Public Release Summary
on

Evaluation of the new active

CYPRODINIL

in the product

CHORUS® FOLIAR 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 co-operation with advisory agencies, including the Department of Health and Family Services (Chemicals and Non-prescription Drug Branch), Environment Australia (Risk Assessment and Policy Section), the National Occupational Health and Safety Commission (Worksafe Australia) and State departments of agriculture and health.

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: Guidelines for Registering Agricultural Chemicals.*

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, Third floor, 10 National Circuit, Barton, ACT.

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

Contents

List of abbreviations and acronyms

ac	active constituent
ADI	acceptable daily intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
d	Day
EC_{50}	concentration at which 50% of the test population are immobilised
EUP	end use product
Fo	original parent generation
h	hour
HPLC	high pressure liquid chromatography *or* high performance liquid chromatography
id	intradermal
ip	intraperitoneal
im	intramuscular
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
L	litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
mg	milligram
mL	millilitre
MRL	maximum residue limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	no observable effect concentration/level
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
s	second
sc	subcutaneous
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

Summary

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) has before it an application to register the product Chorus® Foliar Fungicide which contains the new active ingredient, cyprodinil. The product's claims are the control of black spot (apple scab and pear scab) of apples and pears.

This publication outlines the regulatory considerations and provides a summary of the data evaluated for the proposed registration of Chorus® Foliar Fungicide. Before determining whether to register this product for use in Australia, the NRA invites public comment.

Comments should be submitted by **24 July 1998** to Gavin Hall, National Registration Authority for Agricultural and Veterinary Chemicals, PO Box E 240, KINGSTON ACT 2604

The NRA has assessed the data submitted by the applicant in support of the proposed use of cyprodinil and provides the following information for public comment.

Chorus® Foliar Fungicide is formulated as a water dispersible granule containing 500 g/kg of cyprodinil. This product has been developed to be an alternative chemical available for black spot control on apples and pears which also provides another chemical group (anilinopyrimide) to aid in reducing the level of resistance to fungicides by black spot.

Public health aspects

Toxicology

Cyprodinil, the active ingredient of Chorus® Foliar Fungicide , has low acute oral, dermal and inhalational toxicity. It causes slight eye irritation, does not irritate the skin, but is a skin sensitiser. The product, Chorus® Foliar Fungicide , has not been studied, but a similar formulation containing cyprodinil is of low oral, dermal and inhalational toxicity, causes slight eye irritation, but does not irritate or sensitise the skin.

Following repeated oral administration of moderate to high doses of cyprodinil to mice, rats and dogs, the principal target organs for toxicity were the liver, thyroid gland and kidneys, while in mice alone, the spleen and pancreas were also affected. Toxicity was seen mainly as reduced bodyweight gain and food consumption, increased liver and kidney weights, enlarged liver and thyroid cells, biochemical evidence of liver dysfunction, and inflammation and vacuolation in the kidneys. Anaemia and ovarian cysts were also observed in rats.

No evidence of oncogenic potential was found following long-term dietary exposure of mice and rats. Cyprodinil did not induce genetic damage *in vitro* or *in vivo*. A 2-generation reproduction study in rats and developmental studies in rats and rabbits showed no effect on fertility, reproduction or foetal development.

Conclusion

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

Residues in food and trade aspects

Residues in food

The product will be used for foliar disease control on apple and pear. The product contains the new active cyprodinil at 500 g active ingredient/kg.

MRLs of 0.05 mg/kg for Pome fruits, *0.01 mg/kg for meat [mammalian], *0.01 mg/kg for edible offal [mammalian], and *0.01 mg/kg for milks were recommended based on Australian and overseas residue studies. A harvest withholding period with the statement "DO NOT SPRAY AFTER PETAL FALL" is considered appropriate.

Trade

The residue data suggest that low residues occur in apple and pear fruits and therefore it is unlikely that trade disputes will occur. There is no trade concern for animal commodities when livestock is fed fruit treated with the chemical as formulated by the registered label.

Occupational health and safety aspects

The National Occupational Health and Safety Commission (NOHSC) has conducted a risk assessment on Chorus® Foliar Fungicide (Chorus), containing cyprodinil at 500 g/kg. The product, formulated as water dispersible granules will be used for the control of black spot of apples and pears. It can be safely used by workers when handled in accordance with the control measures indicated in this assessment.

Cyprodinil is not listed as hazardous substances in the *NOHSC List of Designated Hazardous Substances*. Novartis Crop Protection Australasia Limited (Novartis) has determined cyprodinil to be a hazardous substance based on its skin sensitisation effect. Novartis has also determined Chorus to be hazardous based on the amount of a hazardous substance (≥ 1% cyprodinil) present in the formulation. The product will be imported fully packaged in containers. Transport workers, store persons and retailers will only handle the packaged product.

The acute toxicity, irritancy and dermal sensitisation properties of Chorus® Foliar Fungicide have not been investigated. However, a similar formulation (75% cyprodinil, WG) did not cause dermal sensitisation in guinea pigs. The other acute toxicological characteristics of the WG75 formulation are: oral and dermal LD_{50} >2000 mg/kg in rats, acute inhalation LC_{50} >2300 mg/m^3, a slight eye irritant but not a skin irritant in rabbits.

The product is to be diluted with water and sprayed on apple and pear trees. Both high volume (dilute) and low volume (concentrate) sprayings are recommended. The label recommends that the same quantity of chemical per hectare be used when spraying by either the dilute or concentrate method. Individual operators or contract sprayers could use this product. Ground application would be by airblast sprayer.

The risk assessment indicates that elbow-length PVC gloves, faceshield or goggles and overalls are required when opening the container, preparing spray and using the prepared spray.

Environmental aspects

Application of cyprodinil to apples and pears during the spur burst to petal drop period may result in contamination of the soil compartment within the treated area due to direct spray, spray drift or excess spray running off leaves, and off-site contamination could result from spray drift or adsorbed to soil particles in run-off.

Photolysis

Cyprodinil is hydrolytically stable (DT50 pH 5-9 in excess of 1 year at 25°C). A study using monochromatic light indicated that the quantum yield for aqueous photolysis is low and gave an estimated photolysis half-life of 17 days in summer at 40°N to 28 days in spring at 50°N. Estimates of the aqueous photolysis half-life at 20-25°C from other studies varied widely (0.2 to 46.1 estimated Florida summer days) with different solution conditions, in many cases with a lag phase preceding more rapid degradation. In most cases, the overall rate of aqueous photodegradation of cyprodinil was fairly to moderately rapid (DT50 = 4-10 to 10-30 days continuous light), evidence suggesting that the length of the lag phase was affected by the oxygen content of the water and that cyprodinil has a tendency to degrade via direct and indirect photolysis with a synergistic mechanism.

In practical situations in Australia, the rate of aqueous photolysis may also be limited by turbidity. Photolytic effects may increase the rate of microbial degradation in soil, as degradation was faster in vital soil exposed to light (DT50 = 28.2-33.0 estimated Florida Summer days) than when incubated in the dark (DT50 = 54-79 days) and much faster than in sterile soil exposed to light or incubated in the dark (DT50 = 105 and 261 estimated Florida Summer days, respectively).

Soil degradation

The most likely route for degradation of this substance in soil is by aerobic microbial degradation. The aerobic soil degradation DT50 in 4 soils under moist conditions at 20-25°C was 20.8-41.7 (mean = 29.3) days (fairly degradable - DT50 = 20-60 days), often with degradation faster initially, then slowing. Much longer overall half-lives (267-365 days) were found in a fifth soil, but the initial rate of degradation was comparable to the other soils (DT50 in first 21-28 days = 22.1-30.8 days).

Anaerobic conditions led to much slower degradation. The dissipation half-life of cyprodinil in water/sediment systems was 2.4-5.2 days, due largely to partitioning to the sediment, where degradation was much slower (possibly because of anaerobic conditions), making the half-lives in the whole system much longer, at 116-172 days (slightly degradable - DT50 in whole system = 60-180 days). The degradation pathway of cyprodinil in soil appears to involve

small changes to the molecule and/or cleavage of it, followed by adsorption or binding of unchanged or slightly changed cyprodinil and its cleavage products to the soil, and gradual mineralisation of cyprodinil residues.

Soil adsorption characteristics (K_{OC} = 1550-4393, average 2040) indicate that cyprodinil has low to slight mobility in soil (K_{OC} = 500-2000 or 2000-5000, respectively), and this is supported by the results of laboratory leaching studies and field data. Cyprodinil is only slightly volatile and unlikely to mobilise significantly by this means, though a laboratory study suggests that significant losses could nonetheless occur from plant surfaces. Field dissipation half-lives for cyprodinil were 23.1-48.7 days, comparable to the above laboratory data. Repeated application of cyprodinil up to 4 times per annum is not expected to lead to significant accumulation of unchanged cyprodinil in an unbound form, and little uptake by plants of soil residues occurs. A study with cyprodinil and bluegill sunfish indicated that the substance may bioaccumulate in fish (bioconcentration factor in whole fish = 393), but that most of the residues are rapidly eliminated (depuration half-life ≈ 0.5 days).

Toxicity to flora and fauna

Cyprodinil TGAC is practically non-toxic to birds (mallard ducks and bobwhite quail) by both acute oral exposure (LD50 > 2000 mg ai.kg^{-1} bw) and subacute dietary exposure (LC50 > 5000 ppm in diet), and avian reproduction studies with 22 weeks exposure to cyprodinil in the diet indicated a NOEL of ≥ 600 ppm.

The substance has moderate toxicity to fish with both acute and chronic exposure (96 hour LC50 for bluegill sunfish and rainbow trout = 2.17 and 2.41 mg ai.L^{-1}, respectively, and 21 day NOEC, LOEC and MATC for rainbow trout = 83, 130 and 104 µg ai.L^{-1}, respectively).

