Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the new active Proquinazid in the product

Dupont Talendo® Fungicide

APVMA Product Number 64165

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PREFACE

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

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

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

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

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

About this document

This is a Public Release Summary.

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

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

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

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of **DUPONT TALENDO® FUNGICIDE** should be granted. Submissions should relate only to matters that the APVMA is required by legislation to take into account in deciding whether to grant the application. These matters include aspects of **public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade,** and **efficacy and target crop or animal safety**. Submissions should state the grounds on which they are based. Comments received outside these grounds cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **Wednesday 20/06/2012** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling. A summary of relevant comments and the APVMA's response will be published on the APVMA website.

When making a submission please include:

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

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

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

Contact Officer
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[1] A full definition of "confidential commercial information" is contained in the Agvet Code.

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Further information

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

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

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

1 INTRODUCTION

Applicant

DuPont (Australia) Limited

Details of Product

It is proposed to register DuPont Talendo® Fungicide containing 200 g/L proquinazid as an emulsifiable concentrate intended for use in the control of powdery mildew (*Uncinula necator*) in grapevines. DuPont Talendo® Fungicide is intended to be used at the rate of 25 mL product/100 L of water for dilute spraying and may be applied as a concentrate spray (e.g. 75mL product/100L of water) under certain conditions.

Powdery mildew is characterised by white to ash-grey powdery fungal growth capable of infecting green vine tissue. Severe infection of powdery mildew can depress vine vigour because damage to leaves and shoots limits photosynthesis and inhibits berry sugar development. Powdery mildew infection at harvest can cause considerable economic loss because diseased berries cause off-flavours in wine. While powdery mildew only infects green parts of the vine, a complex life cycle allows it to overwinter in dormant buds and in grapevine bark crevices or leaf litter.

Proquinazid is a new active constituent to the Australian market. It is a fungicide that belongs to the Quinazolinones group and exhibits efficacy against powdery mildew. The mode of action is in the inhibition of spore germination and appressorium formation, as such, the proposed product is for use as a protectant treatment and has no curative activity on existing infections.

Proquinazid and its associated 200g/L emulsifiable concentrate formulation are registered for use on table grapes and wine grapes in a range of European countries including Spain, Luxembourg, Italy, Switzerland, France, Romania, Slovakia and Bulgaria. Provisional registration is in place in Germany, Poland and Austria.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of **DuPont Talendo® Fungicide**, and approval of the new active ingredient, proquinazid.

2 CHEMISTRY AND MANUFACTURE

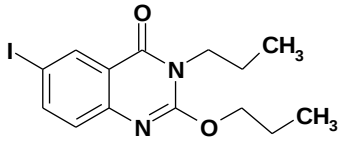
2.1 Active Constituent

Proquinazid is a new active constituent for use in grapevines for the control of powdery mildew.

Manufacturing Site

The active constituent Proquinazid is manufactured by Du Pont (Australia) Ltd at DuPont Iberica, S.L. Valle Dd Tamon-Nubledo; Municipios Carreno/Corvera 33469 Tamon Aviles-Asturias, Spain.

Chemical Characteristics of the Active Constituent

COMMON NAME:	Proquinazid
IUPAC NAME:	6-Iodo-2-propoxy-3-propylquinazolin-4(3H)-one
CAS NAME:	6-Iodo-2-propoxy-3-propylquinazolin-4(3H)-one
CAS REGISTRY NUMBER:	189278-12-4
MANUFACTURER'S CODES:	DPX-KQ926; IN-KQ926
MINIMUM PURITY:	950 g/kg
MOLECULAR FORMULA:	$C_{14}H_{17}IN_2O_2$
MOLECULAR WEIGHT:	372.2
STRUCTURE:	
CHEMICAL FAMILY:	Fungicide

Physical and Chemical Properties of Active Constituent

PHYSICAL STATE	White crystalline solid (pure active constituent) A brown, wax-like, crystalline solid (Technical active constituent)	
ODOUR	Decomposing garbage/food waste (pure active constituent) a faint, sweet odour (Technical active constituent)	
MELTING POINT	61.5 – 62 ºC (pure active constituent)	
DECOMPOSITION	Exotherm at 367.63°C	
RELATIVE DENSITY	1.57 ± 0.043 (pure active constituent)	
PH OF 1% SLURRY	6.28 at 25 ºC (pure active constituent)	
AQUEOUS SOLUBILITY (25˚C)	0.93 μg/mL (pH 7)	
SOLUBILITY IN WATER AND VARIOUS SOLVENTS (25˚C)	Acetone	>250 g/L
	Acetonitrile	154 ± 2.1 g/L
	Dichloromethane	>250 g/L
	N,N-dimethylformamide	>250 g/L
	Ethyl acetate	>250 g/L
	n-Hexane	>250 g/L
	Methanol	136 ± 1.4 g/L
	1-Octanol	>250 g/L
	o-Xylene	>250 g/L
	HPLC grade water	0.97 ppm
	HPLC grade water (pH 7, 0.01M K_2HPO_4 buffer)	0.93 ppm
	Filtered natural sea water	0.73 ppm
VAPOUR PRESSURE (25°C)	7 x 10-7 mm Hg (9 x 10^{-5} Pascals)	
SURFACE TENSION	73.9 dynes/cm at 19.8 ºC	
HENRY'S LAW CONSTANT (25°C)	3 x 10-7 atm -m^3.mol-1 (3 x 10-2 Pascal - $m^3.mol^{-1}$)	
OCTANOL/WATER PARTITION COEFFICIENT (25°C)	Log K_{ow}=5.5 ± 0.09 (effect of pH not relevant as proquinazid does not dissociate between pH 2.4 to pH 11.6)	
HYDROLYSIS	Proquinazid was hydrolytically stable at pH 4, 7, and 9, and no degradates were observed.	

PHOTOCHEMICAL DEGRADATION	The first order rate constant = 25.9 days-1 at pH 7 and 20 ºC Half-life (DT50) = 0.03 days at pH 7 and 20 ºC
DISSOCIATION CONSTANT (PKA)	Proquinazid does not dissociate between pH 2.4 to pH 11.6.
QUANTUM YIELD OF DIRECT PHOTOTRANSFORMATION IN WATER AT > 290 NM	0.007455
UV/VIS ABSORPTION (MAX.)	UV absorb 270 nm Max UV absorbance above 290 nm is 325 nm
FLAMMABILITY	The test substance was found to be non-flammable.
SELF-IGNITION	The test substance did not exotherm up to its melting point.
EXPLOSIVE PROPERTIES	The test substance was not found to be sensitive to thermal, impact, or friction stimuli.
OXIDISING PROPERTIES	The structural argument provided shows that proquinazid is incapable of reacting exothermically with a combustible material.

2.2 Product

DuPont Talendo® Fungicide

DISTINGUISHING NAME	DuPont Talendo® Fungicide
FORMULATION TYPE	Emulsifiable concentrate (EC)
ACTIVE CONSTITUENT CONCENTRATION	Proquinazid (200 g/L)

PHYSICAL AND CHEMICAL PROPERTIES OF THE PRODUCT

COLOUR AND PHYSICAL STATE	A brown liquid, sold as an emulsifiable concentrate. Its colour has been identified as 10YR/7/12 on the Munsell Colour Chart. Although the colour has been officially identified as brown, it can be seen as amber when viewed with a neutral background and yellow when viewed with a white background.
ODOUR	Pungent, sweet ester like odour
EXPLOSIVE PROPERTIES	Not explosive
OXIDISING PROPERTIES	Not classified as an oxidising substance
FLASH POINT OF LIQUIDS (CONTAINING FLAMMABLE SOLVENTS)	74°C
AUTO FLAMMABILITY	Auto-ignition temperature: 285±5°C
PH	6.18 (1% aqueous dilution with distilled water)
VISCOSITY	3.79 mm2/s at 20.0°C
SURFACE TENSION	36.1 mN/m
RELATIVE DENSITY	0.9758 @ 20°C
PERSISTENT FOAMING	2.5 mL of foam after 1 minute
STORAGE STABILITY:	Stability data provided by the applicant indicates that the product is expected to remain within specification for at least 2 years when stored under normal conditions in HDPE coextruded with Ethylene Vinyl Alcohol Polymer(EVOH) packs.
LOW TEMPERATURE STABILITY	Chemically and physically stable in HDPE coextruded with EVOH packs after 6.5 days and 10 days at 0 °C

3 TOXICOLOGICAL ASSESSMENT

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

The Office of Chemical Safety and Environmental Health (OCSEH) within the Department of Health and Ageing, Australia conducted the toxicology assessment of proquinazid and the product DuPont Talendo Fungicide.

3.1 Toxicokinetics and Metabolism

Absorption, distribution, metabolism and excretion of proquinazid was examined in rats following a single oral (gavage) dose with [phenyl-^{14}C]proquinazid at 1 or 20 mg/kg bw. A second study examined tissue levels of radioactivity following daily oral exposure at 1 mg/kg bw/d for 7 days. The findings were generally similar for males and females.

In the single dose study, proquinazid was virtually completely absorbed after low (1 mg/kg bw) and high dosing (20 mg/kg bw). The peak plasma concentration was reached after 4-8h (low dose) or 6-10h (high dose). Radiolabel was widely distributed in the body with the highest levels seen in adrenals, liver, kidneys, fat, pituitary and thyroid. Excretion of proquinazid was rapid and extensive (86-89% within 48 h). Urinary (45-57%) and faecal (33-46%) excretion equally contributed to the elimination process, with biliary excretion accounting for nearly all of the faecal excretion. By 7 days post-dose, no tissue sampled contained more than 0.5 ppm of radiolabel, and total body burden was <1% of the dose administered.

In the repeat dose study at 1 mg/kg bw/d, the highest tissue levels of radiolabel were detected in liver, kidneys and fat. Tissue levels were similar after dosing for 1 day or for 7 days, indicating that proquinazid does not accumulate in tissues. Lack of significant bioaccumulation is also supported by the observation that no tissue (apart from GI tract and contents) contained more than 0.1% of the cumulative dose 48-49 h after the end of repeated dosing, and that the total body burden was only 0.2% of the cumulative dose at 169-170 h post dose.

The metabolism of proquinazid was extensive. The major metabolic reactions were phenyl ring hydroxylation and hydroxylation at the propyl and propoxy side chains, as well as some hydrolysis of side chains. Major metabolites (detected at 10% or more of the dose in faeces and urine combined) were IN-NB673 and its glucuronide, IN-MU715 and metabolite 8. One de-iodinated metabolite, IN-GJ515, was detected in relatively small amounts.

