Public Release Summary
on

Evaluation of the new active

SPIROXAMINE

in the product

PROSPER 500 EC FUNGICIDE

National Registration Authority
for Agricultural and Veterinary Chemicals

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Australia

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Colin Byrnes
National Registration Authority for Agricultural and Veterinary Chemicals
PO Box E 240
KINGSTON ACT 2604

Ph: (02) 6272 4850
Fax: (02) 6272 3218

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 co-operation with advisory agencies, including the Department of Health and Aged Care (Chemicals and Non-prescription Medicines Branch), Environment Australia (Risk Assessment and Policy Section), the National Occupational Health and Safety Commission (NOSHC) and State departments of agriculture and environment.

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

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

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EUP	End Use Product
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Heamatocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be dquantified
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

OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
mg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period

INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of *Prosper 500 EC Fungicide (Prosper)*, containing the new active constituent spiroxamine.

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. They will also be taken into account in determining appropriate conditions of registration and product labelling.

Written comments are invited and should be submitted by 19 November 2001, addressed to:

Colin Byrnes
AgVet Chemicals Evaluation Section
National Registration Authority
PO Box E240
Kingston ACT 2604

Ph 02 6272 4850
Fax 02 6272 3218

Applicant:

Bayer Australia Ltd

Product Details:

Prosper is an emulsifiable concentrate formulation containing 500g/L spiroxamine. Spiroxamine belongs to the new spiroketalamine group (Group E). Spiroxamine is a new protective, curative and eradicative fungicide with activity that results from the inhibition of sterol biosynthesis.

The active constituent is manufactured in Germany by Bayer Ag. The end use product will be formulated by Bayer Agricultural Operations Centre, Australia.

Bayer Australia have provided confirmation that products containing spiroxamine are currently registered for use in Austria, Belgium, the European Community, France, Greece, Hungary, Slovenia, South Africa and Switzerland.

Chemistry and Manufacture Assessment

The product proposed for registration is an emulsifiable concentrate under the trade name *Prosper*. The storage stability of the formulation, physical and chemical properties of the formulated product and active constituent have been evaluated by the NRA are considered acceptable.

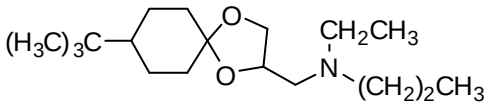
Active Constituent

The source of the Technical Grade Active Constituent (TGAC) to be used in the product is under consideration by the NRA

Manufacturing Site

The active constituent Spiroxamine is manufactured by Bayer AG, 41538-Dormagen, Germany.

Chemical Characteristics of the Active Constituent

Common name:	Spiroxamine (ISO/SA approved/proposed)
Synonyms and code number:	KWG 4168
Chemical name:	8-*tert*-butyl-1,4-dioxaspiro[4.5]decan-2-yl(ethyl)(propyl)amine (IUPAC) 8-(1,1-dimethylethyl)-*N*-ethyl-*N*-propyl-1,4-dioxzspiro[4,5]decane-2-methanamine (CAS)
CAS Number:	118134-30-8
Molecular formula:	$C_{18}H_{35}NO_2$
Molecular weight:	297.5
Chemical structure:	

Physical and Chemical Properties of Pure Active Constituent and TGAC

Stereochemistry:	Mixture of 2 diastereoisomers, A and B, in the proportions 49-56% and 51-44% respectively
Physical state:	oily liquid
Colour:	light brown
Odour:	weak, not characteristic

Melting point:	<-170 °C
Boiling point:	decomposition above 120 °C
Solubility in water	pH 3: >200 g/L Isomer A: pH 7: 470 mg/L pH 9: 14 mg/L Isomer B: pH 7: 340 mg/L pH 9: 10 mg/L
Density/specific gravity:	0.930 g/mL
Solubility in organic solvents	>200 g/L in common organic solvents
pK_a values:	6.9 (aqueous system) 7.9 (water + 40% 2-propanol)
Octanol/water partition coefficient:	Isomer A: 2.79 Isomer B: 2.92
Vapour pressure @ 25°C:	1.7×10^{-2} Pa
Flash point:	147 °C
Flammability:	not flammable
Explosive properties:	not explosive
Oxidising properties:	not an oxidising substance
Storage stability:	stable for 8 weeks @ 54 °C stable for 52 weeks @ 30 °C stable for 24 months @ ambient temperatures
Chemical type:	fungicide
Chemical family:	spiroketalamine

Summary of the NRA's Evaluation of Spiroxamine TGAC

The Chemistry and Residues Evaluation Section of the NRA has evaluated the chemistry aspects of Spiroxamine TGAC (manufacturing process, quality control procedures, batch analysis results and analytical methods) and approval of the TGAC has been granted (Approval No. 53066).

Formulated product

Distinguishing name:	Prosper 500 EC Fungicide
Formulation type:	Emulsifiable concentrate
Active constituent concentration:	500g/L

Physical and Chemical Properties of the Product

Physical state:	clear liquid
Colour:	yellow to brown
Odour:	aromatic
Density or specific gravity:	1.003 at 20°C
pH (1% solution):	9.4
Viscosity:	82 mPas
Flash point:	108 °C
Autoignition:	265 °C
Explodability:	not explosive
Oxidising properties:	not expected to be oxidising
Storage stability:	stable for 2 weeks at 54 °C

TOXICOLOGICAL ASSESSMENT

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

Toxicokinetics and Metabolism

Spiroxamine is rapidly but incompletely absorbed in the rat following oral administration, with peak blood levels reached within 1.5 to 2 hours after doses of 1 mg/kg bw and at 8 hours after a dose of 100 mg/kg bw. Spiroxamine is widely distributed into body tissues and is rapidly excreted, primarily via the urine, with approximately half the dose excreted within 14 hours. Spiroxamine metabolism occurs primarily on two sites of the molecule, oxidisation of the tertiary butyl moiety to form the alcohol product which is excreted as its conjugated (sulphated) form, with further oxidation leading to carboxylic acid metabolites and, secondly, via desalkylation on the amino group with formation of the desethyl or despropyl metabolites. Metabolism was qualitatively similar in both sexes.

Spiroxamine applied to the inside forearm of human volunteers for 8 hours, resulted in negligible plasma levels and a slow, prolonged excretion in the urine over a period of 41 days during which time 18.4% of the applied material was recovered from the urine. Excretion in the faeces was negligible.

Acute Studies

Spiroxamine has moderate acute oral and dermal toxicity in rats (LD_{50} 300 - 400, and 1068 mg/kg bw respectively), moderate acute oral toxicity in mice (LD_{50} 460 mg/kg bw) and moderate inhalational toxicity in rats (LC_{50} 1982 mg/m^3). The compound is a moderate skin and slight eye irritant in rabbits, a skin sensitiser in guinea pigs when administered subcutaneously (the maximisation method) but at most a slight sensitiser when applied to the skin surface (the Buehler method), and has an ip LD_{50} in rats of 114 mg/kg bw.

Prosper, containing 500 g/L spiroxamine, has low acute oral and dermal toxicity in the rat (LD_{50} 200 - 1000 mg/kg bw and $\geq$ 2000 mg/kg bw respectively) is a severe eye and skin irritant in the rabbit but not a skin sensitiser in the guinea pig by the Buehler method.

The primary plant metabolite of spiroxamine, spiroxamine-N-oxide, has an LD_{50} in female rats of approximately 707 mg/kg bw.

Short-Term Studies

Mice received spiroxamine in the feed at levels equivalent to doses of up to 414 mg/kg bw/day. Apart from an increased severity of liver cell enlargement and increased fatty change of the liver in females and thickening of the ears in males at 88 mg/kg bw/day and above, all effects were limited to the top dose as detailed in the following description. Two males and one female died, females consumed less food, males drank more water and both sexes lost weight initially, with males below control weights at termination but the females recovering to control levels by week 4. Emaciation, hair loss and ungroomed fur were observed together with dry or crusted areas of skin of the ear and/or tail due to marked skin thickening (hyperplasia). White cell counts were slightly elevated, platelet count was reduced, blood urea was elevated and cholesterol was lowered. Liver weights were increased. The lining of the urinary bladder and renal pelvis was thickened (hyperplasia) in both sexes and kidney weight was increased in males. The NOEL was 25 mg/kg bw/day.

Mice received spiroxamine at up to 240 mg/kg bw/day by gavage for 13 weeks with recovery groups at 0, 180 and 240 mg/kg bw/day followed for another 8 weeks without treatment. Depressed cholesterol levels were observed in both sexes at 240 mg/kg bw/day at week 13 which resolved in females and persisted but declined in males once treatment was stopped. Induction of liver metabolising enzymes (7-Ethoxycoumarin O-deethylase, 7-Ethoxyresorufin O-deethylase, and Aldrin epoxidase) noted in all treated male groups and in females at 180 and 240 mg/kg bw/day reflects a normal adaptive mechanism to a high chemical load and returned to near control values once treatment was ceased. Thickening (hyperplasia) of the ears (both sexes) and tail tip (males only) was again observed, at 240 mg/kg bw/day. The lining of the urinary bladder was thickened (hyperplasia) more commonly 180 and 240 mg/kg bw/day in males and at 240 mg/kg bw/day in females. Enlarged liver cells in males and reduced glycogen levels in both sexes were found at 180 mg/kg bw/day and above. Effects on the liver, urinary bladder and skin were largely reversible. Thickening of the stomach lining (hyperkeratosis) was increased in intensity and slightly in incidence at 240 mg/kg bw/day. The NOEL was 60 mg/kg bw/day.