It is very highly toxic to the aquatic invertebrate *Daphnia magna* (48 hour acute exposure LC50 = 32.8 µg ai.L^{-1} and 21 day chronic exposure NOEC, LOEC and MATC = 8.16, 19.3 and 12.5 µg ai.L^{-1}, respectively) and is highly toxic to the freshwater green alga, *Scenedesmus subspicatus* (72 hour EC50 for biomass production = 0.75 mg ai.L^{-1}). A microcosm study with cyprodinil TGAC found little evidence of adverse effects on phytoplankton, macrophytes, zooplankton and macroinvertebrates with cyprodinil application regimes producing peak water concentrations of 2.5-18 µg.L^{-1}, but there were greater populations (statistically significant) of rotifer zooplankton than the control in several treatments for part of the study.

Laboratory studies indicate that cyprodinil TGAC is virtually non-toxic (LD50 > 100 µg ai per bee) to honey bees (*Apis mellifera*) with contact exposure and that a WG 50 formulation the same as that proposed for Australia is virtually non-toxic to bees with either contact or oral exposure, and slightly toxic to earthworms (14 day LC50 in the nominal concentration range 111-333 mg.kg^{-1} dry soil). Laboratory and/or semi-field and/or field studies at a rate equivalent to 250 g ai/ha in the field (i.e. less than the proposed maximum label rate for Australia, but on 4-5 occasions in the field study) indicate that the same WG 50 formulation is at most "slightly harmful" to the aphid predators *Orius insidiosus* (minute pirate bug) and *Aphidius matricariae* (a predatory wasp), "harmless" to *Chrysoperla carnea* (green lacewing) and *Coccinella septempunctata* (seven spotted ladybird), and "slightly harmful" to the predatory mite *Typhlodromus pyri*.

No studies investigating phytotoxicity to terrestrial plants were provided, but the applicant is unaware of any reports of phytotoxicity of the formulation to target or non-target terrestrial plants when used according to good agricultural practice. Studies of the effects of cyprodinil

TGAC on soil micro-organisms found negligible effects on short-term soil respiration and only temporary effects on soil nitrification, described as "negligible" to "tolerable," and an activated sludge respiration inhibition test indicated that the substance has low toxicity to sludge micro-organisms.

Conclusion

The use of product CHORUS® Foliar Fungicide as proposed in pome fruit orchards is not expected to present a hazard to birds, mammals, bees and soil micro-organisms, and an acceptable hazard to other terrestrial invertebrates. However, even a single direct overspray of the product over shallow waterbodies may be hazardous to fish, algae and particularly aquatic invertebrates such as Daphnia magna. For this reason, aerial application of the substance should be forbidden.

Spray drift from application of the product may also affect aquatic organisms (particularly daphnids), particularly if significant drift occurs on several occasions to shallow water. However, in practice, the aquatic hazard from spray drift is likely to be acceptable, assuming lower drift and greater water depth than those for worst case analysis, and allowing for dissipation of residues from the water column. Suitable label warnings are essential to minimise the aquatic hazard, and the hazard is further reduced in the expected use situation of up to 3 sprays at 10 day intervals, rather than the label maximum of 4 sprays at 7 day intervals.

Efficacy and safety aspects

The efficacy data provided adequately demonstrated that the product was able to control black spot (apple scab and pear scab) on apples and pears at a commercially acceptible standard. Crop and non target crop phytoxicity was not observed during any of the trials conducted. The applicant also provided evidence that Chorus® Foliar Fungicide had minimal effect on predatory mites and was therefore an acceptable inclusion in orchard Integrated Pest Management.

Introduction

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of the chemical cyprodinil as a fungicide in controlling black spot (apple and pear scab) on apples and pears.

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

Copies of full technical evaluation reports on Cyprodinil, covering toxicology, occupational health and safety aspects, environmental impacts and residues in food, are available from the NRA on request (see order form on page 33). They can also be viewed at the NRA library located at the NRA's offices, Level 1, Computer Associates House, 10 National Circuit, Barton ACT 2604.

Written comments should be received by the NRA by **24 July 1998**. They should be addressed to:

Gavin Hall
Product Evaluator
Agricultural Chemicals Evaluation Section
National Registration Authority
PO Box E240
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Phone (02) 6272 3194 Fax (02) 6272 3218

Applicant

Novartis Crop Protection Australasia Limited.

Product details

Cyprodinil will be marketed under the trade name Chorus® Foliar Fungicide containing 500 g/kg cyprodinil.

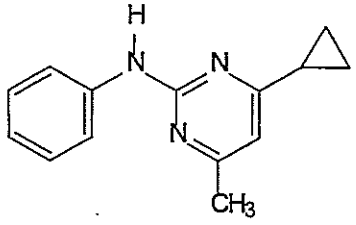
The product Chorus® Foliar Fungicide is fully formulated in Switzerland, then imported, repacked and relabelled in Australia.

Novartis Crop Protection Australasia Limited intend to market Chorus® Foliar Fungicide in all states and territories. Cyprodinil is currently registered in a number of other countries, which includes Switzerland, South Africa, France and New Zealand.

Chemistry and Manufacture

Active constituent

The chemical active constituent Cyprodinil is manufactured in Monthe, Switzerland and has the following properties:

Common name (ISO):	cyprodinil
Chemical name:	
IUPAC:	(4-cyclopropyl-6-methyl-primidin-2-yl)-phenyl-aniline
CA:	4-cyclopropyl-6-methyl-N-phenyl-2-pyrimidinamine
Product name:	Chorus® Foliar Fungicide
CAS Registry Number:	121552-61-2
Empirical formula:	$C_{14}H_{15}N_{13}$
Molecular weight:	225.3
Physical form:	powder
Colour:	beige
Odour:	Weak non-specific to non-specific
Melting point for E/Z mixture (1:1):	75.9°C
Density (SG at 20°C):	1.21 g/cm^3
Octanol/water partition coefficient (K_{ow}):	log K_{ow} @ 25°C = 3.9 (pH 5), 4.0 (pH 7), 4.0 (pH 9)
Vapour pressure at 25°C:	*Pure substance*: 5.1 X 10^{-4} Pa @ 25°C (crystal modification A) 5.1 X 10^{-4} Pa @ 25°C (crystal modification A)
Structural Formula:	

Metabolism and Toxicokinetics Assessment

The toxicological database for cyprodinil, which consists primarily of toxicity tests conducted using animals, is extensive. In interpreting the data, it should be noted that toxicity tests generally use doses which are high compared to likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified.

Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective, however, adverse findings in animal species are assumed to represent potential effects in humans unless convincing evidence of species specificity is available.

Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect Level (NOEL) are used to develop acceptable limits for dietary or other intakes at which no adverse health effects in humans would be expected.

TOXICOKINETICS AND METABOLISM

When cyprodinil is administered orally to rats, it is rapidly absorbed, completely metabolised and excreted in the urine and faeces as conjugated forms of the parent compound, with over 90% of the dose being eliminated within 48 h. Similar findings were obtained in chickens and goats. Concentrations of tissue residues were very low in all three species, with the highest tissue residues detected in the liver and kidneys.

Acute studies

Cyprodinil had low acute oral toxicity in mice (LD50 >5000 mg/kg) and rats (LD50s of 2973 and 2500 mg/kg in males and females, respectively). In rats, the acute dermal LD50 was >2000 mg/kg and the acute inhalational LC50 was >1200 mg/m^3, the highest attainable aerosol concentration. Clinical signs in the acute studies consisted of ruffled fur, hunched posture and laboured breathing. Cyprodinil was a slight eye irritant but not a skin irritant in rabbits, and was a weak skin sensitiser in guinea pigs.

The oral and dermal LD50s of WG75, a formulation containing 75% w/w cyprodinil, were greater than 2000 mg/kg in rats, and the acute inhalational LC50 was greater than 2300 mg/m^3. WG75 was not a skin irritant in rabbits or a skin sensitiser in guinea pigs, but was a slight eye irritant in rabbits. The acute toxicity of Chorus® Foliar Fungicide (WG50), which has very similar composition to WG75, was not studied. A 75% cyprodinil WP formulation was moderately irritating to rabbit eyes.

Short-term studies

Cyprodinil did not produce treatment-related mortalities or clinical signs in rats following oral gavage at 0, 10, 100 or 1000 mg/kg/day for 28 days. However, body weight gain was reduced

in all treated male groups and the high dose female group. The target organs for toxicity were the liver and thyroid gland, indicated by increased liver and thyroid weights, increased plasma levels of total bilirubin, cholesterol, phospholipids, release of liver enzymes into the blood, and enlargement of liver and thyroid cells in the high dose groups. Increased liver weights were also found in both sexes at the mid dose and enlarged liver cells in the mid-dose female group. Indications of anaemia were seen in the mid and high dose groups.

Repeated dermal administration of 0, 5, 25, 125 or 1000 mg/kg/day cyprodinil in rats produced ruffled fur, laboured breathing and hunched posture. Feed intake and body weight gain were reduced in all treated male groups, but not in females, whose body weights were slightly higher than controls. Inflammatory changes at the application site were seen in both control and treated animals.

Subchronic studies

Mice were given 0, 500, 2000 or 6000 ppm cyprodinil in the diet for 3 months. There were no treatment-related mortalities, clinical signs or haematological changes. The high dose males gained slightly less body weight than controls. Absolute and relative liver (male only) and spleen (both sexes) weights of the animals fed 2000 and 6000 ppm cyprodinil were slightly higher than controls. There were no gross lesions, but histological examination revealed death of liver cells in the 2000 and 6000 ppm males. The NOEL was 500 ppm, equivalent to 73 mg/kg/day for males and 103 mg/kg/day for females.

A 3-month feeding study using 0, 50, 300, 2000 or 12000 ppm cyprodinil in rats caused reduced body weight gain and feed consumption in the high dose groups. Haematological changes consisted of anaemia in the high dose male group, and prolonged prothrombin time in the 300, 2000 and 12000 ppm male groups and the high dose female group. Plasma cholesterol and phospholipid levels were increased in a dose-related manner in all treated female groups and in the 2000 and 12000 ppm male groups. Plasma bilirubin levels were elevated in high dose males.