Based on *in vivo* (rat) and *in vitro* (rat and human) dermal absorption studies on the neat formulation (2000 µg/cm^2) and the spray strength dilution (13 µg/cm^2), a dermal absorption factor of 2% was used for mixing/loading (i.e. neat formulation) and 12% during application (i.e. spray strength dilution) in the risk assessment.

Acute toxicity studies

Proquinazid has low acute oral (LD50 > 5000 mg/kg bw in males and 4846 mg/kg bw in females), dermal (LD50 > 5000 mg/kg bw in both sexes) and inhalational toxicity in rats (4-h; LC50 > 5200 mg/m3 in both sexes). It was a slight skin and eye irritant in rabbits but not a skin sensitiser in guinea pigs.

The formulated product, DuPont Talendo® Fungicide containing 200 g/L proquinazid, has low acute oral (LD50 > 2000 mg/kg bw in females) and dermal (LD50 > 5000 mg/kg bw in both sexes) toxicity in rats. It was a severe skin and eye irritant in rabbits but not a skin sensitiser in guinea pigs. No acute inhalational toxicity study was submitted but it is considered that DuPont Talendo® Fungicide will have low acute inhalation toxicity. However, it is expected to be a respiratory irritant.

Short term and subchronic toxicity studies

Repeat dose studies with mice and rats showed that the liver and thyroid were the primary target organs. In rats, altered liver enzyme activities (such as ALT and AST) as well as interference with hepatic synthesis of certain molecules (such as cholesterol and albumin) were observed. Additionally, liver weights were commonly increased in mice and rats and histopathological changes such as hepatocellular hypertrophy were observed in the liver. These effects were considered likely to be due to an induction of hepatic cytochrome P-450 microsomal enzymes and reflective of an adaptive response, rather than a toxic effect.

Long term toxicity and carcinogenicity studies

In a 2-year dietary study, a dose-related increased incidence of thyroid follicular cell hypertrophy was observed in male and female rats at 12 and 16 mg/kg bw/d and higher respectively, with an increased incidence of thyroid follicular cell adenomas seen in male rats at 43 mg/kg bw/d and higher. Additionally, a slight increase in thyroid follicular cell adenomas, considered to show ‘equivocal’ evidence for a carcinogenic potential, was seen in female mice at 415 mg/kg bw/d in a 18-month dietary study. Though these benign tumours are considered to be rodent-specific and not relevant to humans.

An increased incidence of hepatocellular adenoma was observed in female rats in the 2-year dietary study at 35 and 76 mg/kg bw/d (in 11/60 and 29/61 females respectively, compared to 1/60 in the female control group) at dose levels that had exceeded the maximum tolerated dose, as shown by decreases in body weight gain of 32% and 60% respectively. In the same study at the same dose levels, an increased incidence in cholangiocarcinoma, intestinal type, was also observed in the liver of female rats (in 8/60 and

12/61 females respectively, compared to 0/60 in the female control group). While in the 18-month dietary study in mice, a slight increase in hepatocellular adenomas (5.5% [3/55 females] compared to the upper historical control value of 2.6%) considered to show equivocal evidence of a carcinogenic potential, was seen in female mice at a 415 mg/kg bw a dose level that had produced an increased rate of hepatic peroxisome proliferation when investigated at the 1-week and 6-month time points.

Reproduction and Developmental Studies

In a multi-generation study with proquinazid, there were no substance-related effects on reproductive parameters or reproductive organs in adult rats at dose levels producing systemic toxicity in parental animals (reduced bodyweight gains, thyroid and hepatic hypertrophy). The only effect seen in pups was a reduction in total litter weight of F1 pups but not F2 pups during lactation. This reduction in F1 pups was associated with reduced body weight gain and food consumption of parental females during gestation and is considered a secondary effect to maternal toxicity.

Proquinazid was not teratogenic in both a rat and rabbit developmental study. In the rat study, the observed decrease in foetal weight, along with an increased incidence of retarded sternal ossification and patent ductus arteriosus were seen in the presence of marked maternal toxicity (reduced body weight gain) and were considered to be a secondary non-specific consequence of such. Similarly, in the rabbit study, the observed decrease in foetal weight was seen in the presence of marked maternal toxicity (reduced body weight gain) and was considered a secondary non-specific consequence of such.

Genotoxicity Studies

In a range of in vitro and in vivo assays, proquinazid was not mutagenic and/or genotoxic.

Neurotoxicity Studies

No neurotoxic effects were noted in rats after exposure to proquinazid.

3.2 Public Health Standards

Poisons Scheduling

The delegate to the Secretary of the Department of Health and Ageing sought advice from the Advisory Committee on Chemical Scheduling (ACCS) on the scheduling of proquinazid. Proquinazid was discussed at the February 2011 meeting of the ACCS. The delegate noted and agreed with the recommendation of the ACCS that proquinazid be included in Schedule 6 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). This was the interim decision of the delegate. The delegate's finals decision made on 1st June 2011 confirmed that proquinazid be included in Schedule 6 of the SUSMP with an implementation date of 1 September 2011.

NOAEL/ADI /ARfD

The Acceptable Daily Intake (ADI) is that quantity of an agricultural compound which can safely be consumed on a daily basis for a lifetime and is based on the lowest NOAEL obtained in the most sensitive species. This NOAEL is then divided by a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals. The ADI for proquinazid was established at 0.01 mg/kg bw/day based on a NOAEL of 1.2 mg/kg bw/day in a 2-year study in rats and applying a default safety factor of 100.

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

The ARfD for proquinazid was established at 0.2 mg/kg bw/d based on a LOAEL of 19 mg/kg bw/d in 90-day dietary study in dogs and using a default 100-fold safety factor to account for potential inter- and intra-species differences, which is considered sufficient for the minor and largely transient effects seen.

4 RESIDUES ASSESSMENT

4.1 Introduction

DuPont Talendo Fungicide is an emulsifiable concentrate formulation and contains the new active constituent proquinazid and is intended for control of powdery mildew in wine and table grapes. As part of the residues assessment for proquinazid, plant and animal metabolism studies, supervised residue trials, processing studies, feeding studies, and trade aspects were considered and details are provided below.

4.2 Metabolism

Metabolism data for 14C-labelled proquinazid in grapes, wheat, lactating goats and laying hens was provided.

Three applications of phenyl-14C-(U)-proquinazid were made to a grapevine grown outdoors at a rate of 200 g ai/ha, with 39 days between applications 1 and 2, and 24 days between applications 2 and 3. Grapes were harvested 0, 14, and 29 days after the last application. Leaves were harvested at the same intervals, as well as after the first and second applications, and immediately before the second and third applications, to assist in metabolite identification. Samples were extracted initially using ethyl acetate and phosphoric acid, and exhaustively with dichloromethane, acetonitrile/water, methanol/phosphoric acid, enzyme treatment (cellulase, amylase and amylglucosidase), mild alkali digestion, mild acid digestion, and strong acid reflux (to extract the lignin fraction). Extracts were analysed using LSC, HPLC, TLC and GC/MS with reference standards. The metabolic pathway observed for proquinazid in grapes was dehalogenation to give IN-MM671 (desiodo-proquinazid), followed by oxidative dealkylation to give IN-MM991 (3-propylquinazolin-2,4-dione). A number of unidentified polar metabolites were found at low levels (<0.01 mg/kg), while a significant proportion of the residue (22%) was incorporated in lignin. Proquinazid was the largest component of the residue (up to 39% of TRR or 0.093 mg/kg), followed by IN-MM671 (8.2% of TRR and 0.019 mg/kg), then IN-MM991 (2.3% of TRR and 0.005 mg/kg).

Wheat plants were grown under outdoor field conditions in the US and were treated with three foliar applications of phenyl-14C-(U)-proquinazid at 100 g ai/ha. Applications were performed at first/second node formation, flag leaf and water ripe caryopsis. Forage was harvested before the second application at the flag leaf stage (13 days post application 1), hay was collected before the third application at the watery ripe stage (16 days post application 2), and straw and grain were collected 26 days after the last application. Forage was additionally collected after each application. Samples were extracted multiple times with acetonitrile/water; this was partitioned with ethyl acetate. Further extraction was then conducted with methanol/phosphoric acid, followed by exhaustive extraction by enzyme treatment, mild alkali, mild acid, and strong acid reflux. Major residues were isolated from the extracts using preparative TLC, reverse-phase HPLC and solid phase extraction (some eluted fractions were treated with β-glucosidase and HCl). β-Glucosidase and HCl treatment were also employed on the hay aqueous extracts to further characterise residues. Isolated metabolites were identified with HPLC, and TLC by comparison with reference standards. Identities of metabolites were confirmed as far as possible with LC-ESI-MS.

Proquinazid was extensively metabolised in wheat primarily by oxidation of the propoxyl side chain to IN-MW977 isomers (hydroxyl proquinazid). Minor amounts of the carboxylic acid IN-MU210 are also formed. Further oxidation and conjugation resulted in multiple components which gave primarily IN-MM986 (O-dealkylated proquinazid) on acid cleavage. It was also observed that the formation of IN-NB673 and IN-MM991 on acid digestion of the aqueous and methanol fractions indicate ring hydroxylation and dehalogenation may also be occurring. In wheat straw, the applicant proposed that the radioactivity was incorporated into plant lignin. The most significant residues in the various wheat fractions were proquinazid (34.7% of TRR in grain, 0.12 mg/kg) and the metabolite IN-MW977 (comprising 0.06 mg/kg or 18.1% of the TRR in grain). In forage, hay and straw, IN-MW977 isomers were the most significant residues (32.7-44.6% TRR, 0.35-1.6 mg/kg), followed by parent (5.4-11.2 of TRR, or 0.07-0.53 mg/kg).

A study of the effects of simulated processes such as pasteurisation, baking, boiling, brewing and sterilisation on the nature of the residue of 14C-labelled proquinazid showed no changes to the compound, with no degradation products of proquinazid being observed at levels above 2% of the compound used.

Parent compound was by far the most significant component of the radioactive residue in grapes and wheat grain. A residue definition of parent compound only is proposed for proquinazid in plant commodities, for both MRL enforcement and dietary risk assessment.