Rats were fed spiroxamine in the diet for 28 days at doses equal to up to 36 mg/kg bw/day. Males at 34 mg/kg bw/day gained less weight initially, had slight alterations in their white blood cell profiles (reduced polymorph counts), protein and cholesterol levels in the blood were reduced and liver enzymes were increased (P450 levels). In females at 36 mg/kg bw/day spleen weights were slightly elevated, lower creatinine and glucose concentrations and a non significant increase in liver enzyme (P450) levels were seen, and in both sexes sodium levels were slightly but significantly lower. Liver weight was slightly elevated in males at 11 mg/kg bw/day and above. An increase in the severity, but not incidence, of fatty deposits in the liver cells (hepatocytes) and thickening of the oesophageal mucosa was observed in both sexes at 11/12 mg/kg bw/day and above. In addition one female at 36 mg/kg bw/day exhibited moderate thickening (hyperplasia) of the urinary bladder epithelium. There were no effects at 3.4 mg/kg bw.

Rats received spiroxamine orally at up to 90 mg/kg bw/day for 28 days. In all dose-groups salivation, tremor, digging and preening activities were observed after dosing. Animals at 90 mg/kg bw/day ate less and gained less weight, and water intake was elevated in all treated

male groups and in females at 30 and 90 mg/kg bw/day. Elevated liver enzyme (N-demethylase, P450) activities were seen at 90 mg/kg bw/day and in males at 30 mg/kg bw/day, which correlated with elevated liver weights at 90 mg/kg bw/day, at which dose slight fatty accumulation in the liver cells (hepatocellular steatosis in the periportal lobular zones) was observed. Slight elevations of liver cell enzymes in the blood were seen at 30 and 90 mg/kg bw/day (AST in males at 30 and 90 mg/kg bw/day, ALT in males and AP in females at 90 mg/kg bw/day) were observed. Albumin levels were slightly depressed at 90 mg/kg bw/day. The males at this dose had depressed creatinine levels. In the females triglyceride levels at 10 mg/kg bw/day and above were substantially reduced and protein levels were slightly reduced at 90 mg/kg bw/day. In males, elevated spleen weights at 30 and 90 mg/kg bw/day and kidney and testes weights at 90 mg/kg bw/day were seen. Relative pituitary weights were decreased and adrenal weights increased in females at 90 mg/kg bw/day. Thickening (hyperplasia) of the urinary bladder lining (epithelium) of females and thickening of the forestomach lining (hyperkeratosis of the cornifying, multilayer squamous epithelium) in both sexes at 90 mg/kg bw/day are likely to be related to the strong irritant effect of spiroxamine on mucosal tissue. At 90 mg/kg bw/day lenticular fibres were visible in the eyes of a few animals of both sexes.

Rats were exposed, head only, to spiroxamine at 14.3, 87.0 or 518.4 mg/m^3 for 6 hours/day, 5 days/week for 4 weeks. Effects at 87 mg/m^3 and above were; altered white blood cell pattern, slight anaemia (decreased Hb and Hct) in females (and in males at 518.4 mg/m^3), reduced cholesterol, and increased urinary phosphate levels in females. The remaining effects were observed only at 518 mg/m^3, and a large proportion of these were attributable to the irritancy of spiroxamine. Signs of toxicity observed were; ungroomed fur and decreased motility, staggering gait, narrowed palpebral fissure, hypersalivation, reddened conjunctivae, reddened and bloody nostrils, transient breathing sounds, and abnormal digging and preening activities. Males gained less weight, one female died, blood clotting was slowed slightly, platelets were decreased and white blood cell counts elevated. Liver enzymes in the blood (ALT, AST) were slightly elevated, plasma cholinesterase activity and total protein was reduced in females and the globulin:albumin ratio was increased in both sexes. Liver metabolic enzyme levels were slightly altered (N-demethylase and P-450 depressed in males and O-demethylase slightly higher in both sexes). Urinary proteins, bilirubin, urobilinogen, ketone bodies, phosphate and blood cells were elevated. Liver and kidney weights were increased, and spleen weights decreased. Thymus weights were reduced more than 60% and in males degenerative (atrophic) changes were seen. Altered cell appearance (metaplasia) in the lining of the nasal cavity, thickening (hyperplasia/hyperkeratosis) in the lining of the larynx, oesophagus, cornea, and eyelids and signs of irritation in the lungs (bronchiolo-alveolar proliferation, increased alveolar macrophages) were seen. Skin thickening (hyperkeratosis, hyperplasia) was seen in the mammary area, on the tail, and in the lining of the urinary bladder. No effects were observed at 14.3 mg/m^3.

Rats received spiroxamine in the feed at levels equal to up to 75 mg/kg bw/day. Additional recovery groups at 0 or 75 mg/kg bw/day were fed a normal diet for a further four weeks before sacrifice. At 75 mg/kg bw/day, several animals exhibited a “depressed general condition”, an ungroomed coat, gained less weight, despite a higher food intake, and had slightly longer clotting times (females only). In the liver increased cytochrome P-450 levels of the males at 13 mg/kg bw/day and above were increased, serum ALT, AST and AP were slightly but significantly elevated in both sexes at 75 mg/kg bw/day and there were slight degenerative liver changes (hyaline droplets) in some males at 75 mg/kg bw/day. Blood cholesterol levels were depressed at 75 mg/kg bw/day. Spiroxamine irritancy was reflected in

thickening (hyperplasia) in urinary bladder lining at 75 mg/kg bw/day, hyperkeratosis in the superficial epithelium of the upper GIT at 13 mg/kg bw/day and above (oesophagus and forestomach) and at 75 mg/kg bw/day in tongue tissue also, accompanied by thickening (hyperplasia, hypertrophy) in the oesophagus. Most effects were reversible on cessation of treatment but depressed cholesterol levels persisted. The NOEL was 1.9 mg/kg bw/day.

Rats were treated in the feed with spiroxamine N-oxide at levels equal to up to 54 mg/kg bw/day or with spiroxamine at 53 mg/kg bw/day for 13 weeks. Effects observed were similar for both test substances and the study demonstrated that the primary plant and animal spiroxamine metabolite, the N-oxide, produced effects similar to, but less severe than, spiroxamine.

Rabbits were treated with spiroxamine at up to 5 mg/kg bw/day applied to the skin for 6 hours per day over a period of 3 weeks under a gauze dressing. All effects were confined to the skin. A dose related erythema was seen in all groups treated at greater than 0.2 mg/kg bw/day, which was severe at 5 mg/kg bw/day. Scales, swelling, hardening and cracking occurred in all animals at 5 mg/kg bw/day, in some females at 1 mg/kg bw/day and in one male at 0.5 mg/kg bw/day. The skin of all treated animals had diffuse and focal thickening, and inflammation, which were largely reversible once treatment stopped.

In 2 studies, dogs were administered spiroxamine in the feed at doses equivalent to up to 44 mg/kg bw/day, for 13 weeks. Animals given 44 mg/kg bw/day gained less weight, had lower albumin levels and albumin:globulin ratios in the blood, had increased alkaline phosphatase levels and decreased triglyceride levels (in females only). Liver weights were increased and liver cells were enlarged at 21 mg/kg bw/day in males and at 44 mg/kg bw/day ppm in females. The NOEL was 16 mg/kg bw/day.

Long-Term Studies

Life time studies in mice at up to 250 mg/kg bw/day and rats at doses of up to 43 mg/kg bw/day did not reveal any evidence of carcinogenicity. In both species the primary effects of treatment were related to the irritancy of spiroxamine. In mice drying and thickening of the skin of the ears was observed at 103 mg/kg bw/day and above and thickening was also observed in the lining of the oesophagus, and the skin of the tip of the tail at 60 mg/kg bw/day and above. Thickening of the skin of the tongue was observed at 103 mg/kg bw/day. Animals gained less weight at 103 mg/kg bw/day and above. In rats, at 43 mg/kg bw/day animals drank less, body weights were slightly below controls and slightly more females died in the late phase of the study. Thickening (hyperkeratosis and acanthosis) was observed in the oesophagus and there was an increased number of females exhibiting hyperplasia in the urinary bladder. The overall NOEL was 4.2 mg/kg bw/day.