Serum biochemistry also revealed enzymological evidence of liver dysfunction in 300, 2000 and 12000 ppm males and high dose females. Liver and thyroid weights were increased in the 2000 and 12000 ppm groups. Enlarged liver, thyroid and pituitary cells were found in both males (300 ppm or higher) and females (2000 ppm or higher). Vacuolation of the renal tubules and slight focal chronic inflammatory changes were observed in males (300 ppm or higher). Histological abnormalities were observed in the livers of males given 2000 or 12000 ppm cyprodinil. Most of the changes were reversible after 4 weeks recovery period. The NOEL for males was 50 ppm (equivalent to 3.1 mg/kg/day), whereas the NOEL for females was not established.

Dogs were administered 0, 200, 1500, 7000 or 20000 ppm cyprodinil in the diet for 90 days. Vomiting and reduced feed consumption and body weight gain were observed in the high dose groups. Relative liver weights were increased in the high dose male group and in 1500, 7000 and 20000 ppm female groups. Thyroid weights were increased in the 7000 and 20000 ppm groups. However, no gross or histological lesions were observed. The NOEL was 200 ppm (equivalent to 6.8 mg/kg/day).

Long-term studies

Mice were administered 0, 10, 150, 2000 or 5000 ppm cyprodinil in the diet for 18 months. Body weight gain was reduced in the high dose group. At necropsy, relative liver and kidney weights were increased in high dose females, as were relative liver weights in high dose males. Microscopic examination revealed localised areas of increased cell division within the exocrine pancreas in the high dose male group and an increased incidence of iron deposits in the spleen in the high dose female group. No treatment-related tumours were observed. The NOEL was 2000 ppm (approximately 200 mg/kg/day).

A 2-year rat study using dose levels of 0, 5, 75, 1000 or 2000 ppm of cyprodinil in the diet did not reveal treatment-related tumours. No treatment-related clinical signs of toxicity or deaths were observed. Significantly increased absolute and relative liver weights were recorded in high dose males. At microscopic examination, an increased incidence of spongiosis hepatitis, a degenerative change in the liver, was observed in males administered 1000 and 2000 ppm cyprodinil. Macroscopic examination showed increased incidences of mottled lungs and ovarian cysts in the high dose female group. Histologically, mottled lungs correlated with the accumulation of alveolar foam cells. The NOEL was 75 ppm (equivalent to 2.7 mg/kg/day for males and 3.2 mg/kg for females).

Beagle dogs were given 0, 25, 250, 2500 or 15000 ppm cyprodinil in the diet for 12 months. No mortalities occurred, and no clinical signs of toxicity were observed. Haematology, clinical chemistry and urinalysis were normal. Organ weights were not altered by treatment and no treatment-related gross lesions were found. The only treatment-related effects were reduced feed intake and body weight gain and pigmentation of liver cells in the highest dose group. The NOEL was 2500 ppm (equivalent to 66 mg/kg/day for males and 68 mg/kg/day for females).

Reproduction study

Rats were fed 0, 10, 100, 1000 or 4000 ppm cyprodinil in the diet continuously for 2 generations. Maternal toxicity was produced from 1000 ppm. High dose F0 and F1 adults (both sexes) and the 1000 ppm F0 females had reduced body weights. Reduced feed consumption was observed in high dose F0 animals. Absolute and relative liver weights were increased in the male and female adults of both generations receiving 1000 and 4000 ppm. Treatment-related increases in kidney weights mainly occurred in the males given 1000 and 2000 ppm. Gross examination showed enlarged livers in the 4000 ppm F0 and F1 male adults, but no histological changes were detected.

Treatment did not affect fertility and reproduction in either generation. Both F1 and F2 pups of the high dose group gained less body weight than controls. The NOEL was 100 ppm (equivalent to approximately 10 mg/kg/day).

Developmental studies

Pregnant rats were administered 0, 20, 200 or 1000 mg/kg/day cyprodinil by gavage during the period of foetal organ development. Maternal toxicity exhibited as reduced feed consumption and body weight gain was produced in the mid- and high dose groups. One high

dose dam had a mottled liver. Treatment did not give rise to foetal deformities, but did cause foetal toxicity. Delayed bone formation and reduced foetal body weights were observed in the high dose group. The NOEL was 20 mg/kg/day.

The potential for cyprodinil to cause developmental effects in rabbits was assessed by oral administration of 0, 5, 30, 150 or 400 mg/kg/day during the period of foetal organ development. Maternal toxicity was observed at 400 mg/kg/day and indicated by reductions in feed intake and body weight gain. The only effect on foetuses was a slight reduction in body weight, also at 400 mg/kg/day. The NOEL was 150 mg/kg/day.

Genotoxicity studies

Negative results were obtained in a range of genotoxicity studies. The assays conducted were gene mutation (*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, *Escherichia coli* WP2uvrA, and Chinese hamster lung cells V79 *in vitro*), chromosomal effects (Chinese hamster ovary cell cultures and micronucleus formation in mice *in vivo*), and unscheduled DNA synthesis (rat liver cells *in vitro*).

Other studies

An acute oral toxicity study and *in vitro* bacterial mutagenicity study were performed with CGA 249287, a metabolite of cyprodinil which is formed in goats and hens, and is also the principal soil degradation product of cyprodinil. Its oral LD50 in rats was >2000 mg/kg (1/5 male deaths, 0/5 female deaths). CGA 249287 was not mutagenic in *S. typhimurium* or *E. coli* in either the presence or absence of metabolic activation. Three cases of moderate, reversible local irritation (erythema, swelling of eyelids) occurred in laboratory personnel during formulation development.

PUBLIC HEALTH STANDARDS

Poisons scheduling

The National Drugs and Poisons Schedule Committee (NDPSC) considered the toxicity of the product and its active ingredient and assessed the necessary controls to be implemented under States' poisons regulations to prevent the occurrence of poisoning. The NDPSC recommended that formulations containing be placed in Schedule 5 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). There are provisions for appropriate warning statements and first-aid directions on the product label.

NOEL/ADI

The most sensitive species tested was the rat with a NOEL of 2.7 mg/kg bw/day in a 2-year study. In order to calculate an Acceptable Daily Intake (ADI) for humans, a safety factor is applied to the NOEL in the most sensitive species. The magnitude of the safety factor is selected to account for uncertainties in extrapolation from animal data to humans, variation within the human population, the quality of the experimental data, and the nature of the potential hazards. Using a safety factor of 100, an ADI of 0.02 mg/kg bw/day was established for cyprodinil.

Residues Assessment

The product Chorus® Foliar Fungicide contains the active cyprodinil (500 g/kg) for the control of black spot diseases of apple and pear leaves. The chemical is formulated as a water dispersible granule. A maximum of 4 applications will be used per season at the rate of 400 g/ha for low volume application, or 20 g ai. /100L for high volume application. The product is sprayed before petal fall.

Cyprodinil is an anilino-pyrimidine chemical. The full chemical name of cyprodinil is 4-cyclopropyl-6-methyl-N-phenyl-2-pyrimidineamine.

Metabolism studies

Crop metabolism

Metabolism studies were conducted for apple, wheat and tomatoes with radiolabeled cyprodinil. For apple, field grown trees were treated 3 times at a rate of 75 mg/tree. The total radioactive residues at harvest (61 days after last application) were analysed for leaves, whole apple, apple peel and apple pomace. Leaves contained the highest radioactivity (50 mg/kg in parent equivalents and 6 mg/kg as cyprodinil). The unchanged parent accounted for 11% and 12% of the total radioactivity in whole fruits and leaves, respectively. Other extractable or non-extractable fractions were obtained and mostly found to be conjugates and/or bound residues.

Spring wheat was sprayed twice at foliar stage as a WP 50 formulation. The application rate was 750 g ai. /ha for the first spray on 7 day old plants, and 500 g ai. /ha for the second spray at ear emergence. The amount of the total radioactivity in mature plants (63 days after second application) was around 0.2 mg/kg in grains, 7 mg/kg in husk, and 14 mg/kg in the straw. Extensive metabolism proceeded in wheat, resulting in unchanged parent being present at 20 and 7% of the total radioactivity in grain and straw, respectively. Numerous fractions were obtained and mostly found to be conjugates and/or bound residues.

Tomato plants were sprayed twice (28 days apart) at a rate of 750 g ai. /ha. Samples were collected on day 15 after the second application. Radioactive residues were about 7 mg/kg in tomato fruits and 112 mg/kg in foliage. The unchanged parent cyprodinil was 4 mg/kg in tomato fruits and 75 mg/kg in the foliage, respectively. Individual metabolites were found to be at or less than 10% of the total radioactivity.

The crop data suggest that cyprodinil was extensively metabolised with time. The data also suggest that the parent compound cyprodinil is the appropriate chemical for analysis in plant tissues.

Animal metabolism

Animal metabolism studies were conducted in rats, hens and lactating goats. Common metabolic trends were observed in all three animal types. The goats and hens were dosed consecutively for 4 days with radiolabeled cyprodinil. Dosing rates were about 100

mg/kg in the diet for the goats and 5 mg/kg for the hens. The majority of the radioactivity was excreted via urine and faeces for both animals (72% in goat and up to 97% in hens). In goat tissues, the parent cyprodinil and hydroxylated metabolites were identified, with the metabolites present in much higher amounts in kidney and liver than the parent. Fat also contained the metabolites and the parent, but with parent dominating. In hens, both liver and kidney showed the highest radioactivity. Eggs showed only 0.01% of the total radioactivity.

The parent cyprodinil was not detected in meat and liver. Residues of parent were found at 0.011 and 0.002 mg/kg in egg yolk and egg white. Identified metabolites were present in lower amounts than the parent. The majority of radioactivity was non-extractable residues in kidney and liver. Both goat and hen studies showed a great number of unidentified fractions (conjugates) of the radioactivity. The rat studies also showed higher concentrations of radioactivity in kidney and liver. Depletion of the radioactivity was also shown in rats.