Five laying hens each received a capsule containing phenyl-14C-(U)-proquinazid at 15.6 mg/kg diet (corresponding to an average of 1.06 mg/kg bw) daily for five days. Eggs were collected twice daily (morning and afternoon). Excreta samples were collected once daily. Cage wash samples were collected and pooled at the end of dosing. Hens were sacrificed between 22 and 23 hours after the final dose and samples of blood, liver, thigh muscle, breast muscle, gizzard, GI tract with contents, fat and skin with adhering fat were taken at termination. Tissues, egg samples and excreta were exhaustively extracted with acetonitrile/water and acetonitrile alone. Fat and excreta were analysed by HPLC immediately after concentration. Concentrated aqueous extracts of the remaining tissues were pH adjusted and purified by solid phase extraction. A portion of the liver post-extraction solids was hydrolysed by heating with HCl at 37 °C overnight. The extract was then partitioned into an organic and aqueous layer, which were both analysed by LSC. For characterisation and identification of the metabolites, reverse phase HPLC and TLC with co-chromatography using reference standards or isolates extracted from excreta by preparative HPLC were used. Metabolites in excreta were in turn identified using LC/MS/MS.

In the poultry metabolism study, very little of the radioactivity was transferred to eggs (0.2% administered dose) and tissue (0.65% of the administered dose). Proquinazid was mainly excreted in the excreta/cage rinse (87.9% of the dose). Total residues of proquinazid in eggs had not reached a plateau level by the end of the 5-day dosing period. Parent was detected in all matrices except liver. The highest level of parent found was in fat at 0.2 mg/kg (60%TRR). The major metabolic pathways for proquinazid in laying hens are hydroxylation of the propyl and propoxy side chains, with subsequent sulphate conjugation and/or oxidation to carboxylic acids being observed for the various hydroxy groups. Loss of the propyl and propoxy side chains was also observed. All metabolites identified were present at low levels. The highest levels of identified metabolites detected in the study were in eggs (0.04 mg/kg) and in liver (0.04 mg/kg, and 0.03 mg/kg). The highest level of any unidentified metabolite was in fat (0.03 mg/kg, or 9.2% of the fat TRR).

A single lactating goat received a capsule containing the test material at an average of 91.5 mg/kg in feed, or 3.5 mg/kg bw/day, for 3 days. During the dosing period, milk was collected (morning and afternoon). Urine and faeces were collected for one day prior to dosing and thereafter at approximately 24 hour intervals until termination. After collection of daily excreta specimens, samples of cage wash were collected. The treated goat was sacrificed 22 hours after the last dose and samples of blood, liver, kidney, fat (omental and perirenal), muscle, stomach and content, gastro-intestinal tract and content and gall bladder contents were collected. Samples were extracted with acetonitrile/water. Non-extractable residues in liver were further extracted by protease hydrolysis, mild acid treatment, and strong acid reflux. For the characterisation and identification work HPLC and MS were used to confirm metabolite identities, with the aid of reference standards and metabolites isolated from urine and faeces by preparative SPE and HPLC methods, and identified using LC/MS.

Total milk residues in the lactating goat metabolism study reached 0.46 mg/kg on Day 2 of dosing. The highest tissue residues observed were 1.07 and 1.06 mg/kg in liver and kidney respectively, with only 0.07 and 0.04 mg/kg being found in fat and muscle respectively. The major metabolic transformations in the lactating goat were oxidation of the propyl and propoxy side chains to hydroxylated derivatives, the subsequent oxidation of the hydroxyl groups to carboxylic acids, and the loss of the propoxy side chain. Ring hydroxylation was only seen to a limited extent in urine. The most significant residue component in all milk and tissue samples was IN-MU210 (carboxylation of the propoxy group) at 28.4-79.2% of the sample TRR, or 0.02-0.84 mg/kg, with mono-hydroxylated (IN-MU207 and IN-MW977) and di-hydroxylated (IN-MY341) derivatives of the parent also being observed, along with combined hydroxylated/carboxylated derivatives of parent. Levels of parent compound were lower than for hens.

In the lactating cattle feeding study, the most prevalent residue was the carboxylic acid metabolite IN-MU210, which was found above the LOQ in liver and kidney at the lowest feeding level, and in all tissues and milk at the highest feeding level. Parent compound was only found in liver, kidney and fat at or below the LOQ at the highest feeding level. A residue definition of parent compound and the metabolite IN-MU210 is therefore proposed for proquinazid in animal commodities.

4.3 Analytical methods

Determination of proquinazid residues in plant commodities

A GC/MS method was developed and validated for analysis of proquinazid and its metabolite IN-MM671 in apples and grapes. Samples were extracted with ethyl acetate. Clean up was achieved using partition with water or sodium chloride solution, followed by solid phase extraction.

The method was validated with a limit of quantitation (LOQ) of 0.02 mg/kg. Recoveries were conducted with fortification at concentrations of 0.02, 0.1 or 0.5 mg/kg and ranged from 72-96% for parent compound and 75-107% for IN-MM671.

Determination of residues of proquinazid in animal tissues

A method was presented for determination of proquinazid in animal tissues, milk and eggs. Samples were extracted using water/acetone, followed by a clean-up step by liquid/liquid partition, gel permeation

chromatography and column chromatography. Analyses were conducted using GC/MS. Recoveries were determined by fortification of samples at 0.02 or 0.2 mg/kg, and were, 74-94% at the lower level, and 66-101% at the higher level. The LOQ is 0.02 mg/kg.

A second method for proquinazid, and the polar metabolite IN-MU210 in animal commodities involved sample extraction using acetonitrile/water. Samples were analysed by LC/MS/MS. Mean recoveries for proquinazid ranged from 79 to 106% at the 0.01 mg/kg fortification level and from 83 to 107% at the 0.1 mg/kg fortification level. Mean recoveries for IN-MU210 ranged from 93 to 105% at the 0.01 mg/kg fortification level and from 88 to 110% at the 0.1 mg/kg fortification level. The LOQ is 0.01 mg/kg for both analytes.

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

4.4 Residue definition

The following residue definition is recommended for proquinazid for the purposes of dietary exposure assessment and for compliance and monitoring:

Compound	Residue definition
Proquinazid	*Commodities of plant origin:* Proquinazid *Commodities of animal origin:* sum of proquinazid and 3-(6-iodo-4-oxo-3-propyl-3*H*-quinazolin-2-yloxy)propionic acid, expressed as proquinazid

4.5 Storage stability

Stability over 19 months storage at -20 °C was tested for residues of proquinazid and the metabolite IN-MM671 in grapes. While a slight decline (~5-10%) in residue levels was noted over the storage period, all recoveries were well within the generally accepted limits of 70-120%. Proquinazid residues are stable on storage at -20 °C for 19 months.

4.6 Residue trials

The proposed use pattern in grapes is up to four dilute foliar applications of proquinazid using a spray concentration of 5 g ai/100 L. Applications are to be made at no closer than 14-day intervals. The harvest withholding period is 28 days.

Six Australian trials (four magnitude of residue studies and two decline trials) for proquinazid in grapes were provided, including 4 foliar applications at 1x and 3x the proposed application rate. For the trials at 1x the application rate, residues in ripe grapes were <0.01 (2), 0.01, 0.03 (2), and 0.09 mg/kg 28 days after the last application.

A package of 22 residue trials conducted in northern and southern Europe over three seasons was provided. Two emulsifiable concentrate formulations were tested, with applications at 75 g ai/ha with a large range of spray concentrations and spray volumes. Between four and six applications were made, at a target re-treatment interval of 14 days. Both decline trials, and magnitude of residue trials with either a 14-day or a 28-day harvest interval were conducted. Residues at 28 days after the last application from the set of trials that most closely matched the proposed Australian GAP were <0.02, 0.022, 0.03, 0.051, 0.068, 0.074, 0.095, 0.10 (3), 0.12, 0.14 (2), 0.16, 0.18 (2), 0.20, 0.21, 0.22, 0.29, 0.35, and 0.39 mg/kg.

The combined Australian and European dataset is <0.01 (2), 0.01, <0.02, 0.022, 0.03 (3), 0.051, 0.068, 0.074, 0.09, 0.095, 0.10 (3), 0.12, 0.14 (2), 0.16, 0.18 (2), 0.20, 0.21, 0.22, 0.29, 0.35, and 0.39 mg/kg (STMR = 0.10 mg/kg; HR = 0.39 mg/kg). An MRL of 0.5 mg/kg is therefore recommended for proquinazid in grapes.

4.7 Processing studies

Processing studies were conducted in Australia and France. The following processing factors were determined:

Processing factors (French trials)

COMMODITY	PROCESSING FACTORS
Must	0, 0, 0.06
Lees	0.09, 0.30
Must deposit	0.17, 0.29
Wet pomace	2.9, 4.1, 5.0, 5.5
Dry pomace	6.5, 11, 11, 12 (mean = 10)
Juice	<1
AF wine	<1
Wine	<1
Raisins	1.7, 2.3, 2.8, 3.9 (mean = 2.7)

Processing factors (Australian trials)

COMMODITY	PROCESSING FACTOR
Juice	0.11, 0.22, 0.33, 0.33, 0.33, 0.33, 0.42, 0.44, <1, 1 (mean = 0.45)
Wine	0.06, <0.11, 0.11, 0.17, <0.33, <0.33, <0.33, 0.33, <1, <1 (mean = 0.38)
Wet pomace	2.0, 2.7, 3.0, 3.5, 3.7, 3.9, 4.0, 4.0, 5.0, 7.1 (mean = 3.9)
Dry pomace	10, 12, 15, 17, 18, 18, 19, 19, 24, 31 (mean = 18)

Processing of grapes into raisins was only undertaken for the French trials. The raisin processing factors were 1.7, 2.3, 2.8 and 3.9. Multiplying the highest processing factor by the grape highest residue (0.39 mg/kg) gives an HR-P of 1.52 mg/kg. Therefore, an MRL of 2 mg/kg is proposed for DF 0269: dried grapes.

Grapes were processed into juice for both the Australian and French residues trials. Processing factors for juice were all <1 for the French trials (no residues were detected in juice) and 0.11-1 for the Australian trials. Residues are therefore not expected to concentrate in grape juice, and an MRL for grape juice is therefore not required.

In the Australian trials, all wine processing factors were <1, and in the trials conducted at the proposed label rate, no residues were found in wine above the LOQ. In the French processing trials, no residues were detected in wine. This indicates that proquinazid residues do not concentrate in wine. Therefore, a separate MRL for wine is unnecessary.