Spiroxamine was administered in the diet to Beagle dogs at for a period of 52 weeks at up to 57 mg/kg bw/day. From about 9 months after the start of the study, cataracts and lenticular opacity were observed in animals at 2.5 mg/kg bw/day and above and at termination opacity of the lens and subcapsular cataractic change or clouding were more common in these groups. At 2.5 and 5.7 mg/kg bw/day; a mild anaemia (decreased RBC, Hb and Hct) was seen in females, decreased serum albumin levels in both sexes, and decreased triglyceride levels in females were observed and histologically, there was evidence of a enlarged liver cells (minimal diffuse hepatocytomegaly) in both sexes. The NOEL was 2.5 mg/kg bw/day.

Reproduction and Developmental Studies

The reproductive performance of rats fed spiroxamine at up to 42 mg/kg bw/day continuously over 2 generations was unaffected. No histological alterations or malformations were seen in any pups but at 42 mg/kg bw/day litter sizes were slightly smaller, pups gained less weight, were cold to the touch and had a thin appearance. In adult females a slight anaemia (reduced Hct and MCHC values), slightly increased clotting times, reduced platelet counts, increased adrenal weights, and elevated liver enzymes in the blood (AST and ALT) were seen at 42 mg/kg bw/day and increased thymus weights were seen at 11 mg/kg bw/day and above. Both parental generations gained less weight at 42 mg/kg bw/day and had thickening of the oesophagus which was also seen in females at 11 mg/kg bw/day. The NOEL for parental toxicity was 2.1 mg/kg bw/day, and for reproductive toxicity was 9.2 mg/kg bw/day.

Studies were performed on pregnant rats and rabbits to examine the effects of spiroxamine on foetal development during the period of foetal organ formation. In an oral study in rats maternal animals ate less and gained less weight at 100 mg/kg bw/day, foetal body weights were lower and three foetuses (from three litters) had cleft palate. Cleft palate was also seen at the same dose in a range finding study. The incidence of incomplete ossification of the cranial bones and non-ossified cervical bones was increased at all doses. The maternal NOEL was 30 mg/kg bw/day, there was no NOEL for foetal toxicity because of the skeletal effects at the lowest dose tested, and the NOEL for foetal developmental toxicity was 30 mg/kg bw/day. In a dermal study in rats the incidence of foetal skeletal abnormalities, due primarily to an increase in the incidence of wavy ribs, was observed at 80 mg/kg bw/day and the maternal animals gained less weight. There was no maternal toxicity at 5 mg/kg bw/day and no effect on foetal development at 20 mg/kg bw/day. In rabbits maternal toxicity was observed at 80 mg/kg bw/day, reflected in lower gains in body weight together with encrustation in the corner of the mouth, and the incidence of foetal malformations was increased at this dose. The foetal developmental and maternal NOELs were 20 mg/kg bw/day.

Genotoxicity

No evidence of genotoxicity was observed with spiroxamine in; an Ames test, a UDS study in rat hepatocytes, an *in vivo* mouse micronucleus study, or in cytogenetic and forward mutation studies in CHO cells. Similarly an Ames test, and chromosome aberration and forward mutation studies in CH V79 cells using spiroxamine-N-oxide revealed no evidence of genotoxicity.

PUBLIC HEALTH STANDARDS

Poisons Scheduling

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

On the basis of its toxicity, the NDPSC has included spiroxamine in Schedule 6 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) with no cut off. There are provisions for appropriate warning statements and first-aid instructions on the product label.

NOEL/ADI

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

The ADI for spiroxamine was established at 0.02 mg/kg bw/day based on a NOEL of 2.5 mg/kg bw/day in a 12 month dog dietary study and using a 100-fold safety factor in recognition of the extensive toxicological database available for spiroxamine.

Acute Reference Dose (ARfD)

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

The highest acute dose of spiroxamine at which no evidence of toxicity was detected was 20 mg/kg bw (neurotoxicity range finding study). The ARfD was established at 0.2 mg/kg bw on the basis of this NOEL and using a 100-fold safety factor.

METABOLISM AND TOXICOKINETICS ASSESSMENT

Metabolism studies conducted in grapes and spring wheat were provided for evaluation. Spiroxamine was the most significant component of the total radioactive residue (TRR) in both crops. In animals, spiroxamine was readily absorbed and metabolised. The majority of the TRR was eliminated within 48 hours for all animals studied. Important transformations in plants included oxidation to spiroxamine-N-oxide, while in animals, oxidation to spiroxamine carboxylic acid occurred readily. The residue definition for plants should be spiroxamine, and the residue definition for animal tissues, milk and eggs should be spiroxamine carboxylic acid.

Plant Metabolism

The metabolism of spiroxamine in plants was studied in 2 applications of ^{14}C-spiroxamine (cyclohexyl or dioxolane labels) onto spring wheat and grapes.

^{14}C-Spiroxamine was applied to spring wheat grown in a controlled vegetation area. Samples of forage were taken at day 0 and day 14, while grain and straw were sampled after harvest (day 61). The major residues found in all samples were unchanged parent compound and spiroxamine-*N*-oxide. Conventional and exhaustive extraction allowed greater than 85% of the TRR to be characterised. This means????

The metabolism of spiroxamine in grapes was investigated with the parent compound radio-labelled at two different sites (cyclohexyl and dioxolane labels). The radio-labelled spiroxamines were applied to grapes, which were sampled at days 0 and 35 (harvest). The major residue component in each case was unchanged parent compound (25% and 46% of the TRR, at days 0 and 35 respectively), with cyclohexanol derivatives contributing to the total residue of the cyclohexyl-labelled spiroxamine and aminodiol being the next major contributor to the dioxolane-labelled spiroxamine residues. The major metabolic pathways of spiroxamine in grapes involve hydrolysis of the parent into the corresponding cyclohexanone and the aminodiol derivative as well as oxidation to the N-oxide derivative and desalkylation. A translocation study in grapes demonstrated that spiroxamine is not readily translocated from leaves to berries, with only 0.04% of applied radioactivity located in berries after 35 days.

Animal Metabolism

Spiroxamine is extensively metabolised in animals, and the major residue component in animal tissues, milk and eggs was spiroxamine carboxylic acid ([8-(2-methylpropanoic acid-2-yl)-1,4-dioxaspiro[4.5]decan-2-yl]-methyl(ethyl)-(propyl)amine). The major residue component in poultry liver was desalkylspiroxamine, while the major metabolite in fat was the unchanged parent compound. Validated analytical methods were provided that are capable of determining spiroxamine carboxylic acid in animal tissues, milk and eggs. On this basis, it is appropriate to set the definition of the spiroxamine residue in animal tissues, milk and eggs as spiroxamine carboxylic acid. As the current application does not include poultry feed commodities it is not necessary to recommend a separate residue definition for poultry tissues at this stage.

The animal metabolism of spiroxamine was studied in the rat, lactating goat and laying hen following oral administration. For all animals, the radioactive dose was extensively excreted in the urine, and to a lesser extent, in the faeces, within 48 hours.

Spiroxamine was administered to rats at a nominal dose rate of 1, 10 or 100 mg/kg bodyweight. The majority of the administered radioactivity was excreted (70 – 90%) within 48 hours. The radioactivity remaining in the body after 48 hours was determined to reside predominantly in the liver, gastrointestinal tract, gonads and adrenals. Metabolites isolated from excreta show that spiroxamine is extensively metabolised, with no unchanged parent compound being detected. The major metabolite is spiroxamine carboxylic acid.

Spiroxamine was administered orally to lactating goats at 10 mg/kg bw/day for three consecutive days. Spiroxamine was extensively eliminated in urine (63% of total dose) and faeces (12% of total dose) seven hours after the last dose. Less than 5 % of the total dose was found in edible tissues and organs (3.4% of total dose) at sacrifice. Liver accounted for about 2% of the total dose while muscle contributed 1%. Only 0.2% of the total dose was secreted with milk. Spiroxamine carboxylic acid was the major residue component in milk, muscle and fat. The major metabolite in liver was spiroxamine acid glycoside ester, while spiroxamine hydroxy acid was the major metabolite in kidney.

Spiroxamine was administered to laying hens at 10 mg/kg bw/day for 3 consecutive days. The majority of the radioactivity was excreted (between 66% and 83% of the totally administered radioactivity) in the faeces and urine within 5 hours of the last dose, with a further 0.22 % eliminated with the eggs. The edible tissues accounted for another 9.9% of the radioactivity, bringing the recovery to 84%. The liver, kidney and fat accounted for the majority of the residue in the edible tissue/organs with less than 10 mg/kg equivalents of the administered dose in the other tissues/organs analysed. Metabolites were identified in muscle, liver, fat and eggs and four main components were characterised (spiroxamine carboxylic acid, despropyl-spiroxamine, desethyl-spiroxamine and unchanged parent). These accounted for between 65% and 91% of the TRR in these tissues/organs.

The existence and behaviour of the significant plant metabolite, spiroxamine-N-oxide, in animals was investigated. Spiroxamine-N-oxide was shown to be a metabolite of mammals, and the absence of this metabolite in excreta was thought to result from subsequent enzymatic reactions.

