fungicide. Responses to this public release summary will be taken into account by the NRA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

Written comments are invited and should be submitted by **4 July 2000** to the NRA at the address shown in the Introduction.

Public Health Aspects

Toxicology

Following oral administration to rats, kresoxim-methyl was rapidly but incompletely absorbed and widely distributed. It was completely metabolised and excreted via the bile into faeces and also in the urine. Kresoxim-methyl had low acute oral, dermal and inhalation toxicity, and was not a irritant in the eye and skin and not a skin sensitiser. The product Stroby WG Fungicide also has low acute toxicity.

In repeated dose studies in rats and mice and dogs, the adverse effects caused by kresoxim-methyl at high doses consisted of lower body weight gain, higher absolute and relative weight of liver and kidneys, brain and the adrenal glands. In life-time studies in rats but not mice, very high daily oral ingestion of kresoxim-methyl in the diet caused these adverse effects which resulted in an increased incidence of liver cancer.

Special studies to investigate the mechanism of action indicated that the liver cancer was due to an increased rate of cell division and not by any direct damage to the genetic material in the cell. Therefore by keeping the dietary intake below the level which caused toxic effects no liver cancer was observed. This threshold toxicity dose corresponds to the ingestion of about 20 g/day in adult humans over an entire lifetime. Since the Acceptible Daily Intake (ADI) has been established at 0.4 mg/kg bw/day or less than 3 mg/day for an adult human, the margin of safety is in the order of 10,000-fold. There was no evidence of any reproduction or developmental effects.

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 Stroby WG Fungicide when used in accordance with the label directions.

Residues in Food and Trade Aspects

Data concerning residues in apples, metabolism in plants and animals, environmental fate and chemistry were considered as part of the residue evaluation of the application.

Residues in food

In apples, kresoxim-methyl was shown to remain predominantly unchanged as the parent compound, and the residues remained mainly on the peel of the fruit. The animal metabolism studies indicated that kresoxim-methyl was extensively metabolised and rapidly excreted with negligible residues detected in tissues or milk.

With regards to the residue definition, it is appropriate to establish the parent compound as the residue definition for kresoxim-methyl in apples and in animals as the parent kresoxim-methyl. Validated analytical methods were capable of quantifying kresoxim-methyl residues in apples to 0.05 mg/kg for kresoxim-methyl (parent) in apples, and 0.01 mg/kg in animal tissues and 0.001 mg/kg in milk (metabolites).

Residue data from Australia, New Zealand and Europe support the proposed MRL of 0.1 mg/kg for apples with a harvest withholding period of 42 days.

Animals may be fed apple pomace containing quantifiable kresoxim-methyl residues. However, given the rapid metabolism of kresoxim-methyl in animals and the negligible transfer and accumulation of residues in animal tissues and milk, the animal MRLs are set at the Limit of Quantitation.

The following amendments to the *MRL Standard* are recommended:

Table 1

Compound	Food		MRL (mg/kg)
ADD: Kresoxim-methyl			
	FP 0226	Apple	0.1
	MM 0095	Meat (mammalian)	*0.01
	MO 0105	Edible offal (mammalian)	*0.01
	ML 0106	Milks	*0.001

Table 3

Compound	Residue
ADD: Kresoxim-methyl	Kresoxim-methyl

Table 4

Compound	Animal feed commodity		MRL (mg/kg)
ADD:			
Kresoxim-methyl			
	AB0226	Apple pomace, dry	0.5

The following WHPs are recommended in relation to the above MRLs for Stroby WG Fungicide:

Harvest

Apples DO NOT HARVEST FOR 6 WEEKS AFTER APPLICATION

Grazing DO NOT GRAZE ANY TREATED AREA, OR CUT FOR STOCK FOOD

Trade aspects

The main export markets for Australian apples (Singapore, Malaysia, Philippines and PNG) do not have MRLs for kresoxim-methyl. The Australian MRL is similar to that of several other countries. It is generally accepted that signatory countries to the WTO agreement will, in the case of a trade dispute, reference the CODEX MRLs. As the Australian MRL for apples is lower than the corresponding CODEX MRL of 0.2 mg/kg, the risk to Australian trade is low. Residue data indicate that violations of the proposed Australian MRL of 0.1 mg/kg are unlikely.

No quantifiable kresoxim-methyl residues are expected in milk or animal tissues.

Occupational Health and Safety Aspects

NOHSC has conducted a risk assessment on Stroby WG Fungicide containing kresoxim-methyl at 500 g/kg as a water dispersible granule formulation for use on apples. Workers can safely use Stroby WG Fungicide when handled in accordance with the control measures indicated in this assessment.

Kresoxim-methyl is currently not on the NOHSC *List of Designated Hazardous Substances.* Based on the NOHSC *Approved Criteria for Classifying Hazardous Substances,* kresoxim-methyl is classified as hazardous. This classification is based on evidence that very high concentrations of kresoxim-methyl, in the range of the maximum tolerated dose, caused liver tumours in rats after chronic exposure.

Stroby WG Fungicide possesses low acute oral and dermal toxicity in rats. The product was neither an eye and skin irritant in rabbits, nor a skin sensitiser in guinea pigs, and was of low inhalation toxicity in rats.

Stroby WG Fungicide is proposed for the control of black spot (scab) and powdery mildew in apples. It will be applied as a high volume (dilute) or a low volume (concentrate) spray, using orchard spraying equipment. The proposed rate is 150-350 g/ha in a minimum of 100L water/ha.

Worker exposure data was not available for kresoxim-methyl or Stroby WG Fungicide. The occupational health and safety risk assessment was based on estimates obtained from an exposure model.

Based on the risk assessment, elbow length PVC gloves are recommended for users of Stroby WG Fungicide. A re-entry statement is not recommended for this product.

Environmental Aspects

Kresoxim-methyl is to be used for specified fungal disease control in apple trees. Environmental residues will mainly be associated with the soil, or water bodies via spray drift. Residues of kresoxim-methyl and its main degradation product, the acid metabolite BF 490-1, are not expected to persist in the soil or water for any length of time. Hydrolysis, both abiotic (alkaline pH) and biotic, is the major degradation route. Aerobic soil metabolism is an important route for primary degradation with eventual mineralisation occurring.

The short environmental life of kresoxim-methyl is supported by the rapid breakdown in aerobic and anaerobic soils (DT_{50} values of less than 5 days). While measured DT_{50} values of the acid metabolite in aerobic soils were longer (38 to 511 days), mineralisation was still important, and indicative of the acid's non-persistence in soil. In aerobic soil/water systems, kresoxim-methyl had a DT_{50} of 1 to 2 days, indicating ready dissipation occurs. In such systems, the acid metabolite, however, may be more persistent.

Field dissipation studies confirmed the ready dissipation of kresoxim-methyl (DT_{50} of <1 day to several days), with indications that the acid metabolite also readily degrades (DT_{50} values of the order of about 8 to 35 days were reported). While kresoxim-methyl has low to slight soil mobility, its acid metabolite has very high mobility. However, under field conditions neither chemical is a strong leacher.

Kresoxim-methyl residues transferred to aquatic systems rapidly hydrolyse to the free acid which is further broken down by photolysis and microbial degradation. Accumulation in soils or bioaccumulation in aquatic organisms should not occur.

Kresoxim-methyl TGAC is practically non-toxic to birds in acute and sub-acute dietary studies and only of marginal toxicity based on a first generation reproduction study. Acute exposure of fish to kresoxim-methyl TGAC and as the formulated product, showed the chemical was highly toxic. In chronic studies with the TGAC and formulated product, the chemical was classified as, respectively, moderately and slightly toxic to exposed fish. The acid metabolite, BF 490-1, was practically non-toxic to fish.

The TGAC and a formulated product were highly toxic to daphnids under conditions of acute exposure. With respect to chronic exposure, the TGAC and formulated product are respectively, moderately and slightly toxic to daphnids. The TGAC and formulated product are very highly toxic to some alga with the acid metabolite again practically non-toxic.

Kresoxim-methyl was not shown to have any toxic effect on duckweed (*Lemna gibba*) at 310 µg/L or species of *Pseudomonas* bacteria at 1000 mg/L. Acute exposure to algae is the most sensitive aquatic toxicity indicator. The acid metabolite was practically non-toxic to *Daphnia magna*, green algae, or *Pseudomonas putida*. A study of an aquatic ecosystem treated with multiple applications at rates equivalent to direct overspray (200 g formulated product/ha) and at 20% and 4% spraydrift showed no adverse effects on phytoplankton, benthic organisms, insects or fish, and produced changes in several species of zooplankton that were regarded as statistically insignificant.

Laboratory studies indicate that kresoxim-methyl TGAC is slightly toxic to honey bees (*Apis mellifera*) by either contact or ingestion. The formulated product is very slightly toxic to bees. Laboratory studies on predatory ground beetles and parasitic wasps indicated no harmful effects when treated at about 85% of the proposed Australian rate of 175 g ai/ha or on predacious bugs at about 114% of the proposed Australian rate.

Laboratory studies indicated that ladybirds exposed to formulated product at a rate of ca. 150 g kresoxim-methyl/ha showed no mortality effects but there was a reduction in egg hatching rate. However, a semi-field study at the same treatment rate confirmed the absence of mortality and showed no effect on reproduction occurred under the test conditions. Laboratory studies on predacious mites with kresoxim-methyl containing formulated products at rate equivalent to approximately 57 and 86% of the proposed Australian rate showed the exposure was harmless.

Field studies on grapes and apples using excessive numbers of applications and rates of 57 to 100% of that proposed for Australia, confirmed the expectation that the proposed Australian use should not have significant deleterious effects on predacious mite populations although there is a possibility that excessive applications could be associated with a reduction of mite numbers.

Laboratory earthworm tests with *Eisenia foetida* indicated that no adverse effects could be related to exposure over a 14 day period to kresoxim-methyl TGAC at concentrations up to ca. 1000 mg/kg dry soil. The formulated product was slightly toxic at concentrations of 500 and 1000 mg/kg dry soil. The acid metabolite was not shown to be toxic (at up to 1000 mg/kg dry soil) to earthworms.