Processing factors for wet grape pomace ranged from 2.9 to 5.5 in the French trials, and 2.0 to 7.1 in the Australian trials. For dry pomace, the processing factors were 6.5-12 in the French trials and 10-31 in the Australian trials. Multiplying the highest processing factor by the grape highest residue (0.39 mg/kg) gives an HR-P of 12.1 mg/kg. Therefore, an MRL of 15 mg/kg is proposed for AB 0269: grape pomace (dry). The grape pomace STMR-P value of 3.1 mg/kg was calculated by multiplying the processing factor by the grape STMR (0.10 mg/kg).

4.8 Animal feeds

Evaluation of the processing studies for grapes showed that proquinazid residues could concentrate in grape pomace (see the above discussion on processing). The following entry in Table 4 of the MRL Standard was recommended: grape pomace (dry): 15 mg/kg.

4.9 Crop rotation

No rotational crop studies were provided with the application. Grapes are not a rotational crop, therefore rotational crop residue and metabolism studies are not required for registration of the use of proquinazid on grapes.

4.10 Animal commodity MRLs

A lactating cattle feeding study was supplied with the application. Cattle were fed, in groups of 3, proquinazid at levels of 1, 3 and 10 mg/kg dry weight in feed (corresponding to 0.03, 0.09 and 0.30 mg/kg bw/day) daily for 28 days. Two additional animals were dosed at 10 mg/kg in order to provide depuration data. Milk samples were collected at intervals throughout the feeding and depuration phase, with skim milk and cream being additionally collected on feeding days 14 and 21. With the exception of the depuration animals, cattle were slaughtered and samples of liver, kidney, muscle and renal, omental and subcutaneous fat were collected within 24 hours of the last dose. The two depuration animals were slaughtered 7 and 14 days after the last dose. Samples were analysed for proquinazid and two polar metabolites, IN-MU210 and IN-MW977.

Residues in whole milk reached a plateau at around 4 days after the start of dosing, with maximum total residues of 0.009, 0.013 and 0.047 mg/kg being observed for the 1X, 3X and 10X groups respectively. Residue decline in whole milk samples was rapid, with a half-life of around 1 day. There was no significant difference in residue levels in skim milk and cream.

The highest tissue residues observed were in kidney, at 0.027, 0.048, and 0.49 mg/kg at the 1, 3 and 10 mg/kg feeding level, followed by liver at 0.019, 0.040, and 0.14 mg/kg. Residues in muscle and fat were significantly lower, being below the LOQ in all samples for the 1 mg/kg feeding level, and reaching a maximum of 0.005 and 0.015 mg/kg for the 3 and 10 mg/kg feeding levels in muscle, and 0.010 and 0.093 mg/kg in renal fat (the fat tissue in which the highest residues were seen). Clearance of the residues from tissues was rapid, with residues being undetectable in all samples at 7 and 14 days after the last dose.

The dietary intake of proquinazid by cattle consuming treated grape pomace is estimated below:

Cattle - 500 kg bw, 20 kg DM/day

FEED GROUP	COMMODITY	% IN DIET	FEED INTAKE	RESIDUE (mg/kg)	% DM	LIVESTOCK DIETARY EXPOSURE		
						mg/ANIMAL	ppm	mg/kg bw
By-products	Grape pomace, dry	20	4	3.1 (STMR-P)	100	12.4	0.62	0.025

At the 1 mg/kg feeding level in the cattle feeding study, total residues of proquinazid in whole milk, cream, skim milk, muscle and fat were below the limit of quantitation for all samples. Therefore, MRLs at the validated LOQ of 0.01 mg/kg for proquinazid in mammalian products are supported for proquinazid in milk and mammalian meat.

Finite residues were recorded in liver and kidney at a feeding level of 1 mg/kg (0.03 mg/kg bw/day), with maximum total residues of 0.020 and 0.029 mg/kg respectively being observed. It is therefore proposed to establish an MRL of 0.05 mg/kg for proquinazid in edible offal (mammalian).

Grape pomace is not commonly used as a feed for poultry. Therefore, there is unlikely to be a significant dietary burden of proquinazid in poultry feed as a result of registration of products containing proquinazid for use in vineyards. As a consequence, it is proposed to establish MRLs for proquinazid in poultry meat,

poultry edible offal, and eggs at 0.01 mg/kg, which is the validated limit of quantitation for proquinazid in animal tissues.

Based upon the metabolism study, livestock dietary burden calculation, and the stockfeed residues data, the following animal commodity MRLs are recommended: edible offal (mammalian) (0.05 mg/kg); eggs (*0.01 mg/kg); meat (mammalian) (*0.01 mg/kg); milks (*0.01 mg/kg); poultry, edible offal of (*0.01 mg/kg); and poultry meat (*0.01 mg/kg).

4.11 Spray drift

Spray drift modelling shows the risk of drift from vineyard applications onto adjacent pasture resulting in detectable residues of proquinazid in meat or dairy products is very low. No-spray zones are not required to be included on product labels.

Bioaccumulation potential

Proquinazid has an octanol/water partition coefficient (log10POW) of 5.5 at 25 °C. However, residues are not designated as fat soluble given in the feeding study, most of the residue was present as the much more polar metabolite IN-MU210, which did not show a tendency to partition in to milk or body fats.

4.12 Conclusions

Estimated dietary intake

The chronic dietary intake risk for proquinazid has been assessed. The ADI for proquinazid is 0.01 mg/kg bw/day, based upon a NOEL of 1 mg/kg bw/day and a 100-fold safety factor. The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for proquinazid is equivalent to 1.9% of the ADI. DIAMOND Modelling of chronic dietary exposure is also performed on new chemicals. The DIAMOND model estimated the chronic dietary exposure of proquinazid as 8.4% of the ADI for the general population, using MRLs, and 3.9% using Supervised Trial Median Residue (STMR) values where available.

The acute reference dose (ARfD) for proquinazid is 0.2 mg/kg bw, based on a NOEL of 19 mg/kg bw, and a safety factor of 100. The NESTI calculations are made in accordance with the deterministic method used by the JMPR5 with 97.5th percentile food consumption data derived from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. The highest NESTI calculated was 6.6% of the ARfD. It is concluded that the acute dietary exposure is acceptable.

It is concluded that the dietary exposure to proquinazid is low and the risk from residues in food is acceptable when DuPont Talendo Fungicide is used according to label directions.

Recommendations

The following amendments to the MRL Standard are recommended in relation to the proposed use of DuPont Talendo Fungicide:

Table 1:

COMPOUND	FOOD		MRL (mg/kg)
ADD:			
Proquinazid	DF 0269	Dried grapes	2
	MO 0105	Edible offal (mammalian)	0.05
	PE 0112	Eggs	*0.01
	FB 0269	Grapes	0.5
	MM 0095	Meat (mammalian)	*0.01
	ML 0106	Milks	*0.01
	PO 0111	Poultry, edible offal of	*0.01
	PM 0110	Poultry meat	*0.01

*MRL set at the limit of quantitation.

Table 3:

COMPOUND	RESIDUE DEFINITION
ADD:	
Proquinazid	Commodities of plant origin: Proquinazid
	Commodities of animal origin: sum of proquinazid and 3-(6-iodo-4-oxo-3-propyl-3H-quinazolin-2-yloxy)propionic acid, expressed as proquinazid

Table 4:

COMPOUND	ANIMAL FEED COMMODITY		MRL (mg/kg)
ADD:			
Proquinazid	AB 0269	Grape pomace, dry	15

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

HARVEST WITHHOLDING PERIOD

Grapes: Do not harvest for 28 days after application.

GRAZING WITHHOLDING PERIOD

Vineyards: Do not graze or cut for stock food.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported and main destinations

Commodities connected with the application that have a potential for finite residues of proquinazid and are also major export commodities, are grapes (including table grapes, dried grapes and wine), and mammalian offal.

Details of key export destinations for Australian grapes and wine are tabulated below.

Australian Table Grape Exports in 2007/08 (Australian Bureau of Statistics)

DESTINATION	VALUE, $ MILLION
Hong Kong	29.340
Indonesia	16.775
Thailand	12.587
Singapore	7.993
Malaysia	7.208
Vietnam	5.319
New Zealand	4.536
United Arab Emirates	3.667
Taiwan	3.325
Bangladesh	2.036
Sri Lanka	1.379
Other	6.346
TOTAL	**100.511**

Australian wine exports in 2009/10 (Australian Commodities Statistics 2010, ABARES)

DESTINATION	VALUE, $ MILLION
Hong Kong	29.340
USA	629.4
UK	584.7
Canada	202.2
China	143.3
New Zealand	70.6
Netherlands	56.3
Germany	48.7
Japan	44.2
Sweden	42.0
Hong Kong	42.0
Singapore	40.9
Ireland	40.8
Thailand	12.3
Switzerland	12.1
Others	203.2
TOTAL	**2172.5**

Exports of dried vine fruit from Australia are of minor importance in comparison with wine and table grapes, with exports of 4000 tonnes in 2009/10 being worth $13 million.

The significant export markets for Australian meat, including offal, are listed in Appendix 3 of Part 5B of the Agricultural Manual of Requirements and Guidelines (Ag MORAG).

5.2 Overseas registration status

Codex MRLs not have been established for proquinazid.

Proquinazid products are registered for use on grapes in in South Africa, Israel, Albania, Bosnia, Serbia, Montenegro, Switzerland, Turkey, Lebanon and the following EU countries: Bulgaria, the Czech Republic,

Hungary, Italy, Luxembourg, Romania, Slovakia, and Spain. It has provisional registration in Austria, Germany and Portugal. Registration is pending in France. Some MRLs are established for grapes and grape products (see table below).

The following relevant overseas MRLs have been established:

Current Overseas MRLs for Proquinazid in Grapes

COUNTRY/STATUS	COMMODITY	TOLERANCE (mg/kg)	REFERENCE
EU	Table grapes	0.5	EU Pesticides Database (http://ec.europa.eu/sanco_pesticides/public/index.cfm)
	Wine grapes	0.5	
South Africa	Grapes	0.5	South African Department of Health (www.doh.gov.za)
Israel	Grapes	0.05	Israeli Ministry of Agriculture (www.cinadco.moag.gov.il/ppis)
Switzerland	Grapes	0.3	www.admin.ch

The residue definition in the EU is parent compound only.

There are currently no overseas animal commodity MRLs.

5.3 Potential risk to trade

Finite MRLs are proposed for grapes and dried grapes. The grape MRL is the same as the MRLs in the EU, and South Africa, while being significantly higher than the Israeli MRL.