RESIDUES ASSESSMENT

Residues in grapes and processed grape commodities

Australian and overseas residue trials were provided for grapes and processed grape commodities. European trial data were not considered for the purposes of setting an MRL as the residue measured in those trials was significantly different from the recommended Australian residue definition. In Australian trials, two applications of *Prosper 500 EC Fungicide* were made to grapes using different spray concentrations (25, 37.5 and 50 g ai/hL), similar to the proposed rate (30 g ai/hL). Grapes were sampled at various growth stages after application of spiroxamine with harvest of ripe berries at 28 days after last treatment. Residues in/on grapes were found to be present at up to 0.96 mg/kg when treated with 3 applications of spiroxamine at 1.25× the proposed rate, with a 28 day withholding period. Although residues in/on grapes treated with lower levels of spiroxamine were generally lower, one trial detected residues of 0.87 mg/kg on grapes following treatment with 0.8× the proposed rate and applying a 28 day withholding period. Residues in/on grape samples treated with 50 g ai/hL (1.6× label rate) were present at similar levels to samples from trials applying 37.5 g ai/hL. The residues in/on grapes from 12 trials conducted at 0.8 – 1.25× the proposed label rate with a 28 day withholding period and in rank order (median underlined) are 0.17, 0.18, 0.29, 0.39, 0.43, <u>0.46</u>, <u>0.50</u>, 0.58, 0.61, 0.66, 0.87, 0.96 mg/kg. The data support an MRL of 2 mg/kg for grapes when combined with a 28 day withholding period. The STMR is 0.48 mg/kg (n=12) and the HR is 0.96.

Five of the six Australian trials analysed wine for residues. It was found that wine produced from grapes treated with 37.5 g ai/hL and harvested 28 days after final application contained spiroxamine residues at <0.3 mg/kg. The average residue level detected in wine from treated grapes was 0.12 mg/kg. The mean processing factor for grapes from Australian trials harvested 28 days after last application and converted to wine was 0.2.

Spiroxamine residues were found to concentrate in dried grapes. The processing factors determined from the two Australian trials were 0.85 and 1.7, with an average of 1.3. The maximum residue in dried fruit produced from grapes harvested 28 days after last application was 1.64 mg/kg. Due to the small number of trials used in determining the average processing factor, the largest processing factor (rounded up to 2) should be used in setting an MRL for dried grapes. Therefore, the maximum residue of spiroxamine expected in dried grapes is 1.92 mg/kg and, thus, an MRL of 3 mg/kg is appropriate for dried grapes.

Residues in marc (pomace) and foliage 28 days after last treatment with 37.5 g ai/hL were detected at up to 4.5 mg/kg. The STMR was 2.2 mg/kg (0.61, 1.29, <u>2.03</u>, <u>2.42</u>, 2.81, 4.50; n=6) for marc from grapes treated at 0.8 – 1.25× the label rate and harvested 28 days after last treatment. These data support an MRL of 10 mg/kg for grape marc (wet weight basis).

Processing

Processing data were provided for grape commodities. Processing factors for wine ranged from 0.02 – 0.38, with an average of 0.17 (n=10). Processing factors for dried grapes were 0.85 and 1.7, with an average of 1.3 (n=2).

Animal commodities

As the maximum expected dietary burden for cattle in Australia was estimated as 5.4 ppm in the feed, animal transfer data for cattle fed spiroxamine at 6 ppm in the feed has been used to set MRLs. On the basis of the animal transfer data, it is concluded that residues in muscle and

fat will be around the Limit of Quantitation for animals fed commodities containing spiroxamine residues at 6 ppm in the diet. Residues in the milk will be present at about 0.02 mg/kg while residues in offal may be present at up to 0.18 mg/kg when cattle are fed spiroxamine at 6 ppm in the feed. Spiroxamine metabolites were not found to accumulate in the fat or tissues. The results from animal transfer studies support MRLs of 0.05 mg/kg for milk, 0.05 mg/kg for meat and fat and 0.5 mg/kg for edible offal.

Animal Transfer Studies

By-products from grape processing procedures may be fed to stock, and the applicant has submitted animal transfer studies conducted with lactating cattle and laying hens. The maximum expected dietary burden for cattle in Australia, from grape pomace and raisin waste, has been estimated to be 5.4 ppm in the feed. In the cattle feeding study presented, cattle were dosed with spiroxamine at the equivalent of 2, 6 and 20 ppm in feed. Residues of spiroxamine carboxylic acid reached a plateau in milk of 0.040 and 0.015 mg/kg for the animals fed at 6 and 20 ppm, respectively, within 4 days. No quantifiable residues were observed in the milk (LOQ 0.01 mg/kg) of animals administered 2 ppm in the feed. Residues in the muscle and fat were detected at or below the Limit of Quantitation in animals fed spiroxamine at 2 and 6 ppm in the feed. When the animals were administered 20 ppm in the feed, residues were detected at less than 0.06 mg/kg in muscle and at 0.15 mg/kg in fat. The dose levels and average residues determined in muscle and fat had an approximately linear relationship, and from this, it can be estimated that the residues in cows fed at the maximum dietary burden of 5.4 ppm will be around 0.02, the LOQ for muscle and fat. Higher residue levels were found in the liver and kidney due to the metabolism and renal excretion of spiroxamine. The animals fed 2 ppm spiroxamine in the feed showed average residues of 0.045 and 0.05 mg/kg for kidney and liver, respectively. These increased in an approximately linear fashion and the animals fed 20 ppm in the feed showed average residues of 0.22 and 0.27 for kidney and liver, respectively.

Spray Drift

Off-target deposition of spiroxamine could result in residues on adjacent pastures. Residues on adjacent pasture could exceed the maximum animal feeding level as a result. *Prosper* will only be applied by ground rig, with some opportunity for off-target deposition. Spray drift modelling can be used to estimate the size of the buffer zone required on adjacent pasture for resultant grazing animal residue levels to be below the set limits. Spray drift modelling was conducted using the AgDrift computer model[1] with the typical input parameters for orchard/airblast application and normal settings (Stone and pome fruit, vineyards). It is recognised that ground application spray drift models are still rather simplistic, and the calculated buffer zones are conservative. From Australian use patterns, it was calculated that between 0.3 and 1.2 kg ai/ha could be applied to grapevines. These rates were used to calculate the buffer zones required for residues in grazing cattle to be below set limits, as they represented the extremes of likely application rates. For residues in cattle offal to be below the MRL (0.5 mg/kg), pasture residues have to be below 6 mg/kg on a dry weight basis (taken from animal feeding studies). It was extrapolated from feeding studies that pasture residues had to be below 0.5 mg/kg DM for residues in offal to be below the LOQ. Assuming a pasture yield of 2000 kg DM/ha, a pasture threshold can be calculated (pasture residues (mg/kg DM) × pasture yield (kg DM/ha) = pasture threshold (mg/ha)). From these data, buffer zones of 0 – 4 m were estimated for resultant residues in animal to be below the MRL,

[1] Developed by the Spray Drift Task Force in association with the US EPA as part of the Cooperative Research and Development Agreement between US EPA, USDA ARS, USDA Forest Service and SDTF.

while a 50 m buffer zone is needed for residues in offal to be below the LOQ. From the buffer zones calculated above, it is unlikely that there will be sufficient contamination of adjacent pasture from spray drift to lead to residues in offal above the MRL. However, spray drift might result in sufficient deposition of spiroxamine on pasture to lead to residues above the LOQ in edible offal. In this instance, a buffer zone of 50 m has been estimated to ensure no residues in offal are above the LOQ. This submission seeks comment on how practical an imposed restriction of 50m around a treated vineyard would be and on the potential trade risk associated with finite residues in edible offal resulting from the proposed use.

Residue Stability

Spiroxamine residues were stable in grapes, grape juice, raisins, wheat extracts and animal tissues, milk and eggs on storage at -18 °C or below. Grapes were stored for up to 4 years, with grape juice and raisins stored for 18 months. Residues in wheat extracts remained stable for at least 2 years. Bovine tissues, milk and eggs were spiked with spiroxamine and stored for at least 4 weeks at –18 °C or below. Residue levels in all of these tissues did not decline on storage. As samples from crop residue trials were stored for up to 12 months between sampling and analysis, the residue results obtained in the trials are considered to be a true indication of the residues present at sampling.

Maximum Dietary Intake Calculations

The risk to human health from the use of spiroxamine is considered to be low. The chronic dietary risk is estimated by the National Estimate of Dietary Intake (NEDI) calculation. The Acceptable Daily Intake (ADI) for spiroxamine is 0.02 mg/kg body weight and was set based on a NOEL of 2.5 mg/kg bw/day with a hundred-fold safety factor. The NEDI for spiroxamine was calculated to be 3.7 % of the ADI for consumers aged two years and above. As it is widely recognised that this calculation is a gross over-estimate of actual dietary intake, it is concluded that the chronic dietary exposure to spiroxamine is small and the risk is acceptable.