Studies of the effect of kresoxim-methyl as the TGAC and as a formulated product on soil microflora respiration and ammonification/nitrification in soils indicate that kresoxim-methyl should not have long term effects on those processes. Again, the acid metabolite had no significant effect on soil respiration and while low level treatment with the metabolite was assessed as tolerable to nitrogen turnover in the soil, treatment a higher rate did not reproduce this result, giving instead an indication of having negligible effect on nitrogen turnover.

Direct overspray would present a potential hazard to all aquatic species with fish and algae the most sensitive. There was marginal hazard at 10% spray drift and refinement of the hazard assessment showed that under worst case situations hazard was acceptable to fish and algae with a down-wind buffer distance of 30 m. Moreover, an aquatic ecosystem study indicated that formulated kresoxim-methyl had no major adverse effect on the ecosystem after multiple treatments with kresoxim-methyl with environmental concentrations approximately 57% of the maximum expected from the proposed Australian use pattern.

While spray drift, and run-off to a lesser extent, are likely to be the principal routes of entry into water bodies, the hazard assessment suggests that mitigation of hazard arising from the proposed use pattern is possible. Bioaccumulation in aquatic organisms should not occur.

Stroby WG Fungicide is considered very slightly toxic to honey bees and the use pattern should not result in an unacceptable hazard. The formulated product was not hazardous to predatory ground beetles, parasitic wasps, and predacious bugs. A low level hazard to ladybirds was indicated in a laboratory study but did not occur in semi-field studies.

Predacious mites were generally unaffected by treatment with formulated kresoxim-methyl as were earthworms, soil respiration and nitrogen turnover.

The hazard assessment indicates that birds, mammals, and most non-target invertebrates are unlikely to be adversely affected by the proposed use of Stroby WG Fungicide. While spray drift and run-off are likely to be the principal routes of entry into water bodies, exposure to aquatic organisms is not expected to present a major hazard because of the rapid hydrolysis to the non-toxic acid metabolite, the relatively restricted use (apple orchards), and relatively short half-life in aquatic environments. Use of mitigation procedures, including label warnings, will further reduce this hazard and chronic exposure is not expected to be significant because of the ready loss of kresoxim-methyl from the system.

Environment Australia concludes that a low hazard to the environment may be predicted provided the product is used according to the proposed label recommendations and Good Agricultural Practice.

Efficacy and Crop Safety Aspects

Data were presented from fourteen trials to demonstrate efficacy against black spot and from seven trials against powdery mildew.

In all trials comparisons were provided of Stroby treatment with untreated controls and with a number of currently used fungicides. The fungicides in the black spot trials were a protectant, a curative and a combination of protectant and curative schedule products. In the powdery mildew trials there were four different curative fungicides applied for comparison.

Trials included Stroby applied at the proposed label rate on growers properties in commercial orchards or against more severe disease pressure in neglected orchards. They were conducted in four States in Australia on nine apple cultivars and are considered to adequately reflect the potential commercial application of Stroby in Australia.

The data supplied were appropriately statistically analysed and show that the product should provide control of black spot and powdery mildew in apples when used as directed. The product performed similarly to eradicant fungicides tested and was superior to standard protectants. Its effect is on spore germination and penetration, not on mycelium, so it is not an eradicant. However it has translaminar movement.

Crop safety

No adverse reactions were recorded in the trials that included nine cultivars of apples.

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Stroby WG Fungicide, which contains the new active constituent kresoxim-methyl.

Responses to this Public Release Summary will be considered prior to registration of the product. They will be taken into account by the NRA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

Written comments are invited and should be submitted by **4 July 2000,** addressed to:

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National Registration Authority
PO Box E240
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Phone 02 6722 4850 Fax 02 6272 3218

Applicant:

BASF Australia Limited

Product details:

Stroby WG Fungicide (Stroby) is a water dispersible granule formulation containing 500g/kg kresoxim-methyl. The product will initially be marketed for the control of black spot or scab (*Venturia inaequalis)* and powdery mildew (*Podosphaera leucotricha)* on apples in all States.

Kresoxim-methyl is a new fungicide from the strobilurin group of chemicals. The biochemical mode of action is by inhibition of electron transport in the mitochondria of fungal cells, thus preventing the formation of ATP which is necessary for the normal metabolic processes of the fungus.

Formulations of kresoxim-methyl, usually in granular form, are currently registered in more than 18 countries for disease control in apples.

CHEMISTRY AND MANUFACTURE

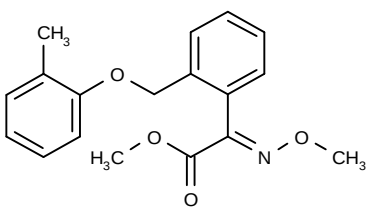
The product proposed for use in Australia is a water dispersible granular formulation under the trade name Stroby WG Fungicide.

The formulation storage stability and the physical and chemical properties of the formulated product and the active constituent have been evaluated by the NRA and are considered acceptable.

The source of Technical Grade Active Constituent to be used in the product hase been approved by NRA (approval no 51350).

Active constituent

The chemical active constituent in Stroby is kresoxim-methyl which has the following properties:

Common name (ISO):	kresoxim-methyl
Chemical name (IUPAC):	methyl (E)-2-methoxyimino-2-[2-(o-tolyloxymethyl) phenyl] acetate
CAS Registry Number:	143390-89-0
Empirical formula:	$C_{18}H_{19}NO_4$
Molecular weight:	313.3
Physical form:	crystalline solid
Colour:	white
Odour:	mild aromatic
Melting point for E/Z mixture (1:1):	101°C
Density:	1.258 at 20°C
Octanol/water partition coefficient (K_{OW}):	2500
Vapour pressure at 20°C:	$2.3x10^{-9}$kPa
Structural formula:	

Formulated product

Product name:	STROBY WG FUNGICIDE
Active content:	500g/kg kresoxim-methyl
Formulation type:	water dispersible granule
Colour and physical state:	dark brown granules
Odour:	mildly sulphurous

TOXICOLOGICAL ASSESSMENT

EVALUATION OF TOXICITY

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

Acute studies

For kresoxim-methyl administered to rats, the oral LD_{50} was greater than 5000 mg/kg bw and greater than 2000 mg/kg bw when dermally applied. The inhalational toxicity (LC_{50}) was greater than 5600 mg/m^3. It was not an irritant to the eyes or skin in rabbits or a skin sensitiser in guinea pigs. The product Stroby WG Fungicide, which contains 500 g/kg kresoxim-methyl, has an identical acute toxicity profile.

Short-term studies

Mice were dosed with 0, 500, 2000 or 8000 ppm of kresoxim-methyl in the diet for 28 days. Food consumption were transiently reduced (up to 20% less) in 500 and 2000 ppm groups. Relative liver weight was significantly increased in the 8000 ppm group due to a slightly lower body weight and higher absolute liver weight. There was an increased brain weight in females at 8000 ppm.

Rats received 0, 1000, 4000 or 16000 ppm of kresoxim-methyl in the diet for 28 days. Serum GGT (?-glutamyl transferase) and albumin increased in males at 16000 ppm. There was a trend towards decreased ALT, AST and ALP in all treatment groups and thyroid-stimulating hormone was higher in females at 16000 ppm. A significantly higher relative liver weight was seen in females at 16000 ppm as a result of slightly lower body weight and higher absolute liver weight. In addition, there was a decrease of fatty infiltration in the liver, predominantly at 4000 and 16000 ppm.

Rats received dermal applications of kresoxim-methyl 1000 mg/kg bw, under an occlusive dressing for 6 hours per day over 21 days. A sub-macroscopic and superficial crust was

observed in the outer layer of the cornified epithelium at the application site of one male of the test group. Fatty infiltration of hepatocytes was slightly lower in males of the test group.

Mice were treated with 0, 250, 1000, 4000 or 8000 ppm of kresoxim-methyl in the diet for 95 days. Terminal body weight of males in the 8000 ppm group was lower. There was a trend for dose-dependent increase in the relative liver weight in males of all test groups with statistical significance at 4000 and 8000 ppm. Hence, the NOEL was 1000 ppm (230 mg/kg bw/day).

Rats fed 0, 500, 2000, 8000 or 16000 ppm of kresoxim-methyl in the diet for 3 months had significantly lower body weight gain at 8000 and 16000 ppm (in males). Significantly decreased activities of ALP, ALT and AST were found in most treatment groups but liver damage as the cause was ruled out by an additional series of experiments. An increased activity of GGT appeared in males of the 8000 and 16000 ppm groups. The relative weight of liver, kidney and adrenal glands was significantly higher in some treatment groups, due to a slightly decreased body weight. In addition, the intensity of diffuse fatty infiltration of hepatocytes was decreased dose dependently. The NOEL was 2000 ppm (146 mg/kg bw/day).

Dogs fed 0, 1000, 5000 or 25000 ppm of kresoxim-methyl in the diet for 3 months had diarrhoea and vomiting at 25000 ppm. There was also a significant decrease in body weight gain for males during the first 7 weeks and for females through the entire study at 25000 ppm. After 4 weeks, reduced levels of albumin and total protein were detected in the 25000 ppm group, but returned to control levels by the end of treatment. The NOEL was 5000 ppm (150 mg/kg bw/day).

Long-term studies

Mice received 0, 400, 2000 or 8000 ppm of kresoxim-methyl in the diet for 18 months (main groups) or 12 months (satellite groups). Food consumption was slightly decreased in all treatment groups and body weight was lower in females at 2000 ppm, and in males and females at 8000 ppm. The mortality was comparable between groups. The increase in relative weight of liver, kidney, adrenal glands and testes in some treatment groups was due to reduced terminal body weight with no histopathological correlation. Females at 8000 ppm showed a higher incidence of papillary necrosis in the kidneys and of amyloidosis in the liver. The incidence of tumours was comparable between treatment groups and the control. Hence kresoxim-methyl did not exhibit a carcinogenic potential in any organ/tissue of mice. The NOEL was 400 ppm (81 mg/kg bw/day).