The metabolism studies showed that most of the administered dose is excreted and of the remaining dose, low levels of the parent compound and its hydroxylated metabolites, plus a great number of unidentified conjugates, are found mainly in the kidney and liver of the animals.

Residue definition

For the purposes of analysing the residues of cyprodinil, the metabolism studies discussed above indicate that an appropriate residue definition would be:

Cyprodinil	Cyprodinil

Analytical methodology

The analytical procedure includes extraction with water/methanol during maceration and acidification with HCL. Filtered extract is cleaned up on a cation exchange sulphonate SCX cartridge. The eluent containing the residue compound is evaporated to dryness and the residues redissolved in mobile phase and the compound determined by HPLC on a C_{18} column with UV detection.

The lLimit of quantitation was 0.01 mg/kg. Satisfactory recovery was obtained for both pear and apple.

Residue trials

Trials on apple

A total of 13 trials were conducted for apple at various locations, of which 5 trials specifically addressed the requested use pattern. A total of 4 applications were made at the application rates of 25, 50 100 and 200 g ai. /hl. Fruit samples were collected at 16 to 22 weeks after final

application. The residue data indicated that the highest residues were 0.02 mg/kg at the rate of 25 g ai. /hl which was slightly higher than the label rate. The residue trials have addressed both early and late season apples.

A total of 8 trials were conducted for pear, of which 6 trials specifically addressed the use pattern. Fruit samples were collected 12 to 15 weeks after last application. Residue results showed that residues were not higher than 0.02 mg/kg in pears at harvest.

Animal transfer study on lactating cows

A transfer study was conducted on lactating cows. The animals were dosed continuously with cyprodinil at 0, 5, 15 and 50 ppm in feed for 28 days. Samples of milk were collected throughout the study and tissues (kidney, liver, fat and muscle) collected after last dosing on day 28, 29 and 30. Collected milk and tissue samples were analysed for cyprodinil residues. The limit of quantitation was 0.01 mg/kg. Milk samples did not show residues higher than 0.01 mg/kg at all three feeding levels.

Tissue residues were not detected at the limit of quantification of 0.01 mg/kg at the feeding levels of 5 and 15 ppm. At the feeding level of 50 ppm, finite residues were detected only in liver, with the maximum level of 0.013 mg/kg. The residue results of the transfer study were consistent with the metabolism studies in terms of distribution and proportion of residues in the tissues.

Summary of trials

The residue trials on apple and pear showed finite but low residues in apple and pear. It is not expected that apple pomace from treated apples will lead to finite residues being detected in animal tissues when fed.

MRL Standard

The following additions to the *MRL Standard* have been recommended:

Table 1

Compound	*Food*	*MRL (mg/kg)*
ADD		
Cyprodinil		
	Pome fruits	0.05
	Meat [mammalian]	*0.01
	Offal, edible of [mammalian]	*0.01
	Milks	*0.01

Withholding period statements

The following label statement is recommended:

DO NOT SPRAY AFTER PETAL FALL.

Dietary intake

The Acceptable Daily Intake for cyprodinil is 0.02 mg/kg/day as set by the TGA. Calculation of the theoretical maximum daily intake (TMDI) incorporating the proposed MRLs and the estimated daily consumption of the food commodities indicates that the TMDI is 3.3% of the ADI.

Fat solubility

Cyprodinil is fat soluble and has a Log Ko/w value of 4. However, the metabolism and animal transfer studies showed its target tissue was kidney and not fat. Based on studies with goat, rat, fish and cow, cyprodinil is unlikely to be a bioaccumulator.

Assessment of Overseas Trade Aspects of Residues in Food

Trade consideration

Cyprodinil has been registered in Belgium, Czech Republic, South Africa and Switzerland for use on cereals and pome fruits. Registration is being sought in the USA, Japan and Canada.

Apple, pear and their processed commodities are exported to South East Asia, including Singapore and Japan. Since the residues that may occur in the export commodities are low (~0.02 mg/kg), it is unlikely that trade dispute will occur for apple and pear.

Feeding of treated apple and pear to livestock results in undetectable residues in livestock commodities. Therefore, there is no trade concern for these commodities.

Occupational Health and Safety Assessment

Cyprodinil is not listed as a hazardous substance in the draft National Occupational Health and Safety Commission (NOHSC) *List of Designated Hazardous Substances*. Novartis Crop Protection Australasia Limited (Novartis) has determined cyprodinil to be a hazardous substance according to NOHSC criteria.

Following risk and safety phrases are allocated to cyprodinil:

Risk phrases

R43	May cause sensitisation by skin contact
R48	Danger of serious damage to health by prolonged exposure

Safety phrases

S2	Keep out of reach of children
S13	Keep away from food, drink and animal feeding stuff
S24	Avoid contact with skin
S36/37/39	Wear suitable protective clothing, gloves and face protection
S38	In case of insufficient ventilation wear suitable respiratory equipment

Substances containing cyprodinil are hazardous when it is present at concentrations ≥1%. Cyprodinil is a beige coloured powder. In experimental animals (rats), cyprodinil had low oral (LD_{50} 2500 mg/kg) and dermal (LD_{50} >2000 mg/kg, no deaths) toxicity. It was slightly irritating to rabbit eyes, was not irritating to rabbit skin and caused moderate dermal sensitisation in guinea pigs. Three cases of moderate, reversible local irritation (erythema, swelling of eyelids) occurred in laboratory personnel during formulation development.

The acute toxicity, irritancy and dermal sensitisation properties of Chorus® Foliar Fungicide have not been investigated. However, a similar formulation (75% cyprodinil, WG) did not cause dermal sensitisation in guinea pigs. The other acute toxicological characteristics of the WG75 formulation are: oral and dermal LD_{50} >2000 mg/kg (rat), acute inhalation LC_{50}>2300 mg/m^3 (rat), a slight eye irritant but not a skin irritant in rabbits.

Transport, storage and retailing

The product will be formulated overseas and imported fully packed in cardboard boxes in 1 kg and 5 kg quantities. Transport, storage and retail workers could only be exposed to the product if packaging is breached.

Advice on the safe handling of the product is provided in the Material Safety Data Sheet (MSDS) of the product.

End use

The product is proposed for the control of black spots in apple and pears. Both high volume (dilute) and low volume (concentrate) sprayings are recommended. The same quantity of chemical is to be used when spraying by either the dilute or concentrate method. Using high volume, the proposed application rate is 40 g/100 L spray (0.04% EUP, 0.02% cyprodinil). The recommended spray volume is 1500-2000 L/ha. The product will be used for a maximum of 16 days per year from September to November.

For low volume spraying, the amount of cyprodinil to be used ranges from 600 - 800 g/ha. The spray volume is not defined. The risk assessment uses a spray volume of 100 and 500 L/ha for low volume spraying (range of 0.12-0.8% EUP, 0.06-0.4% cyprodinil), in determining worker exposure and risk.

Individual operators or contract sprayers could use this product. Ground application would be by airblast sprayer.

No worker exposure data was available to assess the risks of long term use of cyprodinil. The UK POEM was used by NOHSC to provide supplementary information on exposure during mixing/loading and application of Chorus® Foliar Fungicide. The results indicated that workers using high and low volume sprayings can be adequately protected with gloves and an additional layer of protective clothing. The risk assessment indicates that elbow-length PVC gloves, cotton overalls and faceshield or goggles are required when opening the container, preparing spray and elbow-length PVC gloves and cotton overalls are required when using the prepared spray.

Re-entry assessment

The draft label advises workers not to enter treated areas without protective clothing until spray has dried.

Cyprodinil has very low vapour pressure, hence inhalation exposure is not expected to be significant. The main route of exposure upon re-entering sprayed areas is via dermal contact. No data is available on dislodgeable foliar residues of cyprodinil.

The maximum concentrations of cyprodinil indicated under Australian conditions are 0.02% (high volume spraying) and estimated 0.4% (low volume spraying). Considering the dilution of the applied spray and low vapour pressure of cyprodinil, a re-entry period is not recommended at this stage.

A withholding period of up to 22 weeks before harvest is recommended for all crops. This extended period will provide additional protection for those involved in manual harvesting operations.

Recommendations for safe use

End users should follow the instructions and Safety Directions on the product labels. Safety Directions include the use of personal protective equipment (PPE), namely elbow-length PVC gloves, overalls buttoned to the neck and wrist and faceshield or goggles when opening the container and preparing the spray and elbow-length PVC gloves and cotton overalls buttoned to the neck and wrists when using the prepared spray.

The PPE recommended should meet the relevant Standards Australia standard specified below:

> AS 2161-1978 Industrial Safety Gloves and Mittens (Excluding Electrical and Medical Gloves)
>
> AS 1337-1992 Eye Protection for Industrial Applications
>
> AS 3765-1990 Clothing for Protection Against Hazardous Chemicals

Novartis Crop Protection Australasia Limited has produced a MSDS for Chorus® Foliar Fungicide. This 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.

Conclusion

Chorus® Foliar Fungicide can be used safely if handled in accordance with the instructions on the product labels. Additional information is available on the product MSDS.

Environmental Assessment

Introduction

Ciba Geigy Australia Limited (now Novartis Crop Protection Australasia Pty Limited) has applied for registration of the new end-use product CHORUS® Foliar Fungicide, containing the new active ingredient cyprodinil (500 $g.kg^{-1}$ water dispersible granule formulation), for control of black spot (apple scab and pear scab - *Venturia inaequalis*) in apples and pears.

Cyprodinil is an anilinopyrimidine fungicide, its mode of action being that it inhibits the biosynthesis of methionine and represses the secretion of extracellular enzymes involved in pathogenesis. It has activity against a wide range of plant fungal pathogens and is used elsewhere as a foliar fungicide on cereals, stone fruit, almonds, grapes, strawberries, vegetables and ornamentals, as well as pome fruits, and as a seed dressing on barley.