An acute reference dose of 0.20 mg/kg bw/day has been set for spiroxamine by the TGA. The estimated acute intake of spiroxamine from relevant commodities has been calculated using 97.5^{th} percentile consumption figures for infants (2 – 6 years old, body weight 19 kg). The results calculated are well below the acute RfD, at 17, 2, 0, 0, 0 and 1% for grape, dried grape, edible offal (mammalian), meat (mammalian), fat (mammalian) and milks, respectively. Similarly, the estimated acute intakes for adults (7 years and above, body weight 70 kg) were calculated. The results for adults were also well below the acute RfD, at 7, 1, 0, 0, 0 and 0% for grapes, dried grape, edible offal (mammalian), meat (mammalian), fat (mammalian) and milks, respectively. The acute exposure is therefore considered to be low and the risk is acceptable.

MRL Standard

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

Table 1

Compound	Food		MRL (mg/kg)
ADD:			
Spiroxamine			
	FB 0269	Grape	2
	DF 0269	Dried grape (currants, raisins and sultanas)	3
	MO 0105	Edible offal (mammalian)	0.5
	MM 0095	meat (mammalian)	0.05
	MF 0100	fat (mammalian)	0.05
	ML 0106	milks	0.05

Table 3

Compound	Residue
ADD:	
Spiroxamine	
	Commodities of plant origin: Spiroxamine Commodities of animal origin: Spiroxamine carboxylic acid

Table 4

Compound	Animal feed commodity		MRL (mg/kg)
ADD:			
Spiroxamine			
	AB 0269	Grape Pomace	10

The following withholding period is recommended in relation to the above MRLs for *Prosper*:

GRAPEVINES: DO NOT HARVEST FOR 4 WEEKS AFTER APPLICATION.

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Currently, spiroxamine is registered for use in Austria, Belgium, the European Community, France, Greece, Hungary, Slovenia, South Africa and Switzerland. The applicant has indicated that it is their intention to register spiroxamine under various tradenames for the control of powdery mildew on cereal crops and grapevines in Denmark, England, Germany, Ireland, Italy, Kenya, Netherlands, Poland, Portugal, Russia, South America, Sweden and the USA.

The following MRLs have been established for spiroxamine (all formulations) (as of June 2001):

Established MRLs overseas

Country (mg/kg)	Commodity	MRL (mg/kg)	Commodity	MRL
Austria	barley	0.5	other plant commodities	0.05
	rye	0.1	triticale	0.1
	wheat	0.1	wine grape	1
Belgium	barley	0.5	meat by-products	0.1
	wheat	0.1	milk	*0.01
	milk products	0.01	edible offal (mammalian)	0.1
	other food of animal origin	*0.02	other plant commodities	*0.05
European Community (Expiry date: 2005. It is anticipated that MRLs will be permanent by that time)	Eggs	T*0.05	Fat	T*0.05
	Kidney	T0.2	Liver	T0.2
	Meat	T*0.05	Meat by-products	T*0.05
	Milk	T0.02	Milk products	T0.02
	Barley	T0.3	Berry, wild	T*0.05
	citrus fruit	T*0.05	Fruit, wild	T*0.05
	grape	T1	Hop	T*0.1
	Nuts	T*0.05	Oat	T0.3
	Other berries and small fruit	T*0.05	oil plants, seed	T*0.05
	other cereals	T*0.05	Pome fruit	T*0.05
	potato	T*0.05	Pulses	T*0.05
	Rubus species	T*0.05	stone fruit	T*0.05
	strawberry	T*0.05	tea	T*0.1
	Tropical fruit	T*0.05	Vegetables	T*0.05
France	Barley, grain	0.02	Barley, straw	5
	grape	0.5	Oat, grain	0.2
	Oat, straw	5	Rye, grain	0.05
	Rye, straw	5	triticale, grain	0.05
	Triticale, straw	5	wheat, grain	0.05
	wheat, straw	5	wine grape	0.5
Greece	grape	2	grape, wine	2
Hungary	cereals	0.05	pea, garden	0.05
	grape	0.05		
Slovenia	wheat	0.05		
South Africa	Pea	T0.1		

Switzerland	barley	T0.3	grape, wine	T1
	grape	T0.2	Rye	T0.05
	Wheat	T0.05		

Spiroxamine has not been reviewed by the JMPR. There is no CODEX residue definition for spiroxamine and no CODEX MRLs have been set for spiroxamine.

Grapes and Wine Exports
Australian grape production was 1544 kt in 1999/00 with 1122 kt used in wine making and 421 kt for drying and table grapes. Australian table grape production was 70 kt in 1999. About 26 kt of dried grapes (sultanas, currants, raisins) were produced in 1999. The major destinations and export values of Australian grape commodities are shown below.

Major destinations and export values of Australian table grapes, wine and dried grapes 1999/2000

Importing country	Quantity	Value ($ m)
Table Grapes (tonnes)		
Hong Kong	11279	24.8
Singapore	9718	16.96
Malaysia	4306	9.35
New Zealand	1941	4.54
Indonesia	1531	3.37
Vietnam	825	2.07
Thailand	804	2.22
Wine (ML)		
United Kingdom	139.69	
United States	50.03	
New Zealand	20.12	
Canada	12.60	
Germany	9.39	
Netherlands	8.56	
Ireland	7.08	
Sweden	5.96	
Japan	5.53	
Switzerland	4.82	
Singapore	2.10	
Hong Kong	1.72	
Thailand	0.65	
China	0.46	
Total Export Value		1352.28
Dried grapes (tonnes, dry weight)		
Germany	1471	3.82
United Kingdom	888	2.70
New Zealand	888	2.44
Canada	680	1.83

Table grape production in 1999 was approximately 70 kt, with an estimated farm-gate value 1998/99 of $127.9. Approximately 50% of Australian table grapes were exported, with the total export market valued at $74 m for 1999/2000.

Approximately 63 kt of dried vine fruit were produced in 1999/00 from 362 kt of fresh grapes. Sultanas are the major commodity produced (34 kt dry weight 1998, farm gate value of $38 m) with currants (2.4 kt, $3.4 m) and raisins (2.5 kt, $1.3 m) also produced. The total export value in 1999/2000 was $12.6 m.

Australia exported 287 ML of wine, valued at approximately $1 352 m in 1999/2000.

The wine industry has mitigation programs in place for residues in trade. The industry establishes tolerances and WHPs that growers must comply with. Provided the wine industries are consulted adequately, the risk to Australia's export trade in wine is considered small. A similar situation occurs in the dried fruit industry. However, in the case of table grapes, there are no industry programs in place. The table grape industry should be made aware that residues of spiroxamine may present a risk to Australia's export trade in this commodity. There are no import tolerances for spiroxamine residues in/on table grapes in the major export markets (Hong Kong, Singapore and Malaysia) and therefore, any residue detection would constitute a violation. The following statement encouraging growers to seek advice from the applicant should be included on the label:

Export of Treated Produce**:**
Table grape growers should note that suitable MRLs or import tolerances may not be established in all markets for table grapes treated with *Prosper*. If growing table grapes for export, check with Bayer for the latest information on MRLs and export tolerances before using *Prosper.*

Comments on the value of this approach are also sought from industry.

Cattle Exports
Australia's export market for beef and veal was worth approximately $2.9 billion in 1999. Live cattle exports were valued at $416 million. The major export markets for beef and veal and live cattle are listed below with 1999 exports (preliminary figures):

Beef and veal

Country	**kt**	**Country**	**kt**
Japan	313.3	Philippines	20.4
United States	291.1	Middle East	14.1
Rep. of Korea	77.9	Indonesia	11.6
Canada	43.3	Malaysia-Singapore	10.6
Chinese Taipei	34.7	Western Europe	9.3

Live cattle

Country	**'000**	**Country**	**'000**
Philippines	268.8	Malaysia	65.2
Egypt	240.5	Libya	23.1
Indonesia	159.5	Japan	12.4

When cattle were fed with 6 ppm spiroxamine in the feed, residues in beef were found to be about the LOQ (0.02 mg/kg) for muscle and fat. The 6 ppm feeding level is a conservative estimation of the maximum dietary burden, and so it is considered that quantifiable residues in meat and fat are unlikely to be observed. Residues in offal were present at up to 0.18 mg/kg, so although the calculation of maximum dietary burden was conservative, it is possible that quantifiable residues could be detected in offal. Offal exports with detectable residues could

present a risk to Australia's beef trade as no MRLs for beef commodities have been established in most of the major export markets.

Exports of dairy products were worth approximately $2.2 billion in 1999/2000. Dairy products are distributed around the world, with Japan, Saudi Arabia, Egypt, Malaysia, Philippines, Thailand, US and Taiwan being the major export markets by dollar value. Residues in milk were determined to be present at 0.02 mg/kg in animal feeding trials. Given that the estimate of the maximum dietary burden is conservative and that milk is a bulked product, residues in milk are unlikely to be above the LOQ. Hence, the risk to Australian dairy trade from the registration of spiroxamine for use on grapes is considered small.