Most major export destinations for table grapes do not currently have an MRL for grapes, while New Zealand accepts Australian MRLs under the Trans-Tasman Mutual Recognition Agreement. Table grape exports are therefore at possible risk as a result of the proposed use of proquinazid in Australian grapes.

A separate wine MRL is not required, as residues will not exceed the grape MRL. Residues of proquinazid are not expected to be found in wine above the LOQ. The risk to Australian wine exports is therefore low.

No information is available on destinations of Australian exports of dried grapes. The proposed Australian MRL for proquinazid in dried grapes is 2 mg/kg.

Finite residues of proquinazid are not expected to be found in poultry commodities as grape byproducts are not commonly fed to poultry. The lactating cattle feeding study, together with calculations of the expected dietary burden for cattle show that finite residues of proquinazid are not expected in milk, meat or fat of mammalian livestock. Finite residues of proquinazid may be found in mammalian liver and kidney, with maximum residues of 0.020 and 0.029 mg/kg respectively being found in the feeding study at a dose level comparable with the calculated dietary burden for cattle. An MRL of 0.05 mg/kg is proposed for proquinazid

in mammalian offal. Residues cleared rapidly from cattle tissues after dosing ceased, with residues being undetectable 7 days after the last dose.

5.4 CONCLUSIONS

Grapes: The available residues trial data show that grapes from vineyards treated with proquinazid may contain residues when harvested (range of residues from supervised Australian and European grape residues trials (n = 28) was <0.01-0.39 mg/kg; STMR = 0.10 mg/kg. Processing studies showed that finite residues of proquinazid are not expected in wine. A separate MRL for wine is not required. A processing factor of 3.9 for dried grapes was determined. An MRL of 2 mg/kg for dried fruit is proposed. The proposed Australian MRLs for grapes and dried grapes may potentially have an impact on the export of Australian dried and table grapes to the major importing countries. The APVMA welcomes comment on whether proquinazid residues will unduly prejudice Australian trade in table grapes, or dried grapes. There is not expected to be any undue risk to Australian trade in wine, however the APVMA welcomes any comments.

Animal commodities: Feeding study data for lactating cattle and modelling of the expected dietary burden in poultry and mammals feeding on commodities from crops treated with proquinazid show that quantifiable residues are unlikely to be found in mammalian and poultry meat, poultry offal, milk or eggs. MRLs are proposed for these commodities at the limit of quantitation. Low levels of proquinazid residue may be found in mammalian offal, with maximum residues of 0.020 and 0.029 mg/kg respectively being found in the feeding study at a dose level comparable with the calculated dietary burden for cattle. An MRL of 0.05 mg/kg is proposed for proquinazid in mammalian offal. The cattle feeding study showed that residues rapidly cleared from cattle tissues, with no residue being detectable by 7 days after the last dose, well within the specified 60-day period for declaration of feeding of by-product stockfeeds on the National Vendor Declaration form. Therefore there is a possible risk (expected to be low) to Australian exports of offal and the APVMA welcomes comment on the trade risk associated with the proposed uses.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Health hazards

Proquinazid is not listed on the Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2010). With the available toxicology information, OCSEH has determined that proquinazid is classified as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004), with the following risk phrases:

R40 (Carc. Cat. 3)	Limited evidence of a carcinogenic effect

The following cut-off concentrations apply for proquinazid:

Conc. ≥ 1%	Xn; R40

Proquinazid is only considered to provide limited evidence for a carcinogenic effect and, hence Category 3 and not 2 is appropriate, because:

There was some uncertainty as to whether intestinal-type cholangiocarcinomas seen in female rats only should be regarded as malignant tumours, as no metatases were detected in distant organs;

The benign hepatocellular adenomas seen in only female rats and female mice (a slight increase considered 'equivocal' in mice in the presence of peroxisome proliferation) are not considered to provide robust evidence that proquinazid be considered a presumed human carcinogen (i.e. Category 2);

These lesions (intestinal-type cholngiocarcinomas and hepatocellular adenomas) were only seen at doses that exceeded the maximum tolerated dose and are most likely a secondary consequence of prolonged and severe hepatic toxicity;

Proquinazid did not exhibit a mutagenic or genotoxic potential in vitro, or a genotoxic potential in vivo; and

The increased incidence of benign thyroid follicular cell tumours seen in male rats and female mice (a slight increase considered 'equivocal' in mice) are considered to be a rodent-specific and not relevant to humans.

Based on the product toxicology information and concentrations of proquinazid and other ingredients in the product, DuPont Talendo® Fungicide is classified as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrases:

- Irritating to skin
- Irritating to respiratory system
- Risk of serious eye damage
- Limited evidence of a carcinogenic effect

6.2 Formulation, packaging, transport, storage and retailing

DuPont Talendo® Fungicide will be manufactured overseas and imported into Australia as a emulsifiable concentrate liquid in high density polyethylene containers. It will be available in the following pack sizes: 1L, 2.5 L and 5 L. Transport workers and store persons will handle the packaged products and could only become contaminated if packaging is breached.

6.3 Use pattern

DuPont Talendo® Fungicide is a new fungicidal product, which will be used for the control of powdery mildew in grapevines. It contains 200 g/L proquinazid and the formulation is emulsifiable concentrate (EC).

6.4 Exposure during use

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

There are no worker exposure studies on proquinazid or the product (DuPont Talendo® Fungicide) available for assessment. In the absence of worker exposure data, the OCSEH used the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) to estimate the worker exposure during mixing/loading and application based on the maximum product use rate according to the Australian use pattern. These estimations in conjunction with toxicology data demonstrated that:

Provided that worker wear a face shield or goggles, a disposable fume mask covering mouth and nose, cotton overalls buttoned to the neck and wrist and a washable hat and elbow length chemical resistant gloves, no further PPE is required for potential repeat exposure effects when mixing/loading DuPont Talendo® Fungicide .

Provided that worker wear a single layer cotton overall, no further PPE is required for potential repeat exposure effects when using diluted (spray) DuPont Talendo® Fungicide to control of powdery mildew in grapevines.

6.5 Exposure during re-entry

There is no risk associated with re-entry with this product.

6.6 Recommendations for safe use

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

6.7 Conclusion

The registration of DuPont Talendo® Fungicide , containing 200 g/L of proquinazid for the control of powdery mildew in grapevines is supported.

DuPont Talendo® Fungicide can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product MSDS.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

Du Pont (Australia) Ltd have applied for registration of the new agricultural product DuPont Talendo® Fungicide (containing 200 g/L of the new active constituent Proquinazid) to control powdery mildew on grapevines. A comprehensive data package was provided for assessment. The EU assessment report for the active constituent and use of an identical product on grapes in Europe was used to assist preparation of this report.

Proquinazid belongs to a new group of fungicides, quinazolinones, and has a new mode of action: it blocks secondary appressorial development in powdery mildew.

7.2 Environmental fate

Comments on physicochemical properties

Proquinazid is slightly soluble in water (solubility 0.1–10 mg/L), very slightly volatile (< 1×10^{-4} Pa) and moderately volatile from water (non-dimensional Henry's Law Constant H = $1 \times 10^{-5} – 3 \times 10^{-2}$). The molecule does not dissociate at environmentally relevant pH. Based on the n-octanol/water partition coefficient, proquinazid has potential to bioaccumulate and is expected to have low soil mobility.

Hydrolysis

In a laboratory study conducted to standard guidelines, there was no hydrolysis at 20°C after 30 days at pH 4, 7 and 9. The metabolites IN-MM671, IN-MM986, IN-MM991 and IN-MT884 were tested in similar studies: there was no hydrolysis at 20°C after 30 days at pH 4, 7 and 9.

Photolysis

The aqueous photodegradation of proquinazid was investigated in pH 7 buffer at 20°C using a xenon arc simulated sunlight source. Proquinazid was rapidly photolysed with a DT50 (time taken for 50% of the compound to degrade) of 0.03 days under continuous illumination. The major photolysis products were IN-MM671 (maximum of 22% of applied radioactivity [AR]), IN-MM986 (maximum 15% AR), IN-MM991 (maximum 14% AR), and IN-MT884 (maximum 30.5% AR). In addition, a significant amount of radiolabelled carbon dioxide ($^{14}CO_2$ - maximum 21% AR) was produced, showing that the parent molecule was significantly degraded during the study. All the major photolysis products declined during the course of the study with DT50 values of 5, 11, 39 and 4 days for IN-MM671, IN-MM986, IN MT884, and IN-MM991, respectively. Calculations based on the study indicated a theoretical half-life for proquinazid in the top layer of an aqueous system integrated over a full day in summer at 40º N = 0.03 d.

In soil photolysis studies conducted using a microbially active soil, radiolabelled proquinazid was applied to thin layers of soil and irradiated with a simulated solar spectrum. Proquinazid degraded more rapidly under continuously irradiated conditions (DT50 = 15.5 days) than under non-irradiated conditions (DT50 = 82

days). The soil photolysis DT50 value of proquinazid corrected for degradation in the dark control was 19 days continuous irradiation, equivalent to approximately 38 days of natural sunlight (mid June in Phoenix Arizona, 12 h sunlight/day). The primary degradation products of proquinazid in irradiated soil were IN-MM671 and non-extractable residues.

Soil metabolism

The degradation of proquinazid was evaluated under laboratory conditions in four non-sterile soils (1 US soil and 3 European soils). The soils covered a range of soil textures and soil pH (5.5–7.3). Radiolabelled laboratory studies with incubation continuing for 12 months showed that the major aerobic metabolites of proquinazid were IN-MM671 (maximum 65% AR), IN-MM986 (maximum 8% AR), and IN-MM991 (maximum 7% AR). Radiolabelled carbon dioxide ($^{14}CO_2$) was also produced (maximum 28% AR), and radioactive residues remained in the soil after solvent extraction (maximum 32% AR). The degradation pathway is deduced to be loss of iodine to give IN-MM671, then dealkylation to give IN-MM991, with a minor route dealkylation of parent to give IN-MM986 then to IN-MM991. This is followed by further degradation to CO_2 and incorporation of metabolites into soil.