Rats treated with 0, 200, 800, 8000 or 16000 ppm of kresoxim-methyl in the diet for 2 years had lower body weights at 8000 and 16000 ppm. The high mortality in the male 200 ppm group (60 vs 15 in the control) was assessed as being incidental. A decrease in serum enzyme activities of ALP as well as ALT occurred in most treatment groups. In males at 8000 and 16000 ppm, absolute and relative liver weights were increased and GGT activity was significantly higher. The pathological changes in the liver included increased liver masses, cysts, eosinophilic foci and hepatocellular hypertrophy, predominantly in the 16000 ppm group, and to a lesser extent in the 8000 ppm group. Most remarkably, the treatment resulted in a significant increase in hepatocellular carcinomas at 8000 and 16000 ppm. The NOEL was 800 ppm (36 mg/kg bw/day).

Rats were treated with 0, 200, 800, 8000 or 16000 ppm of kresoxim-methyl in the diet for two years to confirm its carcinogenic effect. Similar to observations in the other two-year rat study there was reduced body weight gain, increased relative weight of liver and brain, higher incidence of liver masses and cysts, and more notably, a significantly higher incidence of hepatocellular carcinomas plus two hepatocholangiocarcinomas. Moreover, a concurrent stimulation of cell proliferation in both liver and bile duct cells was observed at 16000 ppm. The NOEL was 800 ppm (36 mg/kg bw/day).

Dogs were treated with 0, 1000, 5000 or 25000 ppm of kresoxim-methyl in the diet for one year. Diarrhoea and vomiting occurred in some animals of the 25000 ppm group. From week 27 to the end, males of the 25000 ppm group had significantly lower body weight gain and food efficiency. There was a dose-dependent trend towards increase in the relative liver weight in both sexes of the two highest dose groups but with significance in males of the 5000 but not 25000 ppm group. The NOEL was 5000 ppm (138 mg/kg bw/day).

Reproduction and Developmental Studies

Rats received 0, 50, 1000, 4000 or 16000 ppm of kresoxim-methyl in the diet through two generations with two matings in the first (F0) and one mating in the second generation (F1a). For F0 and F1 parental females, food consumption and body weight gain were depressed during most of the premating, gestation and lactation period at 16000 ppm, to a lesser extent at 4000 ppm and occasionally at 1000 ppm. Similar changes also appeared in males. Relative weight of liver, kidneys, testes and epididymides were significantly higher due to lower body weight. There were significantly lower serum ALP and ALT activities in most of the treatment groups and a dose related higher GGT activity in 4000 and 16000 groups. Fat storing cells were reduced in F0 and F1 males at 4000 and 16000 ppm. Fertility and reproductive function in both sexes was not affected. Body weight gain of pups was significantly lower during the lactation period of both generations at 4000 and 16000 ppm. This retarded growth led to significant delay of pinna unfolding in F1b pups at 4000 and 16000 ppm and auditory canal opening in F2 pups at 4000 ppm. There was no effect on reproductive function at 16000 ppm (1349 mg/kg bw/day). The NOEL for general toxicity was 1000 ppm (84 mg/kg bw/day).

Pregnant rats were treated with 0, 100, 400 or 1000 mg/kg bw/day of kresoxim-methyl by stomach tube on day 6 to 15 of pregnancy. The food consumption and body weight gains of the dams were unchanged. The treatment did not affect post-implantation losses, the number of resorptions and viable fetuses, the sex distribution of foetuses, and placental and foetal weight. Various skeletal malformations and retardation were either not treatment-related or within the range of historical control. Fetal development was not affected at any level.

Pregnant rabbits were treated with 0, 100, 400 or 1000 mg/kg bw/day of kresoxim-methyl by gavage from day 7 to19 of pregnancy. There were no significant alterations in body weight, uterus weight and no influence on the parameters related to reproductive function (implantation sites, post-implantation losses, the number of resorptions and viable fetuses). The treatment did not affect sex distribution of fetuses, weight of placentae or fetuses. Signs of fetal retardations occurred at a comparable frequency in the control and treatment groups. There were no effects on fetal development even at the highest dose.

Genotoxicity studies

Kresoxim-methyl was not mutagenicic or genotoxic in a range of tests which included; Ames tests covering *S. typhimurium strains* TA 98, 100, 1535, 1537, and *E. coli WP2 uvrA*, gene mutation test in CHO cells, chromosome aberration assay in human lymphocytes, unscheduled DNA synthesis in rat hepatocytes *in vitro* and *in vivo*, and an *in vivo* mouse micronucleus test. The only positive outcome was that kresoxim-methyl stimulated cell proliferation activity in S-phase rat hepatocytes.

Other studies

In order to elucidate the mode of action, a series of mechanistic studies were conducted. Three stages are involved in the process of carcinogenesis: 1) intitiation, 2) promotion, and 3) progression. There was a negative battery of mutagenicity tests, leading to the conclusion that kresoxim-methyl was not a genotoxic chemical and thus unlikely to be an initiator of carcinogenesis. To confirm this assertion, a carefully designed series of initiation, promotion and progression studies were performed. Firstly, a study on the initiating potential of kresoxim-methyl clearly demonstrated that the test compound was devoid of an initiating potential. Foci of cellular alteration which indicates an initiating potential, were not found in the 3-month rat feeding studies at dose levels up to 1200 mg/kg bw/day.

A promotion study in rats with diethylnitrosamine (DEN) as the initiator revealed significant and dose related increases in the number and area of glutathione-s-transferase placenta form (GST-P) positive hepatocellular foci in 8000 and 16000 ppm groups. Cell proliferation is well recognised as a mechanism of cancer induction. The cell-proliferation was fully reversible following cessation of treatment. There was a clear quantitative correlation and link between liver cell proliferation in the mechanistic studies and liver tumours in the carcinogenicity study, both negative at 200 and 800 ppm, but positive at 8000 and 16000 ppm.

Therefore, the increased incidence of liver tumour is considered to originate from a toxic effect exerted on the liver which results in an increased cell proliferation. Non-genotoxic chemicals can stimulate cell proliferation by a variety of means and the molecular mechanism for kresoxim-methyl is so-far unknown. The carcinogenicity potential of kresoxim-methyl is low and it is considered that at expected exposure levels, tumour induction in humans would be unlikely.

A cross-sectional health examination study of employed men assigned to kresoxim-methyl production for 12 months was repeated at an interval of six months. No findings indicative of kresoxim-methyl induced changes in liver function indicators (GGT, AST, ALT and ALP) were seen. Under the conditions of exposure, there was no evidence of kresoxim-methyl induced health effects.

PUBLIC HEALTH STANDARDS

Poisons Scheduling

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

On the basis of its low toxicity, the NDPSC has recommended that kresoxim-methyl need not be scheduled in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP).

NOEL/ADI

The lowest NOEL in the most sensitive animal species was 36 mg/kg bw/day. This NOEL was established in a two-year rat study, based on increased absolute and relative liver weights, ?-glutamyl transferase activity (indicative of liver damage) and pathological changes in the liver at the next higher dose. The magnitude of the safety factor (100-fold) was selected to account for uncertainties in extrapolation from animal data to humans; variation within the human population; the quality of the experimental data; and the nature of the potential hazard. Hence an ADI of 0.4 mg/kg bw/day was established for kresoxim-methyl.

METABOLISM AND TOXICOKINETICS ASSESSMENT

Toxicokinetics and Metabolism

In rats given an oral dose, kresoxim-methyl was rapidly but incompletely absorbed (60% at 50 mg/kg bw and 25% at 500 mg/kg bw) and distributed to all organs and tissues. It was excreted predominantly via the biliary route to faeces, with lesser amount in urine. The highest residue was found in the liver and the kidneys, but the total residue in all tissues was less than 1% after 120 h. Kresoxim-methyl was metabolised extensively and no unchanged compound in the tissue, bile fluid and urine. A total of 34 metabolites were identified in rats.

When rats were given a dermal dose, the absorption was incomplete (max.12% at 0.007 mg/cm^2 for 24 h) and saturable. The total amount of radioactivity absorbed increased with exposure time and dose, while the percentage absorbed increased with exposure time but decreased with increasing dose. Peak plasma level occurred after 8 hours exposure at dose of 0.007 or 0.05 mg/cm^2 and after 24 hours exposure at 0.35 mg/cm^2 The highest tissue concentration was in kidney and liver and excretion was mainly via the urine.

Metabolism

Data concerning metabolism in apples and animals were considered as part of the residue evaluation of the application.

In rats greater than 85% of the kresoxim-methyl derived radioactivity from an oral dose of 50 or 500 mg/kg bw of labelled kresoxim-methyl was excreted in the urine and faeces within 48 hours. No significant accumulation of radioactive residues was found in any tissues or organs. Between 87-101% of administered radioactivity was recovered in all the experiments.

In goats the majority of the kresoxim-methyl derived radioactivity from an oral dose of 50 or 500 mg/kg bw of labelled kresoxim-methyl was eliminated in the urine and faeces (as metabolites). Only negligible residues were transferred into the milk (<0.03%) and tissues (<7%) of the animals. None of the parent compound was identified in any of the tissues analysed apart from fat, in which only a very small amount of kresoxim-methyl was recovered.

The major metabolites identified in the milk and tissues from the animal studies were 490M1 (parent acid) (in muscle, fat, liver and kidney), 490M2 (benzyl hydroxylated kresoxim-acid) (in milk, muscle, fat, liver, kidneys) and 490M9 (phenyl hydroxylated kresoxim-acid) (milk, liver, kidneys).

Plant metabolism studies using 14C-labelled kresoxim-methyl were provided for apples. In the treated apples, labelled kresoxim-methyl remained predominantly unchanged as the parent compound, and between 88-97% of the radioactive residues were located on the peel. Very little translocation of radioactive residues from the peel into the flesh of the apples occurred. There was some translocation of radioactive residues from the leaves to the fruit.

Characterisation of the radioactive residues showed that the major metabolites in apples were the parent isomer, kresoxim acid (490M1), conjugates of benzyl hydroxylated kresoxim-acid (490M2) and phenyl hydroxylated kresoxim-acid (490M9).