Environmental fate

It is proposed that CHORUS® Foliar fungicide will be applied to apples and pears in the spur burst to petal fall period in up to 4 applications at 7-10 day intervals, at a maximum total rate of 3.2 kg product/ha (1.6 kg ai/ha). It is expected that the product will be sprayed on trees via ground-based equipment, including air shear sprayers, orchard air-blast sprayers or controlled droplet application sprayers. The label has been revised to forbid aerial application.

Spray equipment expected to be used in orchards is likely to produce significant spray drift due to the generation of fine droplets and direction of the spray up into foliage, rather than towards the ground. Contamination of the soil compartment within the treated area may occur due to droplets hitting the ground directly or being washed off leaves, and overspray, spraydrift and run-off (adsorbed to soil particles) are potential means of contamination of land and surface water in the vicinity of treated areas.

Hydrolysis

Two hydrolysis studies with radio-labelled cyprodinil were reported, one with incubation in the dark under sterile conditions at pH 4, 7 and 9 at ~50°C for 5 days and the other with incubation in the dark under mostly sterile conditions at pH 5, 7 and 9 at ~25°C for 32 days. The studies showed that cyprodinil was hydrolytically stable, with a calculated hydrolysis half-life in excess of 1 year at 25°C.

Photolysis

A study using monochromatic light (313 nm) at pH 7 and 20°C indicated that, while cyprodinil absorbs UV radiation at wavelengths of ~290-350 nm, the quantum yield is low. This study indicated an estimated direct photolysis half-life under clear skies of 17 days in summer at 40°N to 28 days in spring at 50°N.

Three studies with ^{14}C-labelled cyprodinil found widely differing aqueous photolysis half-lives for the substance at 25°C, depending on the cyprodinil concentration, the choice and concentration of cosolvent, the presence of acetone or humic acid as sensitisers, or the presence of hydrogen peroxide as a source of oxygen radicals [overall half-lives = 0.2 to 30 (and in one case 46.1) estimated Florida summer sunlight days]. Little or no degradation occurred in dark controls (up to ~30 days incubation, with initially sterile conditions in most

cases), while in many cases with irradiation there was a lag phase during which there was very little cyprodinil degradation, followed by more rapid degradation.

The applicant hypothesises that cyprodinil has a tendency to degrade via direct and indirect photolysis with a synergistic mechanism, i.e. that over time, cyprodinil is slowly hydrolysed and/or photo-oxidised to sensitising molecules, which then facilitate the degradation of cyprodinil in the system, and suggests that a likely factor in the extent to which a lag phase was present in the above tests was the dissolved oxygen content of the test solutions, through "oxygen quenching" effects. In most of the above tests, cyprodinil was fairly to moderately degradable by aqueous photolysis (half-life = 4-10 days or 10-30 days continuous light regime, respectively). Evidence indicates that even in natural water, there may be a lag period affected by the dissolved oxygen content of the water before suitable sensitisers accumulate, after which photodegradation occurs readily. However, turbidity often present in Australian channel and dam water is likely to slow aqueous photodegradation.

In a thin layer of soil exposed to filtered xenon arc lamp light for 15 days continuous or 16-22 days cyclic illumination (12 h light: 12 h dark), the rate of degradation of ^{14}C-labelled cyprodinil was somewhat faster in vital soil exposed to light (half-life = 28.2 and 33.0 FSS days, respectively with continuous and cyclic illumination) than in vital soil incubated under similar conditions in the dark (half-life = 78.1 and 53.5 days, respectively), and much faster than sterile soil exposed to cyclic illumination (half-life = 105 FSS days) or incubated similarly in the dark (half-life = 260 days). Thus photolytic effects may increase the rate of microbial degradation in soil.

The aqueous and soil studies indicated a large number of metabolites were present with both [pyrimidinyl-^{14}C] and [phenyl-^{14}C] labelled cyprodinil, but most were present at < 10% applied radioactivity and were not successfully identified. Three metabolites which were identified were a carboxylic acid derivative of the parent molecule (CGA-72749) and two pyrimidinyl cleavage products (CGA-249287 and CGA-321915). By the end of the aqueous photolysis tests, production of $^{14}CO_2$ due to photolysis was indicated to a very minor extent with [pyrimidinyl-^{14}C] cyprodinil (< 1% of applied radioactivity), but occurred to a greater extent with the [phenyl-^{14}C] label (~4-16% of applied radioactivity, depending on solution composition and the duration of incubation).

In soil, apparent carbon dioxide production was again greater with the [phenyl-^{14}C] than the [pyrimidinyl-^{14}C] label (4.6-4.9% and 2.3% of applied radioactivity, respectively) and was absent with incubation in the dark. The percentage of applied radioactivity which was not extractable from soil increased with increasing light exposure, reaching ~18-31% of applied radioactivity under the influence of photolysis, but only ~4.5-15% of applied radioactivity with incubation in the dark.

Degradation in soil and water

Aerobic and anaerobic soil metabolism

Nine studies reported tests conducted with ^{14}C-labelled cyprodinil applied at 1-3 ppm to moist soil (60-75% FC), with incubation for different durations ranging from 90-366 days under aerobic conditions in the dark at 20-25°C. Calculated half-life values for 4 of the soils tested were 20.8-41.7 (mean 29.3) days, a two compartment model often being found preferable to a simple pseudo-first order model. Initially sterile soil or the establishment of anaerobic conditions led to much slower degradation, and degradation was slower under cooler temperatures (10°C - half-life = 79.8 days) or in drier soil (30% FC - half-life = 50.7 days),

while a lower application concentration (0.1 ppm) led to faster degradation (half-life = 13.0 days). Much longer overall half-lives were indicated in a fifth soil (half-life with different ^{14}C labels = 267 and 365 days), though the initial degradation rate in this soil was similar to the overall rate in the above soils (half-life in first 21-28 days = 30.8 and 22.1 days, respectively, with half-life in remaining period = 433 days in both cases). Relatively low soil pH (5.2) and/or less microbial activity may have contributed to the slower degradation rate of cyprodinil in this soil. Thus at ~20-25°C under moist, aerobic conditions, cyprodinil was found to be "fairly degradable" (DT50 = 20-60 days), but under some circumstances, the rate of degradation may become much slower after 21-28 days.

As the degradation rate was significantly retarded by sterile or anaerobic conditions, it can be concluded that in these studies in the dark, aerobic microbiota were primarily responsible for metabolism of the substance. Initial degradation appears to involve small changes to the cyprodinil molecule and/or cleavage of the molecule into the phenyl and pyrimidinyl moieties (the major identified metabolite in soil extracts being a cleavage product, 2-amino-4-cyclopropyl-6-methylpyrimidine). Unchanged or slightly changed cyprodinil and cyprodinil cleavage products are sequestered or covalently bound to the soil, and gradual mineralisation of the molecule also occurs, with tests where the overall half-life was ~21 days and incubation continued for one year showing cumulative production of CO_2 of ~24-25% of applied radioactivity from both the phenyl ring and 2-pyrimidinyl carbon. The extent to which mineralisation occurs from bound radioactivity or extractable residues is unclear.

Aquatic metabolism

Studies of the rate of degradation of cyprodinil at ~20°C in river and pond water/sediment systems (sandy loam and loam sediments, respectively) indicated mean dissipation half lives of 2.4 days in the river water and 5.2 days in the pond water, due largely to partitioning to the sediment. The corresponding half-lives in the whole systems were much longer, at 116 and 172 days respectively ("slightly degradable" - DT50 in whole system = 60-180 days). Cyprodinil residues persisted at a low concentration (1.5-3% of applied) in water for at least 56 days and cyprodinil residues in sediment were still >30% of applied at the end of the study (260 days incubation). While conditions in the water phase were aerobic, there was evidence that the rate of degradation of cyprodinil in deeper, anaerobic parts of the sediment was slower than near the surface of the sediment. Two metabolites occurred at peak concentrations ≥ 10% applied radioactivity, the major one being a cleavage product (2-amino-4-cyclopropyl-6-methylpyrimidine), and the other remaining unidentified, but containing both radiolabels (i.e. U-phenyl and 2-pyrimidinyl ^{14}C). Cumulative carbon dioxide evolution reached 3.7-11.1% of applied radioactivity.

Microcosm study

In an outdoor microcosm study with cyprodinil, the dissipation half-life for cyprodinil in water subsequent to the final application for each of 7 treatments was consistently 14 to 19 days, somewhat longer than in the above laboratory aquatic degradation study. In contrast, the half-life in sediment from peak measured concentration and day when this occurred was generally 20-104 days (note that these estimates were based on limited data and that the calculated half-life was longer in two cases, at 235 and 1537 days). Thus the microcosm study indicated a shorter half-life in sediment (hence overall system) than did the laboratory study.

Ready biodegradability

A CO_2 evolution test found that only 15% of the theoretical C content of cyprodinil was evolved over a 29 day incubation period at 22°C, indicating the substance is classified as "not readily biodegradable" according to this standard test with activated sludge.

Mobility

Laboratory vapour pressure data indicate that cyprodinil is only slightly volatile and the Henry's Law Constant that it is only very slightly volatile from a water surface. A soil and a plant/soil volatilisation study indicated that little volatilisation of cyprodinil is likely to occur from soil, but the plant/soil study indicated that a substantial proportion of residues may be lost by volatilisation from treated plant surfaces.

Batch equilibrium studies of adsorption and desorption of cyprodinil in nine soils found organic carbon adsorption constants (K_{OC}) of 1550 to 4393 (average 2040) for cyprodinil, rating it as having low to slight mobility in soil (K_{OC} = 500-2000 or 2000-5000, respectively), as expected from its high lipophilicity (log $K_{OW} \approx 4$). In each case evaluation of a single desorption cycle also indicated strong adsorption.