The DT50 values for proquinazid in soils incubated at 20ºC were 39.5, 58, 204 and 345 days. Thus proquinazid was “fairly degradable” in two of the soils (DT 50 = 20–60 days), but only “very slightly degradable” in the other two soils (DT50 > 180 days). DT50s for the major initial metabolite IN-MM671 estimated from these studies were 35–223 days. Separate laboratory rate of degradation studies were also performed for the major degradation products in three of the above soils (where proquinazid DT50 = 39.5–204 days). These indicated DT50s at 20ºC in the range 71–94 days for IN-MM671, 16–36 days for IN MM986, and 21–76 days for IN-MM991.

Aquatic metabolism

The fate of proquinazid in aquatic systems was evaluated in studies with two different water/sediment systems at 20ºC under aerobic conditions, and a third water/sediment system under anaerobic conditions. In the systems under aerobic conditions, proquinazid dissipated rapidly from the water phase (DT50 = 0.13 and 0.23 days), but due to movement to sediment rather than degradation. In sediment, proquinazid degraded much more slowly (sediment DT50 = 191 and 38 days, whole system DT50 = 136 and 36.5 days). In the water/sediment system under anaerobic conditions, the DT50 from water was 2 days, and the DT50 from the total system was 61 days. The principal degradate in each case was IN-MM671 (maximum 71% AR in one of the aerobic systems), which was present predominantly in the sediment. Thus proquinazid can be classified as “slightly degradable” (DT50 in whole system 60–180 days) to “fairly degradable” (DT50 20–60 days) in water/sediment systems.

Mobility

Volatility

Studies with radiolabelled proquinazid under laboratory conditions indicate negligible volatility (< 0.4% AR) from soil, and ~14% AR volatilised from wheat plants.

Soil mobility

Laboratory batch equilibrium studies with proquinazid in four different soils indicated $K_{OC\ ads}$ values of 9091–16,769 mL/g, ie immobile in soil (K_{OC} > 5000). Similar evaluations for major metabolites indicated mean K_{OCads} values of 2286, 3051 and 452 mL/g for IN-MM671, IN-MM986 and IN-MM991, respectively – i.e. slight mobility (K_{OC} = 2000–5000) to medium mobility (K_{OC} = 150–500) in soil.

Field dissipation

The rate of degradation of proquinazid in field soils was determined at 8 sites in Europe. Applications were made to bare soil in the late spring to early summer. The soils covered a range of soil textures and soil pH, as well as geographic areas. The DT50 in field soils ranged from 5.5–70 days, while DT90 values ranged from 18–231 days. Additional rate of degradation data for the major soil metabolites were obtained from the field soil dissipation studies performed with proquinazid. In these field studies the maximum molar percent formation of each degradation product was also determined. IN-MM671 reached a maximum of 26.7% of applied (on a mass basis), with DT50 values from 29–394 days (calculated for 7 sites). IN-MM986 reached a maximum of 29.1% of applied, with DT50 values of 34–69 days (calculated for 3 sites). IN-MM991 formed in very small amounts (maximum 13.4% applied), and a rate of degradation could be determined in only one field study, where the DT50 was 54 days. Little or no movement of proquinazid or its major metabolites was detected below the second sampling layer (10–20 cm or 15–30 cm) at any of the field dissipation sites.

Bioaccumulation

Bioaccumulation studies with bluegill sunfish indicated whole fish bioconcentration factors (BCFs) of 821 for ^{14}C-proquinazid and 483 for ^{14}C-IN-MM671 (in both cases based on radiolabelled residues rather than measured test substance). The time to 95% depuration was 5.4–5.8 days for ^{14}C-proquinazid and ~4 days for ^{14}C-IN-MM671. Thus both the parent and metabolite can be classified as “moderately concentrating” (BCF in range 100–1000) in fish.

Soil accumulation

DT90 values for proquinazid in the field dissipation studies were all less than 1 year, therefore proquinazid is not expected to accumulate in soil. Field and laboratory studies indicate that metabolites IN-MM686 and IN-MM991 are not expected to accumulate, whereas IN-MM671 may do so. Calculations of soil concentrations after repeated annual use at the maximum proposed application rate were made, assuming the maximum observed formation percentage and slowest field dissipation rate for each metabolite. These indicated that at worst, IN-MM671 would accumulate to levels approximately double those after a single year of proquinazid use, with little or no accumulation for proquinazid and the other metabolites.

7.3 Environmental effects

In addition to proquinazid, the toxicity of the proposed 200 g ac/L EC formulation or similar formulations was evaluated. Toxicity of the major metabolites IN-MM671, IN-MM986 and IN-MM991 was also evaluated for a range of aquatic and terrestrial invertebrate species, while IN-MT884 was evaluated for daphnids only. Studies were generally conducted to standard test guidelines (eg OECD and US EPA).

Terrestrial vertebrates

Proquinazid is practically non-toxic to birds based on acute oral and short-term dietary toxicity studies (acute oral LD50 > 2250 mg ac/kg bw and > 2250 mg formulation/kg bw for bobwhite quail; 5 d dietary LC50 > 5620 ppm for both bobwhite quail and mallard duck). Reproduction studies indicated NOECs of 28 ppm diet for bobwhite quail and 85 ppm for mallard duck.

Proquinazid is also practically non-toxic to mammals (acute oral LD50 = 4846 mg ac/kg for female rats). The NOAEC for reproduction in rats was 600 ppm diet.

Aquatic organisms

Fish: Proquinazid is highly toxic to fish with acute exposure (96 h LC50 = 349 µg ac/L for rainbow trout, = 454 µg ac/L for bluegill sunfish and > 580 µg ac/L for sheepshead minnow). The formulation is moderately toxic to rainbow trout (96 h LC50 = 2.3 mg formulation/L). The most sensitive chronic exposure endpoints were 3 µg ac/L for rainbow trout in a 90 day early life stage study, and 8.72 µg ac/L for sheepshead minnow in a 36 day early life stage study.

The metabolite IN-MM671 is moderately toxic (96 h LC50 = 2.2 and 4.2 mg as [applied substance]/L) and IN-MM991 slightly toxic (96 h LC50 = 28.4 mg as/L) to fish with acute exposure, while IN-MM986 (96 h LC50 > 1.03 mg as/L, the concentration limit in test water) is at most moderately toxic.

Aquatic invertebrates: Proquinazid is highly toxic to aquatic invertebrates with acute exposure (48 h EC50 = 287 µg ac/L for *Daphnia magna*, 96 h LC50 = 110 µg ac/L for mysid shrimp, and 96 h EC50 = 219 µg ac/L for eastern oyster). The formulation is moderately toxic to *Daphnia magna* (48 h EC50 = 1.8 mg formulation/L). The most sensitive chronic exposure endpoints were 1.8 µg ac/L for *Daphnia magna* in a 21 day reproduction study, and 10.5 µg ac/L for mysid shrimp in a 28 day reproduction study.

The metabolite IN-MM671 is moderately toxic (48 h EC50 = 5.4 mg as/L) and IN-MT884 is practically non-toxic (48 h EC50 > 114 mg as/L) to daphnids with acute exposure. IN-MM986 is at most highly toxic (48 h EC50 > 0.791 mg as/L) and IN-MM991 at most slightly toxic (48 h EC50 > 48.5 mg as/L) to daphnids with acute exposure (both tested to the concentration limit in the test medium). In a 21 day reproduction study with *Daphnia magna*, the NOEC for IN-MM671 was 519 µg as/L.

Benthic invertebrates: In a 28 day test with proquinazid added to the water, the NOEC for both emergence and development of *Chironomus riparius* based on measured concentrations of proquinazid in the water phase at day 0 was 0.456 mg ac**/**L. The corresponding day 28 d concentration in dry sediment was 4.35 mg ac/kg.

Algae and aquatic plants: Results of studies indicate that proquinazid is highly toxic to the most sensitive algal/diatom species *Navicula pelliculosa* and *Skeletonema costatum* with acute exposure, using the 72 h duration EC50 for growth rate as the endpoint (72 h ErC50 = 360 and 330 µg ac/L, respectively). For the other algal species tested, the 72 h ErC50 was greater than the highest concentration tested (ie 140 and 740 µg ac/L for *Pseudokirchneriella subcapitata* and 884 µg ac/L for *Anabaena flos-aquae*, approaching the solubility limit in the test medium). The 7 d EC50 to the duckweed *Lemna gibba* was > 200 µg ac/L. The formulation is moderately toxic to *Pseudokirchneriella subcapitata* (72 h ErC50 = 2.5 and 3.3 mg

formulation/L). The metabolite IN-MM986 is moderately toxic (72 h ErC50 = 4.0 mg as/L) to algae with acute exposure. IN-MM671 and IN-MM991 (both tested to the concentration limit in the test medium) are at most highly toxic to this species of green algae (72 h ErC50 > 725 µg as/L and > 960 µg as/L, respectively).

Terrestrial invertebrates

Honey bees: Proquinazid active constituent and the 200 g ac/L EC formulation are very slightly toxic to bees by both acute oral and acute contact exposure (48 h acute oral LD50 > 125 µg ac/bee, 48 h acute contact LD50 > 197 µg ac/bee; 48 h acute oral LD50 > 99.7 µg formulation/bee, acute contact LD50 > 100 µg formulation/bee).

Predators and parasites: Tier 1 rate response laboratory studies were provided for four terrestrial invertebrate predators/parasites, where the insects/mites were exposed to spray and/or dried spray residues from proquinazid formulation in small enclosures (some tests used earlier formulations to that proposed, but all were 200 g ac/L EC formulations). The 7 d LR50 (mortality) and EC50 (reproduction) for the cereal aphid parasitoid wasp *Aphidius rhopalosiphi* were proquinazid application rates equivalent to 134 g ac/ha and 44.8 g ac/ha, respectively. The 7 d LR50 and EC50 (reproduction) for the predatory mite *Typhlodromus pyri* were 97.2 g ac/ha and 75–150 g ac/ha, respectively. The 14 d LR50 and EC50 (feeding activity) for the ground beetle *Poecilus cupreus* and the 28 d LR50 and EC50 (parasitism success) for the rove beetle *Aleochara bilineata* were all > 450 g ac/ha.

Tier 2 extended laboratory toxicity studies, where exposure occurred to fresh or field aged residues on field-treated plant material, were provided for *Aphidius rhopalosiphi*, the green lacewing (*Chrysoperla carnea*), a predatory bug (*Orius laevigatus*), and the seven-spotted ladybird (*Coccinella septempunctata*). To obtain the treated material, grapevines were treated with 200 g ac/L formulation at 75 g ac/ha at 14 day intervals on four occasions (*Aphidius*, *Chrysoperla* and *Orius*), or wheat plants treated with 200 g ac/L formulation at 50 g ac/ha on three occasions over the growth of the crop (*Aphidius* and *Coccinella*). For each species there were only minor differences in mortality, and reproduction was not statistically significantly different between the proquinazid treatment and control.