In summary, kresoxim-methyl is metabolised to a much greater extent in animals than in apples, however the major metabolites are the same in both animals and apples. Residues in apples remain mainly on the peel of the fruit. Very little translocation of residues occurs to the tissues and milk of animals administered kresoxim-methyl.

RESIDUES ASSESSMENT

Data concerning residues in apples and animals, metabolism in apples and animals, environmental fate and chemistry were considered as part of the residue evaluation of the application.

Analytical methods

Determination of kresoxim-methyl in apples

A validated analytical method was used to determine kresoxim-methyl residues in apples in the Australian, New Zealand and European residue trials. The method involves extraction of the residues with aqueous methanol, then partitioning the residues into iso-octane. Extracts were cleaned up by column chromatography on silica then concentrated and quantified by GC using a constant current EC detector. The methodology is considered adequate for determination of kresoxim-methyl (parent) residues in apples. The LOQ of the method was determined to be 0.05 mg/kg.

Determination of kresoxim-methyl in animal tissues

An additional method was used to quantify the major kresoxim-methyl metabolites (490M1, 490M2 and 490M9) in animal tissues. The method involves extraction of the residues from homogenised tissue samples with methanol, then partitioning of the acidified residues into dichloromethane and purification by HPLC. Final quantification is determined using HPLC with UV detection. The LOQ of the method for all analytes in all tissue matrices was 0.01 mg/kg.

Determination of the kresoxim-methyl metabolites in milk

Another analytical method was used to quantify the kresoxim-methyl derived residues (490M2 and 490M9) in milk. The residues are extracted from milk using acetone, purification of the extract by precipitation of impurities and partitioning of residues firstly into iso-octane, and then into dichloromethane at low pH. The extracts are further purified using ion exchange chromatography and quantified by reverse phase HPLC with UV detection. The LOQ for the method for both analytes is 0.001 mg/L.

Storage stability

A storage stability study of kresoxim-methyl and its major metabolites was presented in the application. Kresoxim-methyl residues were stable on storage at -20°C for up to 24 months in apples. The metabolites were found to be stable for up to 13 months in animal tissues when stored frozen at -20°C, with the exception of the metabolites 490M1 and 490M9 in kidney samples, which decreased by about 50% over 13 months.

Residue definition

Given that kresoxim-methyl is not metabolised in plants it is appropriate to set the definition of the residue in plants as the parent compound, kresoxim-methyl. In animals, kresoxim-methyl is almost completely metabolised, and there is very little transfer or accumulation of residues into the milk and tissues. However, for simplicity, it was considered appropriate to set the definition of the residue in animals as kresoxim-methyl (parent).

Residue trials

Apples

Six Australian, five New Zealand and ten European trials were presented. In the Australian trials kresoxim-methyl was applied at 1 and 2 times the recommended high volume rate of 5 g ai/100 L but with 6-11 applications at 10-20 day intervals. Apples were harvested between 11-37 days after the last treatment. There was a general dose relationship of residues in apples treated at the 1 and 2x rates. Kresoxim-methyl residues were mostly below 0.05 mg/kg (but ranging from 0.01 – 0.09 mg/kg) for apples treated at the 1x rate and harvested 35 days after the last treatment.

In the New Zealand trials kresoxim-methyl was applied at 5 g ai/100 L, with 8 applications at 8-13 day intervals. Apples were harvested between 0 and 42 days after the last treatment. Kresoxim-methyl residues were at or about the Limit of Quantitation of 0.05 mg/kg for all of the samples taken 35 days after the last application. In the European trials, kresoxim-methyl was applied at 100 g ai/ha (less than the maximum Australian rate of 175 g ai/ha) as 8 applications at about 10 day intervals. Apples were harvested up to 28 days after the final treatment and analysed for kresoxim-methyl residues. In all of these trials the residues were below the limit of detection 28 days after the final treatment.

Overall, the residue data presented support the applicant's proposed MRL of 0.1 mg/kg for kresoxim-methyl in apples and a harvest withholding period of 42 days.

Processing studies

Residue data were provided for apples and processed products as part of three of the European residue trials. Apples were treated with kresoxim-methyl at the European rate of 100 g ai/ha, which was less than the proposed Australian rate of 175 g ai/ha. Treated apples harvested 14 days after the last application were analysed before and after washing, and after preparing juice, pomace and sauce. In general the results showed a decrease in the level of kresoxim-methyl residues after processing.

Animal feed commodity MRLs

Apple pomace

Quantifiable kresoxim-methyl residues are expected in apple pomace prepared from treated apples. Kresoxim-methyl residues in apple pomace determined in the European trials (100 g ai/ha, with 14 day harvest WHP) were extrapolated (based on a linear relationship between residues and application rate) to account for the higher Australian application rate of 175 g ai/ha. These were calculated to be less than 0.5 mg/kg on a dry weight basis. The level of kresoxim-methyl residues in pomace prepared from apples harvested 42 days after the final treatment are likely to significantly less than 0.5 mg/kg. The residue data support the applicant's proposed MRL of 0.5 mg/kg for apple pomace (dry).

The level of kresoxim-methyl residues in weeds and plants under the apple trees was not addressed. However, the applicant has proposed the following grazing restraint be applied to the crops: DO NOT GRAZE ANY TREATED AREA, OR CUT FOR STOCK FOOD.

Animal commodity MRLs

Since apple pomace containing quantifiable kresoxim-methyl residues is likely to be used as an animal feed commodity, the applicant has proposed MRLs in animal commodities. In metabolism trials, lactating dairy cows were orally dosed kresoxim-methyl at 0, 120, 360 or 1200 mg/cow/day (about 0, 7, 21 and 70 ppm in the feed). No quantifiable kresoxim-methyl residues (or metabolites) were found in liver, kidney, muscle or fat samples for the animals dosed at 120 mg/day, except in kidney samples where the metabolite 490M1 was present at about 30 ppb (0.03 mg/kg). In these trials kresoxim-methyl was administered at a rate greater than 12 times higher (for lowest dosed rate) than the level expected to be consumed from apple pomace (containing kresoxim-methyl residues at the MRL of 0.5 mg/kg) as the sole feed commodity.

The metabolism and animal feeding studies studies showed that kresoxim-methyl is rapidly and extensively metabolised in animals, and that the residues (parent and metabolites) in animal tissues and milk are likely to be below the LOQ. The animal MRLs are therefore set at the limits of quantitation for mammalian meat and offal and milk. For simplicity, the definition of the residue in animal tissues is set as the parent compound.

Estimated dietary intakes

The theoretical maximum daily intake of kresoxim-methyl from the proposed use pattern is approximately 0.03% of the ADI of 0.4 mg/kg bw/day.

Bioaccumulation potential

Kresoxim-methyl has a log(P_{OW}) (log octanol/water partition coefficient) of 3.40, which suggests that some bioaccumulation may occur. However, results of metabolism and animal transfer studies indicate that kresoxim-methyl and its metabolites do not accumulate in fat or tissues.

Recommended amendments to the MRL Standard:

Table 1

Compound	Food		MRL (mg/kg)
ADD:			
Kresoxim-methyl			
	FP 0226	Apple	0.1
	MM 0095	Meat (mammalian)	*0.01
	MO 0105	Edible offal (mammalian)	*0.01
	ML 0106	Milks	*0.001

Table 3

Compound	Residue
ADD:	
Kresoxim-methyl	Kresoxim-methyl

Table 4

Compound	Animal feed commodity		MRL (mg/kg)
ADD:			
Kresoxim-methyl			
	AB0226	Apple pomace, dry	0.5

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

The following WHPs are recommended in relation to the above MRLs for Stroby WG Fungicide:

Harvest

Apples DO NOT HARVEST FOR 6 WEEKS AFTER APPLICATION

Grazing DO NOT GRAZE ANY TREATED AREA, OR CUT FOR STOCK FOOD

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Overseas registration status

Kresoxim-methyl is registered for use on apples or pome fruits in several countries, and these are summarised in the table below with the relevant established MRLs.

Country	Crop	MRL (mg/kg)
Codex	Pome fruits	0.2
Belgium	Apples, pears	0.05
Brazil	Apples	0.2
EU	Pome fruit	0.1 P
France	Apple, pear	0.1
Germany	Other vegetable food (includes apples, pears)	0.05
Japan	Apple, pear	5.0
Netherlands	Other vegetable food (includes apples, pears)	0.05
New Zealand	Apples	0.1
Portugal	Pome fruit	0.05 P
South Africa	Apple, pear	0.1
Spain	Apples, pear	0.05
UK	Pome fruits	0.05 P
USA	Pome fruits	0.5

* P denotes proposed or pending

CODEX Alimentarius Commission MRL

A provisional Codex MRL of 0.2 mg/kg has been set (JMPR 1998).

Potential risk to Australian export trade

In assessing the risk to Australian export trade the destination, volume and value of apples exported was considered. In 1998 Australia's forecast total production of apples is about 280 kt, valued at around $38 million. In 1997 about 25 kt of apples were exported, at a total value of $28 million. The main export markets for Australian apples are Singapore (6 kt), Malaysia (9 kt), the Philippines (1.3 kt), Papua New Guinea (1.5 kt) and the United Kingdom (1.6 kt). No MRLs or import tolerances were available for Singapore, Malaysia, the Philippines or Papua New Guinea.

The main export markets for Australian apples (Singapore, Malaysia, Philippines and PNG) do not have MRLs for kresoxim-methyl, however the Australian MRL for apples is similar to that of several other countries. It is generally accepted that signatory countries to the WTO agreement will, in the case of a trade dispute, reference the CODEX MRLs. As the Australian MRL for apples is lower than the corresponding CODEX MRL the risk to Australian trade is low. Residue data indicate that violations of the proposed Australian MRL of 0.1 mg/kg are unlikely with a harvest WHP of 6 weeks. No quantifiable kresoxim-methyl residues are expected in milk or animal tissues.