Summary of Export Risks

Overall, the use of *Prosper* on grapes has the potential to prejudice Australian trade as quantifiable residues are expected in grapes, wine, dried grapes and cattle offal when *Prosper* is used following the proposed use pattern. Comment is sought as to whether the potential prejudice to trade is considered undue.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Spiroxamine is not on the NOHSC *List of Designated Hazardous Substances*. The applicant has classified spiroxamine and Prosper 500 EC Fungicide (*Prosper*) as hazardous according to the NOHSC *Approved Criteria for Classifying Hazardous Substances*.

Spiroxamine will be manufactured overseas as a light brown oily liquid. It has moderate oral, dermal and inhalation toxicity in rats. Spiroxamine is a moderate skin irritant and a slight eye irritant in rabbits. It has skin sensitising potential in guinea pigs.

Prosper has low acute oral and dermal toxicity in rats. It is a severe eye and skin irritant in rabbits, but not a skin sensitiser in guinea pigs. A 1% dilution of the product was a slight eye irritant, but not a skin irritant.

Formulation, repackaging, transport, storage and retailing

Technical grade spiroxamine is manufactured overseas and will be imported into Australia. The end-use product (EUP) will be formulated in Australia from the imported active ingredient and will be packed in 1, 5, 10 and 20 L high-density polyethylene (HDPE) containers.

Storemen, transport workers, laboratory staff, formulators and packers will handle the active constituent and the product. The submission contains sufficient information on the categories of workers, nature of work done and prevention of worker exposure required for workplace assessment.

Use and exposure

Prosper is intended for use in controlling powdery mildew in grapevines. It will be applied to grapevines by ground spraying. The maximum application rate is 750 mL/ha, with a minimum spray volume of 250 L/ha (0.3% EUP (v/v) and 0.15% spiroxamine (w/v). It could also be applied as a dilute or a semi-concentrated spray. A maximum of 2 sprays per season is recommended with spray interval not exceeding 21 days.

The main routes of exposure are dermal, inhalation and ocular. Categories of workers that can be exposed to the product are mixer/loaders, ground applicators, clean-up personnel and re-entry workers.

There are no available worker exposure data on *Prosper*. NOHSC used the UK Predictive Operator Exposure Model (POEM) and the Pesticide Handlers Exposure Database (PHED) to estimate applicator exposure to *Prosper*.

These data/estimates in conjunction with toxicology data demonstrated that the use of clothing, hat, gloves and goggles during mixing / loading and, clothing and a hat during spraying is necessary to protect workers from acute and repeated exposure.

Entry into treated areas

Workers entering treated areas can be exposed to product residues and degradation products during crop management activities and harvesting.

Based on generic foliar residue data and the information provided by the applicant on post-application activities, NOHSC recommends a restricted entry period until the spray has dried. When prior entry is necessary, cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves should be worn to reduce exposure.

Recommendations for safe use

Users should follow the instructions and Safety Directions on the product label. Safety Directions include the use of cotton overalls buttoned to the neck and wrist, a washable hat and elbow- length PVC or nitrile gloves and goggles when preparing the spray and use of cotton overalls buttoned to the neck and wrist, and a washable hat when using the prepared spray.

The PPE recommended should meet the relevant *Standards-Australia*.

Re-entry statement

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

Prosper can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the spiroxamine and *Prosper* MSDS.

ENVIRONMENTAL ASSESSMENT

Spiroxamine is proposed for use in Australian in vineyard situations only. The proposed use pattern is part of a 5 spray resistance management program with a maximum of 3 applications of *Prosper* to be applied as a foliar spray.

Environmental Fate

Degradation rates and routes

Spiroxamine only hydrolyses slightly in water, but is subject to aerobic microbial degradation, as noted in one contaminated sample, and is subject to slow photolytic degradation (DT_{50} >200 days sunlight). Also, a photolytic study on soil showed only slow degradation (DT_{50} ~120 days), but this used biologically active soil and the small differences may be due to chemical/microbial interactions. Spiroxamine degradation in air was estimated using computer modelling and indicates relatively rapid degradation (DT_{50} <2 hours) due to reaction with photochemically generated hydroxyl radicals, indicating that any volatilisation losses should not persist.

Standard soil degradation studies in four of soils produced half-lives in the range 35-70 days, with a range of degradation products leading to simple compounds and CO_2, which accounted for 22-45% AR after 100 days. The major degradation products were the desethyl- and despropyl-parent reaching peak concentrations around 4-9% AR, depending on soil types. Other intermediate metabolites were also identified, but these were <2.5% AR at all stages of the tests, often much less.

The DT_{50} of spiroxamine in aquatic situations (aerobic water and sediment) was found to be 28-106 days for the whole systems, but dissipation from the water column is much faster (12-13 hours), reflecting the rapid adsorption to sediment.

In a series of European field trials the DT_{50} and DT_{90} values for total spiroxamine residues were in the range 5-82 days and 45->150 days, respectively. Half-lives for the spiroxamine parent were somewhat shorter and ranged from 1-48 days. The soil half-lives rank spiroxamine as low-moderately persistent according to Dutch guidelines. In the crop rotation trial, practically no detectable residues of spiroxamine were taken up by the following crop, which was planted immediately after soil incorporation of crop residues containing significant residues (~3-7 ppm) from a typical field use pattern. In a further crop rotation trial, low levels of detectable residues of spiroxamine applied to soil were taken up by the following crop (~1 ppm), which was planted 30 days after soil application. These crop residues varied significantly between crop species in this atypical field use. Estimated carryover from normal use will be practically zero. Spiroxamine has an estimated bio-concentration factor <100 based on a test using bluegill sunfish, hence it is unlikely to bioaccumulate in natural systems.

Metabolites

Significant production of CO_2 from complete degradation of spiroxamine was apparent in laboratory metabolism tests and extraction and identification of various metabolites, including the desethyl- and despropyl-parent, indicates a high degree of mineralisation of the molecule can occur. Spiroxamine and its metabolites may also become bound to soil organic matter or clay fractions, but these residues appear partially accessible to further microbial attack. Desethyl- and despropyl-spiroxamine have been identified as main metabolites in aerobic soil and aquatic metabolism studies, but were generally <10% of applied active in all tests. Other metabolites identified include spiroxamine-N-oxide and hydroxy-spiroxamine and a range of intermediates or conjugates leading to t-butylcyclohexanone and eventually CO_2.

Mobility

Evaluations of the K_{oc} of spiroxamine in conventional flask adsorption/desorption studies indicated that it had low mobility in soil, and estimation of the Gustafson Ubiquity Score (GUS) from K_{oc} and soil degradation half life data indicated that spiroxamine is a non-leacher. Laboratory column leaching studies using aged soil residues showed little movement down soil columns from heavy irrigation, with ≤0.3% of applied label emerging in the percolate from the columns during the test period, most likely simple degradation products. A modelling study (PELMO) indicated that no spiroxamine should reach a shallow groundwater table when two applications per season were used on cereal crops. Spiroxamine and known major metabolites were rarely detected below the surface soil layer (0-10 cm) in field dissipation studies, either when applied directly to soil (worst case scenario) or to vegetated sites.

The vapour pressure of spiroxamine indicates it is slightly volatile, and laboratory studies found that ~25% of applied spiroxamine was lost from leaf surfaces, largely in the first hour (17%). Little significant volatilisation was noted from soil surfaces in this study, but the Henry's Law Constant suggests slight volatilisation may occur from water surfaces. Volatilised spiroxamine is likely to be degraded with an estimated DT_{50} of <2 hours due to reaction with photolytically produced hydroxyl radicals in the atmosphere.

Environmental chemistry and fate

The major route for degradation of spiroxamine appears to be microbial degradation. A proportion of applied spiroxamine may volatilise from leaf surfaces, but is unlikely to persist in the atmosphere due to indirect photodegradation. Photolysis on the soil and plant surfaces is not likely to be significant. Hence spiroxamine has low-moderate persistence in soil and water and moderate persistence in sediment. As it should be used a maximum of two times per annum, there should be sufficient time for degradation to near completion between years. Laboratory studies indicate that spiroxamine is unlikely to leach, and field studies suggest that even in extreme situations, spiroxamine and its major metabolites are unlikely to leach deeply into soil and are unlikely to contaminate groundwater.

Environmental Toxicity

Avian

TGAC test results indicate that spiroxamine is moderately toxic to birds in single high doses, but less toxic in dietary studies, probably due to an obvious feed aversion. However, spiroxamine did have minor effects on off-spring in a dietary reproduction trial at doses similar to those likely to be encountered from residues on freshly treated plants.

Aquatic

Test results indicate that spiroxamine TGAC and the EC formulation can be rated as slightly-moderately toxic to rainbow trout and moderately toxic to bluegill sunfish, according to US EPA rankings, but the TGAC proved highly toxic to early life stages of trout in a prolonged test. This results in a very high acute to chronic test ratio (~150X). Similar toxicity was exhibited towards aquatic invertebrates (daphnids), again with the chronic test more sensitive and a relatively high acute to chronic test ratio (~50X). Sediment dwelling midge larvae were not affected when spiroxamine was added to the water phase of a pond-water test, despite the active partitioning rapidly to sediment, but the maximum test level was very low (~2 µg/L).