Field studies were conducted to examine effects on predatory mites in vineyards in Germany, France and Italy, with four applications at 14 day intervals of the 200 g ac/L EC formulation at 75 g ac/ha, ie corresponding to the maximum proposed use on grapevines in Australia. *Typhlodromus pyri* was the predominant predatory mite species at the German and French sites, whereas a range of predatory mite species was present at the Italian study site, most notably *Kampimodromus aberrans* and *Amblyseius andersoni*. At all sites the treatment regime had no statistically significant effect on predatory mite numbers (of adults and of nymphs) compared to the control. The maximum percentage reduction in adult mite numbers was 21% at the French and German sites, and 28% at the Italian site. By the end of the studies (28–31 days after the 4th application) predatory mite numbers in treated rows had recovered to similar (French and German) or higher (Italian) levels to those found in the control plots. However, at the Italian site the relative percentages of the different mite species changed in the proquinazid treated plots, relative to pre-treatment and post-treatment ratios in the control plots.

Earthworms: Proquinazid active constituent and the 200 g ac/L EC formulation proposed for DuPont Talendo® Fungicide are both very slightly toxic to the earthworm species *Eisenia foetida* (14 d LC50 > 1000 mg ac/kg dry soil [NOEC = 562 mg ac/kg soil] and > 1000 mg formulation /kg dry soil [NOEC = 562 mg

formulation/kg soil], nominal initial concentrations). Limit tests with the metabolites IN-MM671, IN-MM986 and IN-MM991 indicated 14 d LC50 values > 100 mg as/kg dry soil in each case (NOEC = 100 mg/kg soil). Earthworm reproduction studies produced NOECs of 256 mg formulation/kg dry soil for the 200 g ac/L formulation (50.9 mg ac/kg dry soil) and 25 mg as/kg dry soil for the metabolite IN-MM671. There were no statistically significant lethal or sublethal effects of an earlier 200 g ac/ha EC formulation on *Eisenia foetida* at the maximum field rate (75 g ac/ha) or maximum seasonal use rate (450 g ac/ha) applied in a laboratory simulation of field use.

Collembola: In a 28 day soil exposure laboratory study with IN-MM671 no significant mortality or reproductive effects compared to the control were observed at soil concentrations up to 50 mg as/kg dry soil (= NOEC). A marked reduction in the number of juveniles produced was evident at 100 mg as/kg dry soil.

Litterbag study: A report was submitted from a field study investigating the effects of proquinazid on the degradation of wheat straw contained in “litter-bags” buried in soil. The soil in the proquinazid plots was treated before and after placement of the bags with the 200 g ac/L EC formulation in a fashion intended to generate soil residues representative of ongoing use at the maximum proposed use rate in grapes (4 × 75 g ac/ha sprays, allowing for at least 50% interception by foliage). Two rates were used, calculated assuming proquinazid soil DT50 values of 80 or 207 days. The differences in straw decomposition between the higher rate (that for DT50 207 d) and the control over the 12 month study were less than 10% and were not statistically significant. Thus levels of proquinazid and the metabolites (including IN-MM671) encountered in the study did not affect organic matter breakdown by soil macro- and micro-organisms.

Microorganisms

Soil respiration and nitrogen turnover: The effects of proquinazid on soil non-target micro-organisms were examined in studies with the 200 g/L EC formulation. With soil concentrations of ~0.1 and 1 mg ac/kg soil dry weight (corresponding to application rates of 1× and 10× an application rate of 75 g ac/ha) deviations in carbon mineralisation and soil nitrogen transformation parameters from the control at the end of the test (28 days) were < 25%. Therefore proquinazid is categorised as low risk to soil microflora (NOEC = 0.994 mg ac/kg soil dry weight). Low risk to soil microflora was also indicated in studies with the metabolites IN-MM671, IN-MM986 and IN-MM991 at 0.67 mg metabolite/kg soil dry weight (equivalent to a soil surface application of 500 g metabolite/ha).

Sewage sludge organisms: An activated sludge, respiration inhibition test indicated < 10% inhibition from proquinazid concentrations up to 100 mg ac/L.

Terrestrial plants

A test indicated that a single application to 6 crop species of proquinazid at 70 g ac/ha (as an earlier 200 g ac/L EC formulation) had no harmful impacts on seedling emergence or early growth when applied pre-emergence to soil, nor on plant growth when applied to the foliage of young seedlings. A Tier I/Tier II study with the proposed formulation of proquinazid applied to seedlings of 6 crop/pasture species indicated a NOEL of 75 g ac/ha, based on relatively minor effects on onions at 150 and 225 g ac/ha. A non-guideline glasshouse study using the 200 g ac/L EC at 75 g ac/ha applied post-emergence found chlorosis in some species observed 7 and 21 days post application (up to 25% in onions and 34% in canola), but there were no

other herbicidal effects. Low phytotoxicity is further supported by data submitted as part of the efficacy package.

7.4 Risk assessment

DuPont Talendo® Fungicide will be applied by ground application only; therefore the risk assessment has considered application by orchard airblast sprayer. The maximum application rate for grapes using dilute spraying is 25 mL product/100 L water, which at a maximum anticipated spray volume of 1500 L/ha results in a rate of 75 g ac/ha. The label stipulates a maximum of 4 applications per year, with no more than 2 consecutive applications and a minimum spray interval of 14 d (for resistance management reasons). As a worst case, a maximum cumulative application rate of 300 g ac/ha was considered, with 4 applications at successive 14 day intervals.

An acceptable risk to birds and mammals with acute or chronic exposure was indicated, based on worst case scenarios where 100% of the diet was obtained from contaminated feed.

For aquatic exposure, predicted concentrations in water in a 15 cm deep, 3 m wide pond downwind of the treated area were compared to endpoints for acute and chronic exposure. These were, respectively, the mysid 96 h LC50 = 110 µg ac/L, and the daphnid 21 d NOEC = 1.8 µg ac/L. A risk to aquatic organisms was indicated with direct overspray on a single occasion, thus direct overspray must be avoided. Assuming a worst case DT50 for proquinazid from water of 2 days, very little accumulation in water was indicated with repeated spraying. Evaluation of spray drift to a 15 cm deep, 3 m wide pond downwind of the treated area indicated that the 15 m Downwind No-Spray Zone proposed on the draft label would provide adequate protection of aquatic organisms from acute or chronic exposure. For sediment-dwelling organisms, endpoints from the chironomid study (28 d NOEC = 0.456 mg ac/L in water phase, 4.35 mg ac/kg sediment weight) were compared to predicted concentrations in sediment in the pond, assuming all the applied proquinazid accumulated in the sediment, without degradation. This also indicated an acceptable risk with the proposed 15 m Downwind No-Spray Zone. Modelling also indicated that the risk to aquatic ecosystems from the run-off of proquinazid is acceptable for both the aquatic and sediment compartments.

The risk to bees from direct exposure to the spray during application to vineyards was found acceptable based on acute toxicity endpoints (acute oral LD50 > 125 µg ac/bee, acute contact LD50 > 197 µg ac/bee), and higher tier tests were not required. Tier II laboratory tests were available for various insect and mite predators and parasites, plus three field studies for predatory mites, all conducted under spray regimes corresponding with the proposed use on grapevines. Based on these studies, it is concluded that the risk to terrestrial invertebrate predators and parasites from the proposed use of proquinazid on grapevines is acceptable.

Comparison of worst case predicted soil concentrations with acute and chronic exposure endpoints for earthworms indicated an acceptable risk to earthworms with acute or chronic exposure to proquinazid or its metabolite IN-MM671 in soil, even after repeated long-term application. Comparison of predicted worst case concentrations of IN-MM671 in soil with the endpoint from a collembola study also indicated an acceptable risk. The litter bag study indicates that the risk to non-target soil macro-organisms and the breakdown of organic matter (from both the parent and its soil metabolites) is acceptable for the proposed use on vines. The risk to soil microorganisms from residues of proquinazid or its metabolites from the proposed use in

grapevines was also found acceptable, based on studies conducted with the proposed formulation and with the major metabolites.

According to standard guideline tests, the product applied at the maximum proposed single application rate for use on grapevines or just below that rate had no significant harmful effects on seedling emergence or early growth for a standard range of test species. Thus the risk to non-target terrestrial plants from direct spray or spray drift of DuPont Talendo® Fungicide is acceptable.

In considering the submitted data, DSEWPaC has given particular attention to the potential risk to soil and sediment organisms from accumulated residues of proquinazid or its major metabolites. The risk to aquatic and sediment-dwelling organisms is acceptable with the 15 m Downwind No-Spray Zone provided on the draft label. The risk assessment determined that the chemical is unlikely to pose an environmental risk under the proposed use pattern and with the proposed environmental protection statements on the draft label, provided some amendments are made to update the label to current requirements.

8 EFFICACY AND CROP SAFETY ASSESSMENT

The data provided covered seven trials conducted from 2003-2009 in traditional grape growing regions of VIC, SA and WA, and included commonly grown varieties such as Chardonnay, Cabernet Sauvignon and Shiraz. DuPont Talendo® Fungicide was compared to a number of fungicides registered for use in controlling Powdery Mildew infections in grape vines to determine its relative efficacy for controlling that disease.

Each supporting efficacy trial included at least four replications of all treatments, with each plot being a section of vine row varying from 5.4m (Yallingup WA) to 36m (Coldstream VIC). From this plot random vines and samples of leaves and bunches were selected, and subsequently assessed for visible expression of the disease (Powdery Mildew). Assessments were made on the basis of Powdery Mildew lesions on the leaves and bunches as a percentage score (0-100) of coverage of the surface under inspection (severity), and a percentage score (0-100) of the leaves and bunches showing some level of infection (incidence).

The treatments were applied to the grapes early after bud-burst, usually when the risk of Powdery Mildew infection was quite high, and then continued through until bunch closure. Spray volumes applied were consistent with the normal practice for the use of protectant fungicide use in grapes.

All assessment data from the trials was subject to ANOVA and LSD techniques to validate the reliability of the responses and to determine where significant differences existed between the various treatments. The data demonstrated that DuPont Talendo® Fungicide, applied at the proposed label rates, resulted in equivalent control of powdery mildew on leaves and bunches of grapes, as other fungicides currently registered for that use.