To further reduce the possibility of violations of the MRLs of importing countries, the company has included the following label statement on the product: *"If you are growing fruit for export, note that MRLs or import tolerances do not exist in all markets for fruit treated with Stroby, however CODEX MRLs do exist. Please contact Aventis CropScience for further information."*

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Kresoxim-methyl is not currentlyon the NOHSC *List of Designated Hazardous Substances*. Based on the NOHSC *Approved Criteria for Classifying Hazardous Substances,* kresoxim-methyl is classified as hazardous. This classification is based on evidence that very high concentrations of kresoxim-methyl, in the range of the maximum tolerated dose, caused liver tumours in rats after chronic exposure. The following risk phrase is allocated to kresoxim-methyl:

R40 Possible risk of irreversible effects

Substances are hazardous when they contain concentrations of ≥1% kresoxim-methyl.

Kresoxim-methyl is in the form of white, crystalline solid with mild aromatic odour. It has low acute oral, dermal and inhalation toxicity in rats and rabbits. It is not an eye or skin irritant in rabbits and is not a skin sensitiser in guinea pigs.

Stroby WG Fungicide is classified as hazardous according to NOSHC criteria based on the amount of a hazardous substance contained in the formulation.

Stroby WG Fungicide is a water dispersible granule formulation. It possesses low acute oral and inhalation toxicity in rats and low acute dermal toxicity in rabbits. The product is not an eye or skin irritant. The product will be supplied in 1 kg polyethylene laminated paper bags and 1.5 kg HDPE bottles.

Formulation, transport, storage and retailing

Stroby WG Fungicide will be formulated overseas and imported into Australia in sale packs. Transport workers, storepersons and retailers will handle the packaged product and could only become contaminated if the packaging were breached.

Advice on safe handling of the active or the product during routine use is provided in the Material Safety Data Sheet (MSDS) for Stroby WG Fungicide.

End use

Stroby WG Fungicide is proposed for the control of black spot (scab) and powdery mildew in apples. It will be applied as a high volume (dilute) or a low volume (concentrate) spray, using orchard spraying equipment fitted with mechanical or hydraulic agitation. The proposed rate is 150-350 g/ha in a minimum 100L water/ha.

The main routes of exposure to the product are inhalational and dermal. The product is a granular formulation, however workers are still likely to be exposed to some product dust formed from broken granules. Workers may also be exposed to spray mist from the product spray. Functions that can lead to exposure to the product include opening containers, mixing/loading, application, cleaning up spills, cleaning/maintaining equipment and re-entry into sprayed areas.

Entry into treated areas or handling treated crops

There are no re-entry studies available for Stroby WG Fungicide. Based on the toxicity of the product and its use pattern, a re-entry statement is not recommended at this stage.

Recommendations for safe use

Workers involved in transport, storage and retailing should be protected by safe work practices and training. End users should follow the instructions on the product label. Based on the toxicity of the active ingredient and the product, elbow-length PVC gloves are recommended for mixers/loaders of Stroby WG Fungicide.

Material Safety Data Sheet

BASF Australia Limited has produced MSDS for kresoxim-methyl and Stroby WG Fungicide. These should contain information relevant to Australian workers, as outlined in the NOHSC National Code of Practice for the Preparation of Material Safety Data Sheets. Employers should obtain the MSDS from the supplier and ensure that their employees have ready access to it.

Conclusions

Stroby WG Fungicide can be used safely if handled in accordance with the instructions on product label. Additional information is available on the MSDS for Stroby WG Fungicide.

ENVIRONMENTAL ASSESSMENT

Introduction

Kresoxim-methyl will be applied to apple trees with high volume (dilute) or low volume (concentrate) orchard sprayers. Spray drift could be significant, and the main non-target contamination of soil and water is likely to be through drift, and run-off from the soil to a lesser degree.

Environmental Fate
Kresoxim-methyl has only very slight volatility and its Henry's Law constant indicates very slight volatility from water. Similarly, the water solubility classifies kresoxim-methyl as slightly soluble. The log *n*-octanol/water coefficient value confirms the low water solubility and indicates a potential for bioaccumulation, soil sorption, and toxicity.

Hydrolysis/Photolysis

While stable at pHs 5, and 7, kresoxim-methyl is hydrolysed at pH 9 with a half-life of approximately 7 hours (34 days at pH 7). Hydrolysis is via cleavage of the ester linkage to form the acid metabolite. Hydrolysis is expected to be a major degradation route in alkaline media. Despite an apparent favourable quantum yield, photolytic degradation of kresoxim-methyl in solution is slow with a calculated half-life of ca. 30 days with parent the main material in the aqueous phase after 370 hours. The half-life of the acid metabolite in laboratory waters was estimated as 37 days but half of this in natural pond water. Sunlight is not expected to be a major route for kresoxim-methyl degradation in the aqueous environment. On soil, kresoxim-methyl underwent limited degradation when exposed to a Xenon irradiation source that was equivalent to natural sunlight. The soil DT_{50} was calculated as approximately 35 days.

Soil metabolism

Aerobic soil

Aerobic soil metabolism studies were conducted on six sandy loams (pHs 5.6 to 7.8) and on a clay loam (pH 7.5) treated with kresoxim-methyl at rates equivalent to 500 g kresoxim-methyl/ha. Mineralisation was a significant degradation process with 24 to 42% of the applied radioactivity present in the form of carbon dioxide at the end of the studies (100-364 days). Carbon dioxide was the only volatile produced. Residual (unextractable) radioactivity was essentially immobilised in the humin fraction. While the acid metabolite, BF 490-1, was the metabolite of significance found in the studies, the diacid metabolite was quantifiable on occasion.

Kresoxim-methyl rapidly degraded in the soils (DT_{50} values were less than 5 days) while DT_{50} values for the acid metabolite were ranged from 38 to 131 days in the sandy loams and 511 days (extrapolated value) in the clay loam. The studies showed that kresoxim-methyl rapidly hydrolyses to the free acid in soil which then either undergoes direct mineralisation to carbon dioxide or binds to the soil with eventual conversion to carbon dioxide. Aerobic degradation in a slightly alkaline sterile sandy loam soil was much slower with kresoxim-methyl being present as the major component after 181 days incubation. This contrasts to the other aerobic

soil studies where kresoxim-methyl rapidly disappeared, showing the importance of microbial action in the degradation of kresoxim-methyl.

Anaerobic soil

Under anaerobic conditions using a sandy loam treated with kresoxim-methyl at 0.5 mg/kg dry soil, carbon dioxide production was reduced and there were fewer bound residues than found in the aerobic degradations. The free acid, BF 490-1, was the major fraction present after 100 days. DT_{50} and DT_{90} times were not determined in the anaerobic soil study but may be estimated as probably a day or less for the parent and >100 days for the acid metabolite. The major degradation route was rapid conversion of kresoxim-methyl to the free acid, BF 490-1, which was then more persistent than under aerobic conditions.

Aerobic soil/water

When ^{14}C-kresoxim-methyl was added to two aerobic water and sediment aquatic systems at 0.17 mg/kg water, radioactivity slowly moved from the aqueous to the sediment phases such that 100 days after application 59 and 64% of the applied material remained in the aqueous phases. At that time, there was 34 and 25% of the radiolabel applied in the sediments. Degradation was primarily by hydrolysis to form the acid metabolite, BF 490-1, (ca 53 and 70% of the applied radioactivity in the water phases and ca. 16 and 12% of the applied radioactivity in the sediment phases after 100 days). Volatiles, characterised as carbon dioxide, accounted for ca 8-10% of the applied radioactivity 100 days after treatment. Observed DT_{50} times for kresoxim-methyl in the water phases were between 1 and 1.6 days (DT_{90} times were ca. 6 days). In the whole systems, DT_{50} times for kresoxim-methyl were ca. 1.5 days and DT_{90} times, ca. 7 days. While kresoxim-methyl is not expected to be persistent in the water phase of aquatic environments, its acid metabolite may be.

Mobility

Kresoxim-methyl has very slight volatility and very slight volatility is expected from water. However, there were no unexplained volatility losses in laboratory experiments indicating little loss through this route may be expected.

Adsorption/desorption

Batch equilibrium studies of adsorption of kresoxim-methyl in one study of four soils found organic carbon adsorption constants (K_{OC}) of 219 to 372 for kresoxim-methyl, rating it as having medium mobility in soil (K_{OC} = 150-500). Because the ester bond is readily hydrolysed in moist soil, the acid metabolite could be mobile and transfer to the aqueous phase. Batch equilibrium studies of the acid metabolite, BF 490-1, on four soils, found K_{OC} values of 17 and 24 for two of the soils with Koc values not being calculable on the other two soils resulting in the respective mobility classification of “very high” for the metabolite. Calculations of the Gustafson Ubiquity Score (GUS) using the available data indicate that kresoxim-methyl is an “improbable” leacher (GUS <1.8), and unlikely to reach groundwater before degrading, while the acid metabolite, BF 490-1, is identified as a probable leacher (GUS>2.8).

Leachability

Soil column studies were conducted with formulations containing unlabelled kresoxim-methyl added to three German standard soils having pHs of 5.6 to 6.6. Kresoxim-methyl, most probably as its acid metabolite, BF 490-1, was mobile in soils of low organic carbon content (0.6-1.3%) with 41 to 99% of the applied kresoxim-methyl being found in the leachate but had low to moderate mobility in soils with organic carbon contents of 2.1-2.6% where less than 3% of the applied kresoxim-methyl was found in leachates from two of the soils and approximately 20% of the applied kresoxim-methyl found in the leachate of the third soil.

After aging a German standard soil treated with ^{14}C-kresoxim-methyl for 30 days, and leaching through columns, approximately 44-45% of the applied radioactivity (as ^{14}C-kresoxim-methyl) was retained on the columns and about 57-58% found in the leachate. When soil treated with ^{14}C-kresoxim-methyl, but unaged, was run through similar columns, 41 and 58% of the radiolabelled residues were retained on the duplicate columns and 56 and 40% of the applied residues were found in the leachates. The acid metabolite, BF 490-1, was the major leachate component in both cases. On the columns, the majority of the retained radioactivity was found in the top segment irrespective of whether the sample was aged or unaged soil. The study showed that in moist soil, the ester bond of the kresoxim-methyl hydrolysed readily and that the resulting acid metabolite was leachable from aged and unaged soils.