That cyprodinil is largely immobile in soil was also indicated in various leaching studies. In one study, ^{14}C-labelled cyprodinil was applied freshly to columns of 4 different soils followed by leaching with the equivalent of 200 mm water over 2 days, while in 4 other studies aged soil (^{14}C-labelled cyprodinil applied to soil and incubated for 20-34 days) was applied to soil columns of two different soils, followed by two different leaching treatments (200 mm water in 2 days, or 508 mm in 40 days). In all cases, little movement of cyprodinil occurred below the first 2 cm of soil, and most of the radioactive residues also remained in the surface layers.

Calculations by Environment Australia of the Gustafson Ubiquity Score (GUS) using the available K_{OC} and half-life data indicate that except for the very worst case combination of these data, cyprodinil is an "improbable leacher" (GUS < 1.8). Together with the laboratory leaching studies, this analysis indicates that cyprodinil is highly unlikely to leach into groundwater.

Field dissipation

Various field dissipation studies were conducted, with cyprodinil applied as a WP 50 or WG 75 formulation to an apple orchard, cereal crops or bare soil in Spring-Summer at rates of 750 or 1000 g ai/ha. Field dissipation half-lives calculated from data at 5 sites ranged from 23.1 to 48.7 days and meteorological data available at some sites suggested that warmer temperatures may have been a factor in hastening degradation. Limited data for two other sites suggested a similar half-life (~ 14 days and < 31 days). Thus cyprodinil has low to moderate persistence in soil in field situations (half-life 2-6 weeks or 6 weeks to 6 months, respectively).

A long term residue study evaluated soil residues over a 4 year period, during which 11 applications of cyprodinil as a WP 50 or WG 75 formulation were made, totalling 7750 g ai/ha, with a maximum total annual rate of 2250 g ai/ha. Soil residues of cyprodinil and of CGA-249287 declined each year to < 0.01-0.02 mg.kg^{-1} in the surface 10 cm, indicating that the substance was not accumulating significantly. Outdoor confined accumulation studies were also conducted, with U-phenyl or 2-pyrimidinyl ^{14}C-labelled cyprodinil applied to spring wheat, followed after 44-315 days by lettuce, winter wheat, sugar beet or corn crops. Little radioactivity was taken up by the crops (< 0.01 ppm with the U-phenyl label and < 0.05 ppm with the 2-pyrimidinyl label) and concentrations of cyprodinil in soil extracts decreased at a

rate comparable to the above half-lives. The importance of bound residues in the fate of the substance was evidenced by total radioactivity in the surface 10 cm remaining relatively constant over > 400 days in these studies, while the percentage of extractable radioactivity decreased greatly.

Other soil residue studies reported included an apple orchard where 6 applications were made of cyprodinil WP 50, totalling 1350 g ai/ha, and winter wheat crops where 3 applications of the WG 75 formulation were made, totalling 1750 g ai/ha. The peak concentrations of parent substance and the major metabolite CGA-249287 measured in any of the field tests were 0.50 and 0.12 $mg.kg^{-1}$ dry soil, respectively, in the 0-10 cm layer of an organic soil 43 days after final application of cyprodinil in one of the latter winter wheat soil residue studies. Both CGA-249287 and cyprodinil were found to be largely immobile in soil, with little movement detected below a depth of 10 cm in any of the field studies.

The rates of degradation, major metabolite and importance of bound residues found in these field dissipation studies are consistent with laboratory soil metabolism studies, and the limited uptake of residues by plants in the field correspond to results with pot studies. Very limited downward movement of cyprodinil and its metabolites evident in the field is as expected from laboratory soil adsorption/desorption and column leaching studies.

Accumulation in soil

Under the conditions of use at a maximum of 4 applications per year in pome fruit crops, cyprodinil is expected to degrade with a half-life of ~20-50 days, with little or no detectable carryover from year to year, as found in field dissipation and long term residue studies. Hence unchanged cyprodinil is not expected to accumulate in soil in an unbound form, even with repeated annual use. Analyses of bound residues indicate that a portion of these may be unchanged cyprodinil, but laboratory and field studies indicate that little uptake of such residues occurs by plants and that mineralisation of residues occurs, though cleavage products may be covalently bound to soil organic matter.

Bioaccumulation

Cyprodinil is lipophilic ($K_{ow} \approx 4$) and a bioaccumulation study at 0.1 mg ai/L with bluegill sunfish confirms that with continuing exposure, it may bioaccumulate in fish (bioconcentration factor in whole fish = 393). However, most of the accumulated residues are rapidly eliminated once exposure ceases (depuration half-life ≈ 0.5 days). As it is non-persistent in water (dissipation half-life ≈ 2-6 days from water, though much longer from sediment) and is applied at a maximum of 4 times per annum, it is unlikely to bioaccumulate in practical aquatic situations.

Environmental toxicity

Birds

Studies of the acute oral toxicity of cyprodinil TGAC indicate that the LD50 from a single oral dose was > 2000 mg ai/kg bodyweight to both mallard ducks (*Anas platyrhynchos*) and bobwhite quail (*Colinus virginianus*). Vomiting by most of the mallard ducks dosed with 1000 or 2000 mg/kg bodyweight was observed, but neither emesis nor other non-lethal effects were observed at lower doses in the duck study or in the acute oral quail study.

Studies of the subacute dietary toxicity of cyprodinil TGAC to the same species indicate that the LC50 after 5 days exposure in the diet was > 5200 ppm cyprodinil. Other than a slight

reduction in mean bodyweight gain at the 2600 and/or 5200 ppm dose in part of the study period, there were no sublethal effects with subacute dietary exposure of either species.

Avian reproduction tests showed that dietary administration of up to 600 ppm cyprodinil to mallard ducks and bobwhite quail had no statistically significant effect on the health, growth or reproductive performance of adult birds or the health and early growth of their offspring. These studies indicate that US EPA classifications, cyprodinil TGAC is practically non-toxic to mallard ducks and bobwhite quail by both acute oral exposure (LD50 > 2000 mg ai/kg bw) and subacute dietary exposure (LC50 > 5000 ppm in diet).

Aquatic organisms

Fish

Studies provided by the applicant of the 96 h exposure acute toxicity of cyprodinil TGAC indicate that it is moderately toxic (LC50 = 1-10 mg ai/L) to fish [96 h acute LC50 = 2.17 (95% confidence limits = 1.35-2.55) mg/L and 2.41 (1.96->2.72) mg/L, respectively, to bluegill sunfish (*Lepomis macrochirus*) and rainbow trout (*Onchorynchus mykiss*)]. Earlier studies also provided indicate LC50s in the range 1.01-1.43, 0.68-1.23 and 0.93-2.14 mg/L, respectively, for bluegill sunfish (*Lepomis macrochirus*), rainbow trout (*Onchorynchus mykiss*) and carp (*Cyprinus carpio*), but Environment Australia places little reliance on these tests as they are based on initial measured concentrations in situations where the concentration increased markedly. A 21 day chronic toxicity study with cyprodinil TGAC and rainbow trout indicates a LC50 > 0.22 mg/L and NOEC for lethal effects of 0.22 mg/L. However, the NOEC, LOEC and MATC for non-lethal effects (increase in length over the study period) were 83, 130 and 104 µg/L, respectively, which indicates moderate toxicity with chronic exposure (NOEC in the range 0.01-0.1 mg/L.

Aquatic invertebrates

Two studies of the acute (48 hour exposure) toxicity of cyprodinil TGAC to the daphnid *Daphnia magna* were provided by the applicant, one (under static conditions) indicating an EC50 (immobilisation) of 100 (80-120) µg ai/L and the other (under flow through conditions) an LC50 of 32.8 (27.5-38.2) µg ai/L (the EC50 based on immobilisation and lethargy was in the range 22.3-34.0 µg ai/L). A 21 day chronic exposure study with cyprodinil TGAC and *D. magna* indicated a NOEC, LOEC and MATC of 8.16, 19.3 and 12.5 µg ai/L, respectively, while the EC50 was in the range 19.3-40.2 µg ai/L. Thus cyprodinil is very highly toxic to daphnids with acute exposure (LC50 < 0.1 mg ai/L) and highly toxic with chronic exposure (NOEC < 0.01 mg/L).

Diatoms, algae and aquatic plants

In a study provided by the applicant with cyprodinil TGAC and the freshwater green alga, *Scenedesmus subspicatus*, evaluation of biomass production indicated an EC50 (0-72 hours) of 0.75 (0.72-0.78) mg/L, indicating high toxicity (EC50 < 1 mg ai/L) to this algal species.

Microcosm study

A study was provided wherein 7 cyprodinil TGAC treatments were compared with an untreated control in outdoor microcosms (3 m diameter with a water depth of 1.4 m; treatments including rates equivalent to 1.3, 2.6 and 5.2 ppb in the microcosm water applied on 3 or 6 occasions or 7.0 ppb applied on a single occasion only, evidently based on expected environmental concentrations from 10% drift at 250-1400 g ai/ha to 2 m deep water). Peak concentrations of cyprodinil reached ranged from 2.5-18 ppb. There were some statistically significant effects indicated in the phytoplankton data, but these did not appear to be dose

related or associated with a trend over time and may not be actual treatment effects. No statistically significant effects or trends were evident in data for macrophytes or fish at the end of the study.

Among zooplankton, there were no adverse effects evident on cladocerans (principally *Bosmina longirostris* and *Diaphanosoma brachyurum*), while statistically significant increases occurred in rotifer populations (8 of the 33 taxa identified) in Treatments 2 to 6 (i.e. not Treatment 1 or 7), particularly in Week 4 of the study. Among macroinvertebrates (principally Oligochaeta and Chironomidae), while in general there were no dose related statistically significant effects of treatments compared to the control, the investigator noted trends in the data suggesting that there were reductions in populations of Oligochaeta, Tanypodinae, Chaoboridae and Ceratopogonidae associated with Treatment 7 (the highest single dose) during the study, but that these differences had diminished by the end of the study.