Spiroxamine was very highly toxic to green algae with EC_{50} values from acute tests of ~3-6 µg/L, or 3 orders of magnitude more sensitive than fish/daphnids. However, in one test where exposed algae were cultured for up to 22 DAT the growth rates in affected treatments recovered

and cell counts were practically equal to controls after 22 days, indicating that spiroxamine has an algistatic rather than algicidal effect. The TGAC and the EC 500 formulation gave similar results in aquatic toxicity tests. The quoted EC_{50} value for *Lemna gibba* indicates spiroxamine exhibits much lower toxicity towards aquatic macrophytes, ranking it as moderately toxic.

Terrestrial Organisms

Spiroxamine is rated as slightly toxic to wildlife mammals (LD_{50}~500 mg/kg bw), and did not affect soil microbial activity, but was evidently inhibitory to sewage sludge microbial activity at relatively high doses. Spiroxamine showed slight to moderate toxicity to bees in direct dosing tests, but field and semi-field exposures in flowering plants indicate no adverse effects and a field rating of harmless to bees. The spiroxamine EC formulation showed low toxicity to earthworms at 1X and 4X the field use rate, indicating it is unlikely to harm earthworms.

Laboratory studies indicate spiroxamine exhibits harmful effects to a range of beneficial species (predatory mites, parasitic wasps, lacewings, beetles and spiders), noting these are "worst case" direct exposures. However, results showed a degree of variability due to different factors, for example beetles and spiders exposed on a sand substrate had high mortalities while on a natural soil substrate the mortalities were very low. As well, spiders sprayed once had low mortalities but were all killed by a second application, while juvenile stages (larvae/pupae) appear more susceptible than the adults in several tests (wasps, mites and beetles). Field and semi-field tests resulted in exposures more allied to field usage, and resulted in fewer adverse effects compared to the directly applied laboratory tests. For predatory mites, field evaluation appears to indicate little or no impact, even from several applications of the chemical in vineyards.

These variable effects in tests on beneficial invertebrates with results ranging from harmful in some laboratory exposures (100% mortality) to harmless in others (<5% mortality) raise some queries. Exposures on simple media (glass plates/sand) caused more severe effects than comparable test exposures on more complex substrates (plants/soil) indicating spiroxamine may be less available from soil/plant surfaces. As well, juvenile stages appear more susceptible to spiroxamine than the adults, and there was a clear dose response in some tests where a single treatment caused few effects while a second application caused severe effects. These factors indicate spiroxamine may affect some part of the moulting/ecdysis functions in arthropods.

No data are available regarding phytotoxicity to non-target native plants. However, the absence of any reports of phytotoxicity to grapes or cereals suggests that spiroxamine is unlikely to cause serious phytotoxicity to non-target species, at least at field use rates or the lower rates that might be expected from spray drift.

PREDICTION OF ENVIRONMENTAL HAZARD

Spiroxamine residues may be expected from directed spray on plant surfaces, including the plant canopy, fruit and inter-row plant cover, soil, invertebrates exposed to spray and trellises. Possible contamination of surface water, uncultivated land and nearby non-target plants (eg trees and grasses) may occur through overspray, spray drift and/or run-off.

It is expected that the majority of farmers will use trailer mounted air blast sprayers or over the row boom spray equipment, with hollow cone nozzles. Exposure of non-target organisms may occur through direct contact with spray drift or from ingestion of residues on vegetation, soil or sprayed insects. Volatilisation from plant or soil surfaces is unlikely to occur.

Terrestrial organisms

Birds could be exposed to spiroxamine from residues on sprayed plants or insects. Spiroxamine will be applied to grapevines during their growth period (spring-summer) and using EPA methodology the residues are expected to be ~45 ppm on grape leaves and ~5 ppm on insects at the proposed maximum application rate (~ 375 g ai/ ha). These levels are well below the five-day dietary NOEC values for both bobwhite quail and mallard duck. In a 21-week dietary reproduction study there was a minor effect noted in off-spring of quail fed at 77 mg ai/kg, but this was the entire diet. Therefore, under normal conditions of use this fungicide should present a negligible hazard to herbivorous or insectivorous birds, noting that grapevine leaves are unlikely to be eaten by birds. Similar calculations performed for herbivorous mammals also indicate negligible hazard.

Laboratory tests indicate spiroxamine may be hazardous to bees with contact LD_{50} results <10 µg/bee, but field tests with bee hives in treated flowering crops indicate there were no discernible effects on hive populations or foraging activity. This provides reasonable assurance that spiroxamine is unlikely to present a hazard to bees from the use in grapevines, since grapes are generally self-pollinating and bees are largely casual visitors.

Spiroxamine is not expected to have any adverse effects on earthworms, given that no adverse effects were noted in tests where 1X and 4X the EU field rate were applied directly to soil. Likewise, soil microbes were not inhibited by spiroxamine in tests at 1 and 10 times the proposed European use rate (2X Australian rate).

Spiroxamine had variable effects in tests on beneficial invertebrates with results ranging from harmful in some laboratory exposures (100% mortality) to harmless in field tests (<5% mortality). Exposures on simple substrates (glass plates/sand) caused more severe effects than comparable test exposures on more complex substrates (plants/soil) indicating some "binding effect" on exposure from soil/plant surfaces. As well, juvenile stages appear more susceptible to spiroxamine than the adults, and there was a clear dose response in the laboratory where a single treatment caused few effects while a second application caused severe effects, which indicates spiroxamine may affect some part of the moulting/ecdysis functions in arthropods.

As for bees, the hazard from applications of Prosper® EC 500 in the field at the proposed rates (maximum two applications per season at least several weeks apart) is likely to be low and significant effects on invertebrate populations appear unlikely.

Aquatic organisms

Fish and aquatic invertebrates

Even when assuming an absolute "worst-case" scenario, that is direct application of spiroxamine at 375 g ai/ha to pond water 15 cm deep, the water EEC is 250 µg/L. This concentration is ~ 20 times less than the acute LC_{50} for daphnia and fish and therefore there is a considerable safety margin. The chronic reproduction test for daphnia provided a LOEC of the same order as this EEC, while the ELS test in fish provided a much lower TEC, half this value, indicating the hazard assessment may need to be refined.

However, spiroxamine was speedily removed from the water column through rapid dissipation to sediment in the chironomid midge study (DT_{50} of ~1 day) and aerobic water/sediment degradation study. Further this chironomid study showed no adverse effects on midge emergence, but test levels

were very low (<2.5 µg ai/L), equivalent to ~1% spray drift in the EEC calculation above. Chronic exposures are not expected and exposure should be limited by the low likelihood of spiroxamine applications reaching or persisting in natural water bodies. Spiroxamine should not provide an acute or chronic hazard to fish or aquatic invertebrates in surface waters adjacent to application areas.

Algae and aquatic plants
A worst case EEC (direct over-spray of a shallow pond) is 250 µg ai/L for application to grapevines. The lowest test values (EC_{50}s 3.2-6 µg ai/L) are from green algae toxicity tests and result in Q-values for algae of ~40-80, while the EC_{50} for duckweed is 1.91 mg/L, resulting in a Q-value of ~0.1. This initial step indicates that there is no hazard to duckweed from spiroxamine application, but a higher tiered analysis is needed to evaluate the potential hazards to green algae, which are the most sensitive aquatic test organisms.

Spray drift
A more likely assessment of contamination from spray drift in the practical use of Prosper in vineyard applications uses field data from German field trials (known as the Ganzelmeier Tables). Pesticide spray drift from air/mist blowers and boom sprayers is evaluated using tables derived from monitoring field use. These data indicate that conventional spraying in vineyards results in spray drift reaching soil that decreases rapidly as a function of distance from the sprayer (~10% applied active at 1 m, ~0.5% at 10 m and ~0.1% at 15 m). Q-values (0.04-0.08) calculated from this lower expected contamination indicate that outside 10 m from the sprayer hazards to green algae are likely to be acceptable. Given that very few vines, even the edges of vineyard plots, will be growing within 15 m of natural ponds or waterways plus the rapid dissipation from water (see above), then the hazard is likely to be low. Further, it is noted algae recover after spiroxamine exposure (algistatic) and algal populations are known to recover quickly, so that any adverse effects would be expected to be transient only.

Run-off

Run-off from vineyard soils is considered to be low, given the increasing use of inter-row ground covers such as grass swards. Even on bare soil, the low amounts of residual spiroxamine reaching soil will be rapidly sorbed to soil and are therefore unlikely to be moved out of vineyards by erosion under these permanent vine plantings.

Leaching

The field dissipation studies showed that under field conditions leaching was not observed, despite rates higher than that proposed for Australia. The laboratory column leaching studies and the physical properties of the chemical indicate a low potential for leaching. Leaching under Australian conditions would not be anticipated based on these studies.