Lysimeter study

Two or four applications of ^{14}C-kresoxim-methyl were applied at a nominal 0.15 kg kresoxim-methyl/ha to three lysimeters sown initially with winter barley. Total radioactive residues remaining in the top 20 cm of soil after the first two years of the study were between 0.03 and 0.09 mg/kg (as kresoxim-methyl). Based on examination of the soil in one of the lysimeter, 34% of the applied radioactivity was in the soil with the majority (26%) in the top two layers. The maximum total radioactive residues concentration was 0.034 mg/kg (as kresoxim-methyl in the top soil layer). Below 30 cm, total radioactive residues were <0.005 mg/kg soil. In the top layers of soil, the concentrations of ^{14}C-kresoxim-methyl and its acid metabolite, BF 490-1 were respectively 0.79 and 0.33 µg/kg (0-10 cm layer), 0.38 and 0.25 µg/kg (10-20 cm layer), and 0.12 and 0.10 µg/kg (20-30 cm layer).

Total amounts of radioactivity found in the leachates over the two years of the study were between 0.66 and 0.88% of the radioactivity administered. Concentrations of ^{14}C-kresoxim-methyl in the leachates were all <0.01 µg/L while mean concentrations of the free acid metabolite ranged from 0.003 to 0.038 µg/L. ^{14}C-carbon dioxide in the leachates made up between 0.01 and 0.07% of the applied radioactivity. Limited residues were found in crops indicating a lack of accumulation.

The study showed that while kresoxim-methyl degraded readily in soil with the formation of the acid metabolite BF 490-1, neither chemical was a strong leacher. After two years approximately two-thirds of the administered material had been degraded or mineralised.

Field dissipation

Field studies have been conducted at locations in Germany, the United Kingdom, and the USA, involving single applications to bare soil or, with one of the US studies, four treatment at 7 day intervals. A total of ten soil types were investigated in the studies. All the studies showed kresoxim-methyl dissipated rapidly after application, with half-lives of less than 4 days (several hours in some instances). The main metabolite, kresoxim-methyl acid, BF 490-1, was the major residue found in the studies with the diacid found in one of the US studies.

Field dissipation appears to predominantly involve hydrolysis to form the acid metabolite which further degrades. Residues were mainly confined to the surface fractions (0-15 cm) of all the tested soils with parent rapidly converting to its acid metabolite before further degrading further. The field studies show that neither kresoxim-methyl or its major metabolite, the acid hydrolysis product, BF 490-1, translocated to any great depth in the soil and that both compounds readily broke down in the soil.

Bioaccumulation

Rainbow trout (*Oncorhynchus mykiss*) were exposed to a continuous flow of dilution water containing ^{14}C-kresoxim-methyl at a nominal concentration of 25 µg/L for 28 days followed by a 14 day depuration period. Exposure of trout to kresoxim-methyl via the water resulted in steady state situations being reached within a few days followed by rapid depuration of residues from the fish when exposure ceased. Mean concentrations of radioactivity in the whole fish reached a plateau at 5-6 ppm after 3 days. Mean concentrations of radioactivity in the viscera and edible portions of the fish over the 28 day exposure period were in the respective ranges of 9-15 ppm and 1-2 ppm. Depuration was quick, with mean radioactivity concentrations in the viscera, edible portion, and whole fish being respectively 0.05, 0.02, and 0.03 ppm at day 14 of the depuration. Kresoxim-methyl concentrates slightly in the edible portion of the trout and moderately in the whole trout.

Kresoxim-methyl was also the major radioactive component in the viscera and fillets with hydroxylated kresoxim-methyl (BF 490-4) also of significance in those compartments. Minor components were the Z isomer, 242010, the free acid BF 490-1, and the hydroxylated free acids BF 490-2 and BF 490-9.

Environmental Toxicity

Birds

Bobwhite quail were used in both acute and sub-acute oral dietary studies. The LD_{50} determined was greater than 2150 mg kresoxim-methyl.kg^{-1} bodyweight in the acute study with the NOEC set at 2150 mg.kg^{-1} while the LC_{50} and the NOEL for the 5 d sub-acute dietary study were respectively >5000 mg/kg and 5000 mg/kg. When mallard ducks were fed kresoxim-methyl treated feed in a 5 d sub-acute dietary study, the LC_{50} and the NOEL were also respectively >5000 mg/kg and 5000 mg/kg. These studies indicate that by US EPA classifications, kresoxim-methyl TGAC is practically non-toxic to bobwhite quail by both acute oral exposure (LD_{50} > 2000 mg ai/kg bw) and to bobwhite quail and mallard ducks by subacute dietary exposure (LC_{50} > 5000 ppm in diet). A first generation reproduction study

with bobwhite quail showed a marginal effect occurred at 1000 mg/kg feed with the NOEL being greater than 500 and less than 1000 mg/kg feed.

Aquatic species

The acute aquatic toxicity of kresoxim-methyl, either as the pure active, or in a commercial formulation, to rainbow trout (*Oncorhynchus mykiss*), common carp (*Cyprinus carpio*), bluegill (*Lepomis macrochirus*), *Daphnia magna,* algae, duckweed (*Lemna gibba*), and bacteria was assessed in separate studies. The chronic aquatic toxicology on rainbow trout and *Daphnia magna* of kresoxim-methyl as the TGAC and formulated product was also assessed in separate studies. The effect of repeated applications of a formulated product to an aquatic ecosystem and the acute toxicity of the acid metabolite, BF 490-1, to fish, *D. magna*, algae, and bacteria were also assessed.

Fish

In the acute studies with fish, all measured LC_{50}s were between 150 and 621 µg kresoxim-methyl/L (as the TGAC and as a formulated product) and the chemical is classified as "highly toxic" to fish under conditions of acute exposure. In contrast, the acid metabolite is practically non-toxic to fish. In chronic studies with kresoxim-methyl as the TGAC and as a formulated product, the no observable effect concentrations were 13 and 143 µg/L respectively. These values categorise kresoxim-methyl as moderately toxic to fish and the formulated product used as slightly toxic to fish following chronic exposure. The acute to chronic NOEC ratios for kresoxim-methyl as the TGAC and as formulated product are low, confirming that acute effects are most likely.

Aquatic invertebrates

Daphnid acute toxicity studies with kresoxim-methyl as the TGAC and as a formulated product were carried out under static and semi-static conditions. Based on EC_{50} values of 1510 (24 h) and 186 (48 h) µg kresoxim-methyl/L, the TGAC is regarded as highly to moderately toxic, depending on the species, under conditions of acute exposure. A 48 h LC_{50} of ca. 350 µg/L was found for the formulated product with a toxicity classification of "highly toxic". The acid metabolite, BF 490-1, was practically non-toxic to daphnids under acute exposure conditions. Chronic exposure of daphnids resulted in a reproduction no observable effect concentration of 32 µg/L for the TGAC and 150 µg/L for the formulated product. These results indicate chronic exposure of kresoxim-methyl and the formulated product is, respectively, moderately and slightly toxic to daphnids.

Algae

Exposure of algae to kresoxim-methyl, as the TGAC and as a formulated product, showed the active was very highly toxic with the green algae *Ankistrodesmus bibraianus (*synonyms *Pseudokirchneriella subcapita* and *Selenastrum capricornutum),* having a 0-72 h EC_{50} = 63 µg/L for the TGAC and 71 µg/L for the formulated product. These values indicate kresoxim-methyl is very highly toxic to the algal species involved.

Additionally Tier I testing on the algae *Selenastrum capricornutum, Anabaena flos-aquae,* and the freshwater and marine diatoms, *Navicula pelliculosa* and *Skeletonema costatum* indicated significant growth inhibition at a nominal 310 µg/L of *S. capricornutum, N.*

pelliculosa, and *S. costatum* (98, 64, and 62% growth inhibition respectively). Tier II testing of kresoxim-methyl confirmed the active was very highly toxic to *Selenastrum capricornutum* (5 day EC_{50} = 59 µg/L) and *Navicula pelliculosa* (5 day EC_{50} = 29 µg/L) but was without effect on *Anabaena flos-aquae* at concentrations of kresoxim-methyl of 295 µg/L or less.

The Tier II testing also showed such concentrations of kresoxim-methyl were without effect on the marine diatom, *Skeletonema costatum*. The difference between the Tier I and Tier II results for this organism can be explained by the less accurate cell count used at the Tier I stage.

Algae were not affected by levels of the acid metabolite, RP 490-1, of up to ca. 500 mg/L, based on growth curve area and growth curve rates. The 72 h EC_{50} value was >500 mg/L, giving a classification of practically non-toxic for the metabolite.

Aquatic plants

Exposure of duckweed to kresoxim-methyl showed the active, at a nominal 301 µg/L of kresoxim-methyl for 14 days under aerobic conditions. resulted in 10% inhibition for *L. gibba*. Such a result was indicative of kresoxim-methyl at the level tested not having a toxic effect in the duckweed. A 14 day Tier II study with kresoxim-methyl confirmed these observations (NOEC of 305 µ/.L).

Bacteria

Exposure of the bacterium, *Pseudomonas putida* to nominal concentrations of kresoxim-methyl or the acid metabolite, RP 490-1, of 100 to 1000 mg/L resulted in no significant inhibition of the bacterial activity as measured by oxygen uptake.

Aquatic ecosystem

An aquatic microsystem was given six applications of kresoxim-methyl as a formulated product at rates equivalent to direct overspray at 200 g formulation/ha and at rates equivalent to 20% and 4% spray drift, calculated concentrations of kresoxim-methyl in the water were ca. 33, 6.5, and ca. 1.3 µg kresoxim-methyl/L. While some effect on several species of zooplankton was observed, the changes were not of statistical significance. In contrast to laboratory toxicity tests, the study recorded no adverse effects on phytoplankton, benthic organisms, insects, and fish but levels were generally below those expected to be toxic.