Environment Australia stresses that these effects were not supported by statistical evidence. Thus there is little or no evidence of adverse effects on phytoplankton, macrophytes, zooplankton and macroinvertebrates, but there were greater populations (statistically significant) of rotifer zooplankton than the control in several treatments for part of the study.

Terrestrial invertebrates

Two studies provided by the applicant investigated the toxicity of cyprodinil TGAC to honey bees (*Apis mellifera*) with contact exposure, and a third study examined the toxicity to bees of the same WG 50 formulation proposed for Australia with contact and with oral exposure. All 3 studies indicated cyprodinil as either the TGAC or formulation is virtually non-toxic (LD50 > 100 µg ai per bee) to bees by contact exposure (48 hour observation contact LD50 > 101 or 784 µg ai per bee as TGAC, 72 hour observation contact LD50 > 250 µg formulation per bee). The WG 50 study also indicated the formulation is virtually non-toxic to bees with oral exposure (72 hour observation oral exposure > 250 µg per bee).

Laboratory studies with the same WG 50 formulation at a rate equivalent to 250 g ai/ha in the field (i.e. less than the proposed maximum label rate for Australia) indicated that the overall effect of the substance on mortality and reproduction of the aphid predators *Orius insidiosus* (minute pirate bug - E = 65.0%) and *Aphidius matricariae* (a predatory wasp - E = 46.8%) were in the IOBC "slightly harmful" range (E = 30-80%). A semi-field study with the same rate of the same formulation and *Orius insidiosus* indicated a mortality corrected for data from the untreated control of 19.2%, i.e. "harmless" according to the relevant IOBC scale (M < 25%). Other semi-field tests with the same rate and formulation indicated it was "harmless" to *Chrysoperla carnea* (the green lacewing - M = 23%) and *Coccinella septempunctata* (seven spotted ladybird - M = 18%) and "slightly harmful" to *Orius insidiosus* (M = 26%, just outside the "harmless" range).

A field study in an apple orchard with the WG 50 formulation applied on 5 occasions at 250 g ai/ha led to Henderson-Tilton mortality scores for toxicity to predatory mites (the species not stated) of -23% to +19% relative to a penconazole-treated control, i.e. continually in the "harmless" category (reduction in population < 25%, but in this case relative to a standard treatment, rather than untreated control). Another field study with the WG 50 formulation applied to grape vines on 4 occasions at 250 g ai/ha led to Henderson-Tilton mortality scores for toxicity to the predatory mite *Typhlodromus pyri* of +17.9 to +39.1% relative to an untreated control, rating as "harmless" until the 4th spray application and then "slightly

harmful" (>26-50% reduction) when mites were sampled 7 and 35 days after the fourth application.

A 14-day study in artificial soil indicated a 14 day LC50 for cyprodinil TGAC to earthworms (*Eisenia foetida foetida*) in the concentration range (nominal) 111-333 mg/kg, hence the substance is slightly toxic (LC50 = 100-1000 mg/kg dry soil) to earthworms.

Phytotoxicity

Specific studies of phytotoxicity are not available, but the applicant reports that in the Australian field trials with CHORUS, no phytotoxicity has been observed in apples or pears and no adverse effects on native flora were reported. Cyprodinil is used overseas as a foliar fungicide on a wider range of crops, including cereals, grapes, stone fruit, strawberries, vegetables, field crops and ornamentals, and as a seed dressing on barley, and the applicant advises that no phytotoxic effects to non-target terrestrial plants have been observed under good agricultural practice.

Micro-organisms

A study of the effects of cyprodinil on soil microflora at concentrations of 2.67 or 26.7 mg ai/kg dry soil, simulating 1X and 10X a rate of 2000 g ai/ha (i.e. greater than the cumulative maximum proposed rate in Australia) in the surface 5 cm of soil. Effects of both treatments on short term respiration in a sandy loam and a loam soil at 0-3 hours, 14 days and 28 days after treatment were relatively minor and transient and in most cases not statistically significant, and overall were judged to be "negligible" according to a descriptive scheme cited by the author. There were some short term effects on soil nitrification evident in lower soil nitrate concentrations 14 and 28 days after incubation commenced, but nitrate levels were generally comparable to those in untreated soil after 56 days, and there was no clear effect of increasing rate on the extent to which nitrate production was inhibited. According to a descriptive scheme cited by the author, effects on nitrification in soil were judged to be "negligible" in the sandy loam and "tolerable" in the loam. An activated sludge respiration inhibition test indicated that the substance has low toxicity to sludge micro-organisms (3 hour EC50 = 100 mg/L nominal concentration, but test result questionable due to solubility problems).

Environmental hazard

Hazard to birds and mammals

Estimated concentrations resulting in a diet exclusively based on feed contaminated by cyprodinil at the maximum rate on 4 occasions (without degradation or dissipation) are well below the 5 day subacute dietary exposure NOEL (1300 and 2600 ppm, respectively, for bobwhite quail and mallard ducks) and 22 week dietary exposure avian reproduction test NOEL (600 ppm for both species). Hence cyprodinil used in accordance with label recommendations is not likely to present a hazard to birds ingesting these residues. Acute or chronic toxicity to mammals is also highly unlikely from the proposed use in pome fruit orchards.

Aquatic hazard

A range of scenarios was considered in assessing the aquatic hazard from the use of cyprodinil according to label rates, covering a single spray event, the maximum application intensity situation of 4 sprays at 7 day intervals, and the more likely situation of 3 sprays at 10 day

intervals, and allowing for differing rates of dissipation (no dissipation, and dissipation half-life in water = 2.35 days or 16.3 days). The expected environmental concentration (EEC) in 15 cm deep water was calculated for each of these scenarios and compared with acute and chronic toxicity data (LC50 or EC50 and NOEC/LOEC, respectively) for the most sensitive fish, aquatic invertebrate and algae species. With acute toxicity data, the environmental hazard quotient Q = EEC/LC50 or EC50 was calculated and interpreted according to US EPA practices, i.e. a "presumption of no risk" being indicated if $Q < 0.1$, a "presumption of risk that may be mitigated by restricted use" with $0.1 \leq Q \leq 0.5$, and a "presumption of unacceptable risk" with $Q > 0.5$. With chronic toxicity data, no risk was presumed if EEC < NOEC (no observed effect concentration) and an unacceptable risk was presumed if the EEC > LOEC (lowest observed effect concentration).

Direct overspray of a shallow (15 cm deep), lentic waterbodies on a single occasion with CHORUS at the maximum proposed rate was found to present a presumption of unacceptable risk to fish, algae and particularly aquatic invertebrates with most of the above scenarios. Environment Australia therefore concludes that there is an unacceptable aquatic hazard from direct overspray and requested that the label should forbid aerial application, to which the applicant has agreed.

Similar analysis for 10% spray drift reaching a 15 cm deep waterbody on one or more occasions also indicated an unacceptable risk to daphnids, but even with repeated incidents of 10% drift reaching such a waterbody, no hazard is indicated to fish or algae, assuming dissipation from water occurs at rates at least as fast as those reported in a microcosm study with the substance (dissipation half-life of cyprodinil in water = 16.3 days in microcosms, 2.4-5.2 days in laboratory studies). Thus the hazard to daphnids was examined further in more likely practical situations.

Environment Australia considers that in the majority of situations, ≤ 3% drift is likely to be deposited at a distance of 30 m from a sprayed dormant pome fruit orchard, and that waterbodies reached by spray are likely to be deeper than 15 cm. A presumption of risk that may be mitigated by restricted use was still indicated to daphnids with 3% drift to 15 cm deep water on a single occasion, and similar drift repeated on 3-4 occasions also led to EECs exceeding the NOEC, though not always the LOEC, depending on the number of sprays and dissipation rate. However, based on chronic daphnid toxicity data and assuming a dissipation half-life of ≤ 16.3 days, even with 4 sprays at 7 day intervals, no environmental hazard is indicated with greater water depth (3% drift onto ≥40 cm deep water) or lower drift (≤1% onto 15 cm deep water).

The above conclusions are supported by the results of the microcosm study, where peak concentrations of cyprodinil reached ranged from 2.5-18 µg ai/L, with little evidence of any adverse effects on phytoplankton, macrophytes, zooplankton (not *D. magna*, but including other cladocerans, principally *Bosmina longirostris* and *Diaphanosoma brachyurum*) and macroinvertebrates. The EEC for the expected practical use regime of 3 sprays at 10 day intervals is less than the highest peak concentration in the microcosm studies, indicating no hazard should be expected, even at a relatively slow dissipation rate of cyprodinil from the water column. The concentrations reached in the microcosms were too low to confirm whether or not a hazard is likely from 4 sprays.

Hazard to terrestrial invertebrates and soil micro-organisms

As cyprodinil has been found virtually non-toxic to honey bees (*Apis mellifera*), it is unlikely to present a hazard to bees. Similarly, cyprodinil has only slight toxicity to the earthworm species *Eisenia foetida foetida*, hence use of the product as described is unlikely to present a hazard to earthworms. At the label rate, the concentration of cyprodinil resulting in the top 5 cm of soil (bulk density = 1.4) from 4 applications without degradation occurring is ~2.3 mg ai/kg soil dry wt, well below the 14 day LC50 to *Eisenia foetida foetida* of 111-333 mg ai/kg soil dry wt. At the rates used, the substance is also unlikely to lead to significant effects on soil micro-organisms.

Toxicity studies indicate ratings of at most "slightly harmful" to the aphid predators *Orius insidiosus* (minute pirate bug) and *Aphidius matricariae* (a predatory wasp), "harmless" to *Chrysoperla carnea* (green lacewing) and *Coccinella septempunctata* (seven spotted ladybird), and "slightly harmful" to the predatory mite *Typhlodromus pyri*. However, these were all obtained with field rates of 250 g ai/ha, rather than the Australian label rate of 400 g ai/ha. Thus caution is required in extending these conclusions to the Australian situation, but the substance appears relatively non-toxic to beneficial terrestrial invertebrates.