Desirable vegetation

When used according to label directions, the hazard to native and non-target vegetation should be negligible, given no reports of phytotoxicity in crop plants.

Conclusion
The application contains adequate environmental fate and toxicity data to demonstrate that the use of spiroxamine according to the label and Good Agricultural Practice is unlikely to result in acute poisoning of wildlife, fish, and most non-target organisms, except for algae, which may be adversely affected by very low accessions to natural bodies of standing water.

The principal degradation pathway of spiroxamine is metabolism via enzymatic or microbial breakdown in plants and soils. There was little degradation via hydrolysis or aquatic metabolism,

but spiroxamine was noted as partitioning to sediments in aquatic systems. Laboratory studies indicate a low potential for leaching, while field dissipation studies indicate that spiroxamine binds readily to soils and is fairly degradable.

Spiroxamine is essentially non-toxic to birds, bees, earthworms and soil microbes, but exhibits moderate toxicity to fish and aquatic plants and invertebrates, and is very highly toxic to algae. Since spiroxamine is very highly toxic to algae and to reduce the hazard to aquatic systems every care should be taken not to contaminate water with this product. The draft labels contain warning statements to this effect and the company has agreed to add specific statements to highlight to operators the hazard to algae and minimise spray drift.

EFFICACY AND SAFETY ASSESSMENT

Justification for Use

The product *Prosper*, containing the active constituent spiroxamine, is proposed to be registered for control of powdery mildew on grapes (table, wine and dried). Powdery mildew is one of the most common diseases of grapevines in Australia and recently has been found to be more resistant to the currently available Group C (DMI fungicides). Therefore it is important to note that the introduction of a new group of fungicides (spiroketalamines) resulting from the registration of this product will assist in delaying the further development of resistance to DMI fungicides in the field, and will provide for a more flexible approach to disease management.

Efficacy

Data from 9 Australian field trials was presented, each trial was completed using 3-5 applications of *Prosper*, each application being 12.5mL (6.25g ai) – 100mL (50g ai) per 100L of water or with spray volumes ranging from 510-2100L/ha. The results provided adequate confirmation that the product claims are valid. These trials were conducted in a suitable manner. They were appropriately designed and carried out and the results were correctly analysed and interpreted. The trials were also carried out in a manner that allowed comparisons between *Prosper* and other standard fungicide treatments. The trials demonstrated that *Prosper* is equivalent to, or better than other standard fungicide treatments.

Safety

The potential for the use of *Prosper* to be phytotoxic to grapevines was also considered. A specific phytotoxicity study was presented and phytotoxicity was considered in each of the efficacy trials. The data presented supports *Prosper* as being safe when used as proposed. The phytoxicity study showed that when the product is used at 200mL/100L as a concentrate spray some yellowing of foliage occurred but no berry damage. A label restraint precluding the use of concentrations greater than this is proposed in order to address this issue. No other phytotoxic effects were observed on any treated plants.

LABELLING REQUIREMENTS

POISON

KEEP OUT OF REACH OF CHILDREN

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Prosper® 500 EC
Fungicide

Active Constituent: 500 g/L SPIROXAMINE

GROUP	E	FUNGICIDE

For control of powdery mildew on grapevines

1 Litre
5 Litres
10 Litres
20 Litres

Directions for use

Crop	Disease	Rate	Critical Comments
Grapevines	Powdery mildew	**Dilute spraying** 60 mL/100 L **Concentrate spraying** Refer to the Mixing/ Application section	Apply thoroughly as part of the following 5 spray program: 1. when shoots 10-20 cm long. 2. pre-flowering. 3. flowering. 4. after fruit set. 5. before bunches close. Do not allow spray intervals in the above program to exceed 21 days. In some seasons, additional non-schedule sprays may be necessary later in the season. Do not apply more than 2 Prosper sprays per season. Do not apply more than one Prosper spray late season. Apply by dilute or concentrate spraying equipment. Apply the same total amount of product to the target crop whether applying this product by dilute or concentrate spraying methods. Do not use in equipment that requires rates greater than 180 mL/100 L of water. Do not apply in volumes less than 250 L/ha.

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

WITHHOLDING PERIOD:
GRAPEVINES: DO NOT HARVEST FOR 4 WEEKS AFTER APPLICATION

*drum*Muster logo

PESTICIDE, LIQUID, TOXIC, N.O.S.		(TOXIC 6 DIAMOND)
UN No. 2902	PG III	
Bayer Australia Limited emergency contact 1800 033 111 Australia wide, 24 hours		
Bayer Australia Limited 875 Pacific Highway Pymble NSW 2073 Telephone (02) 9391 6000 www.bayercrop.com.au		

General Instructions

Fungicide Resistance Warning

GROUP	E	FUNGICIDE

Prosper is a member of the morpholine group of fungicides. For fungicide resistance management the product is a Group E fungicide. Some naturally occurring individual fungi resistant to the product and other Group E 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 this product and other Group E 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, Bayer Australia Limited accepts no liability for any losses that result from failure of this product to control resistant fungi.

Mixing/Application

Half fill the spray tank or vat with clean water. Then add the required amount of Prosper with agitator going and top up the tank with water. Agitate thoroughly prior to and during spraying.

Dilute Spraying

Use a sprayer designed to apply high volumes of water up to the point of run-off and matched to the crop being sprayed.

- Set up and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient water to cover the crop to the point of run-off. Avoid excessive run-off.
- The required water volume may be determined by applying different test volumes, using different settings on the sprayer, from industry guidelines or expert advice.
- Add the amount of product specified in the Directions for Use table for each 100 L of water. Spray to the point of run-off.
- The required dilute spray volume will change and the sprayer set up and operation may also need to be changed, as the crop grows.

Concentrate Spraying

- Use a sprayer designed and set up for concentrate spraying (that is a sprayer which applies water volumes less than those required to reach the point of run-off) and matched to the crop being sprayed.
- Set up and operate the sprayer to achieve even coverage throughout the crop canopy using your chosen water volume.
- Determine an appropriate dilute spray volume (See Dilute Spraying above) for the crop canopy. This is needed to calculate the concentrate mixing rate.
- The mixing rate for concentrate spraying can then be calculated in the following way:

  EXAMPLE ONLY

  1. Dilute spray volume as determined above: For example 1500 L/ha
  2. Your chosen concentrate spray volume: For example 500 L/ha
  3. The concentration factor in this example is: 3 X (ie 1500 L ÷ 500 L = 3)
  4. As the dilute label rate is 60 mL/100 L, then the concentrate rate becomes 3 x 60, that is 180 mL/100 L of concentrate spray.
- The chosen spray volume, amount of product per 100 L of water, and the sprayer set up and operation may need to be changed as the crop grows.
- Do not use a concentrate rate higher than that specified in the Critical Comments.

- For further information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow industry Best Practices.

Re-entry

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

Export of Treated Produce

Table grape growers should note that suitable MRLs or import tolerances may not be established in all markets for table grapes treated with *Prosper*. If growing table grapes for export, check with Bayer for the latest information on MRLs and export tolerances before using *Prosper.*

Protection of Wildlife, Fish, Crustaceans and Environment

This product is highly toxic to algae and harmful to fish and aquatic invertebrates. DO NOT contaminate dams, ponds, waterways or drains with this product or used container. DO NOT apply under meteorological conditions or from spray equipment that will cause spray drift onto non-target areas, and in particular avoid any natural wetland or standing water body.

Storage and Disposal (1 litre pack size)

Store in the closed, original container in a cool, well ventilated area. Do not store for prolonged periods in direct sunlight. Rinse container before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. Dispose of at a local authority landfill. If no landfill is available, bury the container 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.

Storage and Disposal (other pack sizes)

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

Safety Directions

Harmful if swallowed. Will damage the eyes and skin. Avoid contact with eyesand skin. Do not inhale vapour or spray mist. If clothing becomes contaminated with product, remove clothing immediately. If product on skin, immediately wash the area with soap and water. If product in eyes, wash it out immediately with water. Wash hands after use.

First Aid

If poisoning occurs, contact a doctor or Poisons Information Centre (131126).
For further information refer to the Material Safety Data Sheet for the product.

Liability

This product must be used strictly as directed. Bayer Australia Limited may not be liable for loss or damage arising from failure to follow directions for use.

Prosper® is a registered trademark of Bayer AG MN
NRA Approval Number 52817/

GLOSSARY

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

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NRA PUBLICATIONS ORDER FORM

To receive a copy of the full technical report for the evaluation of spiroxamine in the product PROSPER 500 EC FUNGICIDE, please fill in this form and send it, along with payment of $30 to:

David Hutchison
Agricultural and Veterinary Chemical Evaluation Section
National Registration Authority for Agricultural and Veterinary Chemicals
PO Box E240
Kingston ACT 2604

Alternatively, fax this form, along with your credit card details, to:
David Hutchison at (02) 6272 3218.

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