Non-target invertebrates

Honey bees

The oral LD_{50} of kresoxim-methyl TGAC to honeybees was 14 µg/bee and the contact $LD_{50,}$ ≥20 µg/bee. Based on results of two studies with formulated product, the oral LD_{50}s were either >100 µg/bee [>50 µg kresoxim-methyl/bee] or >200 µg/bee. A contact LD_{50} of >413 µg/bee was reported for the formulated product. While mortality was seen in bees orally treated with kresoxim-methyl, exposure to higher concentrations of the active via formulated product resulted in no significant bee mortality. On the basis of the LD values determined, formulated product is considered to be very slightly toxic to bees while kresoxim-methyl TGAC is slightly toxic by either contact or ingestion.

Predatory ground beetles, parasitic wasps, and predacious bugs

Predatory ground beetles suffered no adverse effect following exposure to sand treated with the kresoxim-methyl formulation BAS 490 04 F (500 g kresoxim-methyl/L) at a rate of 0.3 L/ha (ca. 150 g kresoxim-methyl/ha, cf. the proposed Australian use rate of 175 g kresoxim-methyl/ha). A similar result occurred when parasitic wasps were exposed to glass plates treated with formulated kresoxim-methyl at 0.3 kg/ha (about 145 g kresoxim-methyl/ha). Parasitic wasps exposed to kresoxim-methyl formulated as BAS 492 01 F (150 g kresoxim-methyl/ha) at a concentration of 105 g kresoxim-methyl/ha, with exposure via parasitised aphid mummies or by contact with aged residues, showed no adverse effects. Additionally the exposure resulted in no statistically significant effect on reproduction in wasps treated with the formulated product. Predacious bugs exposed to glass plates treated with formulated kresoxim-methyl at a concentration of ca. 200 g/ha were not affected with respect to survival to maturity or reproductive capacity. For all these invertebrates, kresoxim-methyl is considered as harmless at the expected levels of exposure.

Ladybirds

In a laboratory study, ladybirds exposed to kresoxim-methyl as a formulated product at a rate of ca. 150 g kresoxim-methyl/ha, showed no mortality effects but there was almost a 60% reduction in the hatching rate of eggs from treated ladybirds. A follow-up semi-field study using the same treatment rate confirmed the negligible toxicity to ladybird larvae and showed no effect on reproduction under the test conditions.

Predacious mites

The effect of kresoxim-methyl in formulated products on predacious mites was examined in laboratory studies with glass sprayed with rates equivalent ca. 100 or 150 g kresoxim-methyl/ha. Based on the low numbers of mortalities and lack of significant effects on reproduction, the laboratory studies indicate that use of kresoxim-methyl should be harmless to predacious mites. Field studies on grape vines confirmed the absence of adverse effects on the mites. This was further confirmed in field studies on apple trees where, after eight applications (three are allowed under the proposed Australian use pattern) of a kresoxim-methyl formulation at ca. 150 g ai/ha, a “harmless” categorisation of the active was possible although there was an indication that higher numbers of applications could lead to a reduction in the number of predacious mites. However, Australian field trials on apple trees using the proposed Australian rate of 175 g kresoxim-methyl/ha with six or seven applications showed that predacious mite numbers were not adversely affected by the excessive treatments. It is concluded that the proposed use of Stroby WG Fungicide is unlikely to seriously adversely affect populations of predacious mites.

Earthworms

In tests with kresoxim-methyl TGAC, the No Observed Effect Concentration (NOEC) on earthworms for kresoxim-methyl was reported as 937 mg/kg and the 14 day kresoxim-methyl LC_{50} as >937 mg/kg. When tested with formulated product (50% kresoxim-methyl), the NOEC was 250 mg/kg and the 14 day LC_{50}, 644 mg/kg, with the increased toxicity in the study with the formulated product perhaps due to component toxicity. The acid metabolite, RF 490-1 showed no adverse effects on earthworms and its NOEC was taken as 1000 mg/kg.

Soil micro-organisms

Following treatment of two soils at 150 and 1500 g kresoxim-methyl/ha as formulated product containing ca. 50% kresoxim-methyl, there were only negligible effects on soil respiration and nitrogen turnover after 28 days with some apparent decrease of nitrate nitrogen content in a clay soil treated at the lower rate not observed in the higher rate study.

After treatment of two soils with the acid metabolite, BF 490-1, at concentrations based on the application rates of formulated kresoxim-methyl, there were only negligible effects on microflora respiration. With respect to soil nitrogen transformations at 28 days after treatment, the differences between the treated sandy loam soil and control soil exceeded 15% and the study was continued for a further 14 days. According to toxicity classification, the acid metabolite is of negligible effect at the highest concentration tested (10 X times the proposed Australian rate) and of tolerable effect to the sandy loam soil at the proposed rate.

Prediction of Environmental hazard

It is proposed that Stroby WG Fungicide be used on apple trees to control black spot (scab) and powdery mildew via conventional spray equipment with a maximum of three applications per season at a maximum rate of 10 g of product per 100 L in high volume spraying or 150 to 350 g of product per hectare using low volume applications. These rates are equivalent to application of 150 to 350 g of product per hectare [75 to 175 g kresoxim-methyl per hectare]). Early applications should be at intervals of 7 to 10 days and later applications at 10 to 14 day intervals.

Residues could be expected in the sprayed area and on soil surface with spray drift and run-off potential means of contamination of adjacent areas and surface water. While laboratory data indicate that kresoxim-methyl has medium mobility in the soil it is not persistent for long enough time to leach significantly because of its ready breakdown to its non-toxic acid metabolite. Field studies indicate that in practice leaching only occurs to a very limited extent and that residues of the parent and its acid metabolite undergo mineralisation and are unlikely to accumulate to give unacceptable soil concentrations.

Hazard to birds and mammals

Estimated residues on feed at the maximum proposed rate are likely to be well below the acute oral LD_{50}s and 5 day dietary exposure NOECs for bobwhite quail and mallard duck and also for the first generation reproduction NOEC for bobwhite quail. Hence, kresoxim-methyl used in accordance with label recommendations is not likely to present a hazard to birds ingesting these residues. Acute or chronic hazard to mammals is also highly unlikely.

Aquatic hazard

The hazard presented by direct overspray of a shallow (15 cm deep), lentic waterbody with a single application (i.e. 175 g ai/ha, representing a worst case situation) was evaluated for representative aquatic species from those for which toxicity data were available. While a hazard was indicated for all tested species with direct overspray, rainbow trout and freshwater green algae were clearly the most sensitive. Spray drift reaching a similar waterbody at 10% of this rate gave similar hazard predictions. Taking 4% spray drift as realistic for early season

orchard spraying of bare trees with limited ability to capture drift, acceptable hazard to fish and algae was indicated provided a down-wind buffer distance of about 30 metres was maintained. For trees with a full canopy, the buffer distance is reduced to 20 metres. A low hazard is supported by an aquatic ecosystem study that showed no serious effects on aquatic organisms including phytoplankton but as the study's use rate was approximately 57% of the use rate proposed for the Australian situation, its value in the Australian hazard assessment is restricted.

A 1% run-off produces a level of contamination similar to the 10% spray drift scenario and identifies the need to minimise water contamination by this route. The hazard from run-off is expected to be further reduced as the proposed use pattern requires that kresoxim-methyl be applied to the point of run-off with any actual run-off expected to be trapped by grassed areas between the tree rows.

While the aquatic hazard from this substance is high, the actual exposure levels are unlikely to be of concern, especially when coupled with the ready loss of kresoxim-methyl from the water column. This should result in minimal impact from spray drift and run-off. Chronic exposure was moderately toxic to rainbow trout and daphnids. However, the relatively short life of kresoxim-methyl in natural water systems means that such exposure is not expected to be of significance. A suitable label warning has been included to indicate the potential hazard to aquatic organisms.

Hazard to terrestrial invertebrates and soil micro-organisms

Kresoxim-methyl TGAC has been classified as slightly-toxic to honey bees (*Apis mellifera*) while Stroby WG Fungicide, the formulated product, is classified as very slightly toxic. The proposed use with the formulated product is unlikely to present a hazard to honey bees. Laboratory studies were provided with kresoxim-methyl as formulated product covering a range of insect and mite predators and parasitoids.

Predatory ground beetles, parasitic wasps, predacious bugs, and ladybirds (semi-field study) were not adversely affected by exposure to kresoxim-methyl formulations although a laboratory exposure of ladybirds did indicate there was some low level harmful effects from formulated kresoxim-methyl at concentrations near those proposed for the Australian use pattern. Laboratory and field studies (including use on apples) showed that the treatments were generally harmless or without adverse effect .

One field trial on apples that used eight applications (compared to the maximum of three proposed for Australia) showed that the treatments were initially "harmless" but "harmful" at the last assessment. As the use pattern used far exceeds that proposed for Australia, it is concluded that the proposed Australian use is unlikely to be harmful to predacious mites. The product is not expected to present a hazard to earthworms or to adversely affect soil respiration or cause long-term detrimental effects on the turnover of nitrogen in soils.

Desirable terrestrial vegetation

While no studies were presented on the effect of Stroby WG Fungicide on non-target native vegetation, no adverse herbicidal or phytotoxic effect on plants have been reported. In all the trials conducted in Australia with Stroby WG Fungicide, there has been no report of harmful effects on native vegetation.

Conclusion

Environment Australia concludes that a low hazard to the environment may be predicted provided the product is used according to the proposed label recommendations and Good Agricultural Practice.

EFFICACY AND SAFETY ASSESSMENT

Justification

Powdery mildew (*Podosphaera leucotricha)* and black spot or scab (*Venturia inaequalis)* are major diseases of apples. To overcome the development of resistance by both fungi there is an on-going need for fungicides from new groups. Stroby is in the strobilurin group. This is a new group to be applied on pome fruit so products from this group will be useful in resistance management.

Efficacy

Kresoxim-methyl works by inhibition of electron transfer in the mitochondria of fungal cells, thus preventing the formation of ATP which is necessary for the normal metabolic processes of the fungus. It arrests development of black spot by prevention of spore germination and sporulation. Kresoxim-methyl is not active against the mycelial stage of the disease. It provides protection against powdery mildew by preventing spore germination and penetration into the leaf. Kresoxim-methyl will not eradicate over-wintering powdery mildew infection.