In the majority of the trials, the amount of active ingredient applied was increased over the growing season, by increasing the volume of liquid sprayed out, while keeping the rate constant for every 100L. This is sensible as it ensures that as the amount of vegetation or biomass increases, there is a concomitant increase in fungicide to protect that vegetation, by ensuring that the critical level of residual fungicide in or on the leaves is kept at a point that protects it from the pathogen.

In all trials and after all applications, the vines were assessed for any symptoms of phytotoxicity to the grape vines. There were no recorded incidences of any symptoms of damage to the foliage in these trials. It is assumed that DuPont Talendo® Fungicide is not phytotoxic or otherwise damaging to the grapevines or grapes.

The supporting data from efficacy trials demonstrate that DuPont Talendo® Fungicide is an effective control agent of powdery mildew, and its performance was equal to or slightly superior to all the standard control agents it was tested against. There were no instances of crop phytotoxicity or damage found with its use. The efficacy reviewer concluded that the conclusion is that DuPont Talendo® Fungicide should be an effective protectant fungicide for the purpose of control of powdery mildew in grapes when used according to the directions on the proposed product label relating to its use.

9 LABELLING REQUIREMENTS

POISON

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

DuPont™ Talendo®

fungicide

ACTIVE CONSTITUENT: 200 g/L PROQUINAZID

GROUP	13	FUNGICIDE

For the control of Powdery mildew in Grapes as per the Directions for Use

DIRECTIONS FOR USE
RESTRAINTS
DO NOT apply with aircraft.

SPRAY DRIFT RESTRAINTS
DO NOT apply with spray droplets smaller than a MEDIUM spray droplet size category according to nozzle manufacturer specifications that refer to the ASAE S572 Standard or the BCPC Guideline.
DO NOT apply during surface temperature inversion conditions at the application site.
DO NOT apply in vineyards when wind speed is less than 3 or more than 20 km per hour when measured 15 m outside of the vineyard on the upwind side.
DO NOT direct the spray above vines during airblast applications.
TURN OFF outward pointing nozzles at row ends and outer rows during airblast applications.
Users of this product MUST make an accurate written record of the details of each spray application within 24 hours following application and KEEP this record for a minimum of 2 years.
The spray application details that must be recorded are:

1. date with start and finish times of application;
2. location address and paddock/s sprayed;
3. full name of this product;
4. amount of product used per hectare and number of hectares applied to;
5. crop/situation and weed/pest;
6. wind speed and direction during application;
7. air temperature and relative humidity during application;
8. nozzle brand, type, spray angle, nozzle capacity and spray system pressure measured during application;
9. name and address of person applying this product.

(Additional record details may be required by the state or territory where this product is used.)
MANDATORY NO-SPRAY ZONES
DO NOT apply if there are aquatic and wetland areas including aquacultural ponds, surface streams and rivers within 15 m downwind from the application area.

ALL STATES

All rates are for dilute spraying. For concentrate spraying rates, refer to the Mixing/Application section. If using concentrate application, apply the same total amount of product to the target crop.

CROP	DISEASE	Rate	CRITICAL COMMENTS
Grapes	Powdery mildew (*Uncinula necator)*	**Dilute Spraying** 25 mL/100 L water	Use as a protectant treatment only. DuPont™ Talendo® fungicide has no curative activity and does not control existing infections (i.e. between infection and visible stage). Apply Talendo® fungicide at a minimum interval of 14 days. **DO NOT** apply more than three (3) applications to per crop in any one season. **DO NOT** apply more than two (2) consecutive sprays per crop, with a minimum spray interval of 14 days. Further treatments should be made with fungicides from a different fungicide group. Concentrated spray: **DO NOT** apply in water volumes less than 250 L/ha, or with a concentration factor greater than 4X. This low water volume is dependent on the suitability of concentrated spray application equipment. More reliable application may be gained through increased water volumes.
		Concentrate Spraying: Refer to the Mixing/Application Section	

DuPont™ Talendo® is a foliar applied protectant fungicide that has only preventative action. DuPont™ Talendo® fungicide has the ability to volatilise and be reabsorbed on to new untreated plant tissue. Protection is not limited to the plant tissue to which it is applied.

WITHHOLDING PERIOD:
GRAPES: DO NOT HARVEST FOR 28 DAYS AFTER APPLICATION.

GRAPES FOR EXPORT WINE: REFER TO THE AWRI WINEGRID

EXPORT OF TREATED PRODUCT
Table grape growers should note that suitable Maximum Residue Levels (MRLs) or import tolerances may not be established in all markets for table grapes treated with Talendo® fungicide. If you are growing table grapes for export, please check with DuPont for the latest information on MRLs and export tolerances before using this product.

GENERAL INSTRUCTIONS
DuPont™ Talendo® fungicide is an emulsifiable concentrate containing 200 g/L proquinazid for the control of grape powdery mildew. Proquinazid is a new quinazolinone fungicide with a novel mode of action; it acts preventively on grape powdery mildew by inhibiting spore germination and appressorium formation.

GROUP	13	FUNGICIDE

FUNGICIDE RESISTANCE WARNING
DuPont™ Talendo® is a member of the Quinazolinone group of fungicides. For resistance management the product is a Group 13 fungicide.
Some naturally occurring individual fungi resistant to Group 13 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungal population if these fungicides are used repeatedly. These resistant fungi will not be controlled this product or other Group 13 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, DuPont accepts no liability for any losses that may result from the failure of this product to control resistant fungi.

Mixing Instructions:
Ensure the spraying equipment is clean and properly calibrated prior to application. DuPont™ Talendo® mixes easily with water and should be added directly to the spray tank during filling. Washout container and add washings to the spray tank. Continue agitation until spraying is complete.

Mixing Order
The mixing sequence recommended is: water soluble bags, dry flowable or water dispersible granules, wettable powders, water based suspension concentrates, water soluble concentrates, oil based suspension concentrates, emulsifiable concentrates such as Talendo® fungicide, soluble fertilisers.

Ground application
Use a sprayer fitted with high flow rate nozzles to apply the highest practical spray volume. Nozzles with higher rated flows produce larger droplets. Use the lower spray pressures recommended for the nozzle. Higher pressure reduces droplet size, DOES NOT improve canopy penetration and may increase drift potential. WHEN HIGHER FLOW RATES ARE NEEDED, USE A HIGHER-CAPACITY NOZZLE INSTEAD OF INCREASING PRESSURE. Use a nozzle type that is designed for the intended application. With most nozzle types, narrower spray angles produce larger droplets. Consider using low-drift nozzles.
Use a sprayer designed to apply high volumes of water up to the point of run-off and matched to the crop being sprayed.
Set up and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient water to cover the crop to the point of runoff. Avoid excessive run-off.
The required water volume may be determined by applying different test volumes, using different settings on the sprayer, from industry guidelines or expert advice.

Add the amount of product specified in the Directions for Use table for each 100 L of water. Spray to the point of run-off.
The required dilute spray volume will change and the sprayer set up and operation may also need to be changed, as the crop grows.
Always apply sufficient water to cover the crop to the point of runoff, otherwise under dosing will occur and disease control may be inadequate.

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

Example Only
Dilute spray as determined above: For example 1500 L/ha
Your chosen concentrate spray volume: For example 500 L/ha
The concentration factor in this example is 3X (i.e 1500 L ÷ 500 L = 3)
If the dilute label rate is 25 mL/100 L, then the concentrate rate becomes 3 x 25, that is 75 mL/100 L of concentrate spray.
The chosen spray volume, amount of product per 100 L of water, and the sprayer set up and operation may need to be changed as the crop grows.
For further technical information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow Industry Best Practices.

Wetting Agents
Not required

COMPATIBILITY

DuPont™ Talendo® fungicide can be tank mixed with most fungicides and insecticides used in grapes, such as:

Fungicides: Kocide® Opti™, Kocide® Blue Xtra™, mancozeb, Rubigan*, boscalid, pyrimthanil.

Insecticides: Avatar®, formulations containing *Bacillius thuringiensis*.

However, since the formulations of products are always changing, it is advisable to test the physical compatibility of desired tank mixes and check for adverse effects like settling out or flocculation. To determine the physical compatibility, add the recommended proportions of the tank mix products to water, mix thoroughly and allow to stand for 20 minutes. If the combination remains mixed, or can be re-mixed readily, it is considered physically compatible.

The crop safety of all potential tank-mixes, including additives and other pesticides, on all crops has not been tested. Before applying any tank-mixture not specifically recommended on this label or other DuPont supplemental labelling, the safety to the target crop must be confirmed. To test for crop safety, apply the combination to a small area of the target crop in accordance with the label instructions to ensure that a phytotoxic response will not occur.

RAINFASTNESS
DuPont™ Talendo® is rainfast two hours after application.

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

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

Very toxic to aquatic life. **DO NOT** contaminate streams, rivers or watercourses with this product or used containers.

STORAGE AND DISPOSAL

Store in the closed, original container in a cool, well-ventilated area. **DO NOT** store for prolonged periods in direct sunlight.

Triple rinse containers before disposal. Add rinsings to spray tank. **DO NOT** dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and deliver empty packaging for appropriate disposal to an approved waste management facility. If an approved waste management facility is not available bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots, in compliance with relevant Local, State or Territory government regulations. **DO NOT** burn empty containers or product.

SAFETY DIRECTIONS

Will irritate the nose and throat. Will damage the eyes and skin.
Avoid contact with eyes and skin. **DO NOT** inhale vapour. If product on skin, immediately wash the area with soap and water.
If product in eyes, wash it out immediately with water. If clothing is contaminated with product, remove clothing immediately.
When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist and a washable hat, elbow-length chemical resistant gloves, face shield or goggles and a disposable fume face mask covering mouth and nose.
When using prepared spray (airblast) wear cotton overalls buttoned to the neck and wrists.
Wash hands after use. After each day's use, wash gloves, face shield or goggles, and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26.

IN A MEDICAL EMERGENCY CALL
1800 674 415 All hours

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet available from www.cropprotection.dupont.com.au.

NOTICE TO BUYER

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ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute reference dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EUP	End Use Product
EVOH	Ethylene Vinyl Alcohol Polymer
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GI	Gastro-Intestinal
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare

Hct	Heamatocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
ng	nanogram
NHMRC	National Health and Medical Research Council
NOAEL	No Observable Adverse Effect Concentration Level
NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon

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

GLOSSARY

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

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