Desirable terrestrial vegetation

As there is no indication of crop phytotoxicity from use in a range of crops at specified application rates, it appears unlikely that phytotoxicity should arise from drift onto native plants. The applicant also reports that there have been no observations of phytotoxicity to native plants in Australian trials. Environment Australia notes that it appears that the label rate proposed for Australia is greater than that generally used elsewhere (400 g ai/ha rather than 250 g ai/ha), hence it is possible that damage to some species from direct overspray could occur at the higher rate but not the lower.

Conclusions

Environment Australia has assessed data in support of Chorus® Foliar Fungicide and believes that the application contains adequate environmental fate and toxicity data to demonstrate that providing no aerial application occurs and the product is used according to proposed label recommendations and good agricultural practice, overall an acceptable hazard to aquatic environments may be predicted. Available data indicate that the greatest environmental hazard from use of the product is to aquatic invertebrates such as daphnids, hence aerial application has been forbidden and suitable label warnings included to minimise the likelihood of aquatic contamination.

Efficacy and Safety Assessment

Justification for use

Chorus® Foliar Fungicide will be a useful addition to the fungicides used in the management of fungal disease of apple and pear orchards. This product has been developed to be an alternative chemical available for black spot control on apples and pears which will provide another chemical group (Group I) to aid in reducing the level of resistance to fungicides by black spot.

Proposed use pattern

Chorus® Foliar Fungicide will be applied from spur burst to petal drop, with a maximum of 4 applications at 7 to 10 day intervals at an application rate of 40 g/100L (high volume) or 800 g/ha (low volume). The label advises to begin spraying with another registered fungicide at green tip and to follow, no later than 7 to 10 days after the last Chorus application, with registered DMI and protectant fungicides.

Evaluation of efficacy

Data presented by Novartis Crop Protection Australasia Limited supported the claim that Chorus® Foliar Fungicide is effective for the control of black spot (apple and pear scab) of apples and pears and label rates.

Of the 20 trials provided, 15 were on apples, including 2 which tested compatibility with other pesticides. All trials were replicated and covered a satisfactory representation of the major fruit growing districts of Australia (Victoria, NSW, Tasmania and South Australia). Trial design, treatments and data analysis were satisfactory.

Disease pressure was adequate in all but one trial on each crop, however all trials which adequately demonstrated efficacy also included use of a wetting agent with all treatments. As such the label carries an instruction in the Critical Comments to add 25 mL of a 100% non-ionic surfactant.

Crop safety

In all 20 trials there were no reports of phytoxicity observed. In regards to phytoxicity to other crops which may be grown close by, the applicant has informed that Chorus® Foliar Fungicide is well tolerated at all development stages of both pome and stone fruit. Chorus® Foliar Fungicide is also registered for use on stone fruit in the USA and Switzerland and is in the process of being registered for various vegetable crops in other countries.

Integrated Pest Management issues

The applicant was requested to provide additional studies to justify the product's claims of being suitable for IPM programs. Six additional studies were provided which adequately demonstrated that Chorus® Foliar Fungicide was rated at harmless to harmless – slightly

harmful for the predatory mite *Typhlodromus pyri.* Additionally, the Environment Australia report concluded the formulation is at most "slightly harmful" to the aphid predators *Orius insidiosus* (minute pirate bug) and *Aphidius matricariae* (a predatory wasp), "harmless" to *Chrysoperla carnea* (green lacewing) and *Coccinella septempunctata* (seven spotted ladybird), and "slightly harmful" to the predatory mite *Typhlodromus pyri.*

Hence the label justifiably includes the statement – 'At label rates and timing, Chorus® Foliar Fungicide has minimal effect on predatory mites'. The product will be able to be used as part of pome fruit orchard IPM programs.

Labelling Requirements

CAUTION

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

CHORUS®

FOLIAR FUNGICIDE

ACTIVE CONSTITUENT: 500 g/kg CYPRODINIL

GROUP	I	FUNGICIDE

CONTROLS BLACK SPOT

(APPLE SCAB AND PEAR SCAB) OF APPLES AND PEARS

1 or 5 kg Net

Novartis Crop Protection Australasia Limited, 140-150 Bungaree Road, Pendle Hill NSW 2145

UN-Free **N1**

In a Transport Emergency Dial 000, Police or Fire Brigade
For specialist advice in an emergency only, call 1800 033 111 (24 hrs)

NRA Approval No.: 49660/0798

DIRECTIONS FOR USE

RESTRAINTS: DO NOT apply more than 4 applications of this product per season. The effect of CHORUS could be diminished if rain falls within 2 hours of application.

DO NOT spray after petal fall.

DO NOT apply by aircraft.

Crop	Disease	Rate		Critical Comments
		Dilute (high volume) per 100L	**Concentrate** (low volume) per ha	
Apples, pears	**Apple scab,** *Venturia inaequalis* and **Pear scab,** *Venturia pirina*	40 g	800 g	Commence spraying at green tip with an approved fungicide, then apply a maximum of 4 applications between spur burst and petal fall at 7-10 day intervals. Add a 25 mL/100 L of a 100% non-ionic surfactant. Continue the scab/black spot program commencing no later than 7-10 days after the last CHORUS application. Using an approved DMI plus protectant fungicides.

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

WITHHOLDING PERIOD:
DO NOT USE AFTER PETAL FALL

Batch No.	
Date of Manufacture	

GENERAL INSTRUCTIONS

Fungicide Resistance Warning

GROUP	I	FUNGICIDE

CHORUS Foliar Fungicide is a member of the anilinopyrimidine group of fungicides. For fungicide resistance management CHORUS Foliar Fungicide is a Group I fungicide. Some naturally occurring individual fungi resistant to CHORUS Foliar Fungicide and other Group I fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungi population if these fungicides are used repeatedly. These resistant fungi will not be controlled by CHORUS Foliar Fungicide and other Group I 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, Novartis Crop Protection Australasia Limited accepts no liability for any losses that may result from the failure of CHORUS Foliar Fungicide to control resistant fungi.

Mixing
CHORUS Foliar Fungicide is a water dispersible granule (WG) fungicide which mixes readily with water. Partly fill the spray tank with water. Start the agitation and add the correct amount of product to the spray tank with the agitation system running. Continue agitation while topping up the spray tank with water. Add the surfactant at the completion of filling of the spray tank. Continue agitation while spraying.

Tank Mixing - When mixing CHORUS and other water dispersible granule (WG) or wettable powder (WP) formulations, ensure they are added and mixed well prior to adding emulsifiable concentrate (EC) or suspension concentrate (SC) products. Wettable powder (WP) formulations should be pre-mixed separately and then added to the spray tank.

Application in Apple and Pear Orchards
Apply by high volume (dilute) sprayer or by concentrate sprayer as recommended in the Directions for Use.
Dilute (high volume) spraying - Apply to the point of run-off to ensure thorough coverage of foliage.
Concentrate (low volume) spraying - The spray volumes determined for dilute spraying should be used to calculate the quantity per hectare required when using a concentrate sprayer. The same quantity of chemical per hectare should be used when spraying by either the dilute or concentrate method.

Compatibility: CHORUS® can be mixed with Anvil*, Bogard®, Delfin®, Gusathion*, Insegar®, Lorsban*, Nustar*, Parathion*, Pirimor*, Supracide®, Systhane*, Topas®.

Re-entry Period
Do not enter treated areas without protective clothing until spray has dried.

PROTECTION OF LIVESTOCK
Low hazard to bees.
PROTECTION OF WILDLIFE, FISH, CRUSTACEA AND ENVIRONMENT
DANGEROUS TO FISH AND OTHER AQUATIC ORGANISMS. Do not contaminate dams, waterways or drains with the product or its containers. Do not apply under meteorological conditions or from spraying equipment which could be expected to cause spray to drift onto adjacent areas, particularly wetlands, waterbodies or watercourses.

INTEGRATED PEST MANAGEMENT
At label rates and timing, CHORUS Foliar Fungicide has minimal effect on predatory mites.

STORAGE AND DISPOSAL
Store in the closed, original container in a dry, well ventilated area, as cool as possible out of direct sunlight.
Single rinse liner before disposal. Add rinsings to the spray tank. Do not dispose of undiluted chemicals on-site. Puncture and bury empty containers in a local authority landfill. If not

available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, vegetation and roots. Empty containers and product should not be burnt.

SAFETY DIRECTIONS

Will irritate the eyes. Avoid contact with eyes. When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves and face shield or goggles. When using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length PVC gloves. Wash hands after use.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone 13 1126.

MATERIAL SAFETY DATA SHEET

If additional hazard information is required refer to the Material Safety Data Sheet. For a copy phone 1800 025 931.

MANUFACTURER'S WARRANTY AND EXCLUSION OF LIABILITY

Novartis has no control over storage, handling and manner of use of this product. Where this material is not stored, handled or used correctly and in accordance with directions, no express or implied representations or warranties concerning this product (other than non-excludable statutory warranties) will apply. Novartis accepts no liability for any loss or damage arising from incorrect storage, handling or use.

Glossary

Active constituent	The component of a formulation which is responsible for its biological effect.
Acute toxicity	Immediately measurable effects of a toxin on an organism.
Groundwater Ubiquity score	A measure of whether a compound is likely to leach through soil into groundwater.
IC_{50}	Inhibition concentration where 50% of algal growth is inhibited.
IPM	Integrated Pest Management. The combination of chemical and biological aspects of pest control to achieve pest management.
LC_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms within a specified period. It is usually expressed as milligrams per litre (mg/L) or milligrams per kilogram (mg/kg) as a concentration in food, water or air.
LD_{50}	The dose of a substance that produces death in 50% of a population of experimental organisms within a specified period. It is usually expressed as milligrams per kilogram (mg/kg) of body weight.
Photolysis	Breakdown caused by light.
Schedule	The category into which a chemical is placed according to its human toxicity.

References

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

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.