Data were presented from fourteen trials to demonstrate efficacy against black spot and from seven trials against powdery mildew.

In all trials comparisons were provided of Stroby treatment with untreated controls and with a number of currently used fungicides. The fungicides in the black spot trials were a protectant, a curative and a combination of protectant and curative schedule products. In the powdery mildew trials there were four different curative fungicides applied for comparison.

Experimental conditions resulted in good disease pressure in all seven powdery mildew trials. Conditions resulted in sufficient disease pressure in 11 of the 14 black spot trials.

Trials included Stroby applied at the proposed label rate and currently registered curative and protective fungicides at their label rates. In all black spot trials Stroby was applied either in a program with another fungicide or with more that the number of sprays recommended on the label. It is accepted that black spot control requires a number of applications commercially and this approach to demonstrate efficacy is accepted.

Relative success in disease control was indicated by assessment of the percentage leaf and/or fruit infection levels with black spot and percentage shoot infection or rated severity for powdery mildew. Statistical analyses were provides for all trials. Documentation of all trials was thorough.

Trials were conducted on growers properties in commercial orchards or against more severe disease pressure in neglected orchards. They were conducted in four States in Australia on nine apple cultivars and are considered to adequately reflect the potential commercial application of Stroby in Australia.

The data supplied were appropriately statistically analysed and show that the product should provide control of black spot and powdery mildew in apples when used as directed. The product performed similarly to eradicant fungicides tested and was superior to standard

protectants. Its effect is on spore germination and penetration, not on mycelium, so it is not an eradicant.

Crop safety

No adverse reactions were recorded in the trials that included nine cultivars of apples.

Compatability trials when both components were used at double the recommended rates showed some leaf damage for Stroby combined with Omite (propargite) or calcium nitrate. The calcium nitrate effects were further investigated. These further trials showed that the effects were not due to the combination specifically but were related to the high application rates tested. No warning on incompatability is considered necessary for calcium nitrate. The Omite effects have not been further investigated and the label specifically advises against using this mixture.

LABELLING REQUIREMENTS

The label proposed for the product is as follows:

MAIN PANEL

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Stroby â

WG FUNGICIDE

Active Constituent: 500 g/kg KRESOXIM-METHYL

GROUP *K* FUNGICIDE

* kg
NET

ot (For Control of Black Spot (Scab) and Powdery Mildew in Apples.

IMPORTANT: READ THE ATTACHED BOOKLET BEFORE USE

Aventis

(label code)

*0.2 (200 g), 1, 1.5 kg

REAR PANEL

STROBY WG FUNGICIDE

STORAGE AND DISPOSAL

Keep out of reach of children. Store in the closed, original container in a dry, cool, well-ventilated area out of direct sunlight.

For 200 g pack

Rinse containers before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. Dispose at a local authority landfill. If no landfill is available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should not be burnt.

For 1 kg pack

Single rinse before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. Puncture and bury empty containers in a local authority landfill. If no landfill is available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should not be burnt.

For 1.5 kg pack

Triple or preferably pressure rinse containers before disposal. Dispose of rinsings in disposal pit, or use for diluting product to required volume. Do not dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and bury empty containers in a local authority landfill. If no landfill is available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should not be burnt.

SAFETY DIRECTIONS

When preparing spray, wear elbow-length PVC gloves. After each days use wash gloves.

FIRST AID

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

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet available from Aventis CropScience Pty Ltd.

CONDITIONS OF SALE

This product is sold on the Conditions of Sale more fully set out in the booklet accompanying the product.

NRA Approval No.: 51346/

Stroby® is a Registered Trademark of, and is produced by BASF

IMPORTANT: READ THE ATTACHED BOOKLET BEFORE USE

REAR PANEL (cont)

BASF

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Noble Park, Victoria, 3174.

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Website: www.aventis.com.au

BAR CODE

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

Batch number:
Date of Manufacture:

* drummuster logo required for 1.5 kg pack only (not 200 g or 1 kg packs).

FRONT PAGE OF BOOKLET

STROBY WG FUNGICIDE

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BOOKLET CONTENTS

STROBY WG FUNGICIDE

Active Constituent: 500 g/kg KRESOXIM-METHYL

DIRECTIONS FOR USE

CROP	DISEASE	RATE	CRITICAL COMMENTS
Apples	Black spot (scab) (*Venturia inaequalis*), Powdery mildew (*Podosphaera leucotricha*)	High volume: 10 g/100 L Low volume*: 150 to 350 g/ha (refer to Critical Comments)	Application may commence at spurburst for black spot, and at early pink stage for powdery mildew control. Apply at 7 to 10 day intervals prior to petal fall and during periods of rapid growth. Later applications should be at 10 to 14 day intervals, or according to prevailing weather conditions and disease incidence. Ensure thorough and even coverage of all plant parts. * For low volume application use a rate per hectare based on that which would have been applied per hectare if high volume application was used to the point of run-off. May be used with the recommended rate of a non-ionic wetting agent. The use of Stroby is subject to an Avcare Resistance Management Strategy. Do not apply more than three applications of Stroby or other Group K fungicides per season. Refer to Resistance Management Strategy in General Instructions for further details.

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

WITHHOLDING PERIOD: DO NOT HARVEST FOR 6 WEEKS AFTER APPLICATION.

DO NOT GRAZE ANY TREATED AREA, OR CUT FOR STOCK FOOD.

BOOKLET CONTENTS (cont.)

GENERAL INSTRUCTIONS

Fungicide Resistance Warning **GROUP K FUNGICIDE**

Stroby is a member of the strobilurin group of fungicides. For fungicide resistance management, Stroby is a Group **K** fungicide.
Some naturally-occurring fungal biotypes resistant to Stroby, and other Group **K** fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungal population if these fungicides are used repeatedly. These resistant fungi will not be controlled by Stroby and other Group **K** 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, Aventis CropScience Pty. Ltd. accepts no liability for any losses that may result from the failure of Stroby to control resistant fungi.

Resistance Management Strategy

To prevent or delay the onset of resistance, DO NOT apply more than three sprays per season of Stroby or other Group K fungicides. If consecutive applications of Group K fungicides are used, then they must be followed by at least the same number of applications of fungicide(s) from a different group(s) before a Group K fungicide is used again, either in the current or following season.

Integrated Pest Management
Stroby is suitable for use in Integrated Pest Management (IPM) programs.

Export of treated fruit
If growing fruit for export, note that MRLs or import tolerances do not exist in all markets for fruit treated with Stroby, however Codex MRLs do exist. Please contact Aventis CropScience for further information.

Equipment
Ground application
Stroby can be applied with high volume (dilute) or low volume (concentrate) orchard spraying equipment that is fitted with mechanical or hydraulic agitation. Equipment should produce a fine, uniform spray coverage of all plant surfaces (stems, leaves and fruit).

Aerial application
Do not apply by aircraft.

Application
High Volume (dilute) spraying: Apply approximately 1,500 to 3,500 L spray mixture per ha, depending upon tree size. Trees should be thoroughly and evenly sprayed to the point of run-off.
Low Volume (concentrate) spraying: Apply with sufficient water to ensure thorough and even coverage of all plant surfaces. Application rates of Stroby should be the same per hectare as if a high volume spray was being applied to the point of run-off. Therefore as tree size and density increase, so should the application rate.

BOOKLET CONTENTS (cont.)

Mixing
Add the required amount of Stroby directly to the half filled spray vat with agitators in motion. Complete the filling of spray vat under constant agitation. Do not allow the spray mixture to remain in the tank for long periods without agitation.

Compatibility
Stroby is compatible with Acaban®, carbaryl 500, Gusathion® SC, Insegar®, Klartan®, Lorsban® 250 WP, Mimic® 700 WP, Pyranica® and Thiodan® EC. For information on compatibility with other products please contact your local reseller or Aventis CropScience representative.
Do not mix with Omite® or products giving an alkaline reaction eg. Bordeaux mixtures or lime sulphur.

Rainfall
Stroby exhibits good rainfastness once spray has dried on the tree, however its protectant cover may be reduced after 50-60 mm of rainfall.

PRECAUTION
Re-entry Period
Avoid entering treated areas until spray deposits have dried. When prior entry and handling of treated surfaces is necessary wear rubber gloves.

PROTECTION OF LIVESTOCK
Stroby presents a low hazard to bees and can be applied to crop at any time.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
HIGHLY TOXIC TO AQUATIC ORGANISMS.
DO NOT apply if heavy rains are imminent.
DO NOT contaminate streams, rivers or waterways with this product or used container.

DRIFT WARNING
DO NOT apply under weather conditions or from spraying equipment, which could be expected to cause spray to drift onto adjacent crops, crop lands, pasture or livestock.

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.

NRA Approval No.: 51346/

BOOKLET CONTENTS (cont.)

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GLOSSARY

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

References

Felton, J.C., Oomen, P.A. & Stevenson, J.H. 1986, 'Toxicity and hazard of pesticides to honeybees: harmonisation of test methods', *Bee World*, vol. 67, no. 3, pp. 114-24.

Goring, C.A.I. et al. 1975, 'Principles of pesticide degradation in soil', in *Environmental Dynamics of Pesticides*, edited by R. Haque and V.H. Freed, Plenum Press, New York, pp 135-72.

Matthews, G.A. 1992, *Pesticide Application Methods*, 2nd ed., Longman, London.

National Registration Authority for Agricultural and Veterinary Chemicals 1996, *Ag Manual: The Requirements Manual for Agricultural Chemicals*, NRA, Canberra.

National Registration Authority for Agricultural and Veterinary Chemicals 1997, *Ag Requirements Series: Guidelines for Registering Agricultural Chemicals*, NRA, Canberra.

National Registration Authority for Agricultural and Veterinary Chemicals 1996, *MRL Standard: Maximum Residue Limits in Food and Animal Feedstuffs*, NRA, Canberra.

National Registration Authority for Agricultural and Veterinary Chemicals 1997, *Ag Labelling Code—Code of Practice for Labelling Agricultural Chemical Products*, NRA, Canberra.

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