Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of Penthiopyrad in the new Product DuPont™ Fontelis® Fungicide

APVMA Product Number 65100

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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™ Fontelis® Fungicide** should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of **public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade,** and **efficacy and target crop or animal safety**. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **28 September 2012** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- Contact name
- Company or group name (if relevant)
- Email or postal address (if available)
- The date you made the submission.

All personal information, and confidential information judged by the APVMA to be ***confidential commercial information (CCI)***[1] contained in submissions will be treated confidentially.

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

Contact Officer
Pesticides Program
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

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

Phone: 02 6210 4748
Fax: 02 6210 4776
Email: pesticides@apvma.gov.au

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

DuPont (Australia) Pty Limited applied to the APVMA for approval of the new active constituent penthiopyrad and the registration of the new product DuPont™ Fontelis® Fungicide.

Penthiopyrad is a broad spectrum fungicide with preventative, curative and locally systemic activity. It controls foliar and soil-borne fungal diseases, acting by stopping spore germination, and inhibiting mycelium growth and sporulation.

It is proposed to register DuPont™ Fontelis® Fungicide, containing 200g/L penthiopyrad as a suspension concentrate in a wide range of fruit and vegetable crops, including strawberries, pome fruit, stone fruits, tree nuts, bulb vegetables, brassicas, cucurbits, leafy vegetables, bulb vegetables, root vegetables and non-cucurbitaceous fruiting vegetables. It is intended for the control of various fungal diseases including botrytis, powdery mildew, various scab diseases, rots, gummy stem blight, white mould and blights. Application rates are 1.0 -1.75 L/ha in water to a spray volume of 1000 L/ha using a conventional ground boom sprayer with either mechanical or by-pass agitation or by air-blast application. It is applied to crops up to three times as part of either a preventative or curative programme.

Fontelis® will be imported fully formulated and be available in 50-100ml, 150-250mL, 500ml, 1L, 3L and 5L pack sizes

Penthiopyrad belongs to the pyrazole caboxamide fungicide chemical group. The Fungicides Resistance Action Committee (FRAC), a specialist technical group of CropLife International, has classified penthiopyrad's pesticidal mode of action as inhibition of succinate dehydrogenase in complex II of the mitochondrial respiratory chain, resulting in inhibition of spore germination, germ tubes and mycelial growth. CropLife Australia's Fungicide Resistance Management Review Group has designated penthipyrad as a Group 7 fungicide. The proposed use pattern is subject to a CropLife anti-resistance strategy. Restraints included on the proposed label are consistent with the current CropLife Australia resistance management strategy for Group 7 fungicides.

Penthiopyrad and DuPont™ Fontelis® Fungicide are currently registered for use in the USA, Canada and New Zealand.

This submission has been assessed under a joint review/ workshare arrangement where registrations for the same formulations and uses have been submitted concurrently in Canada, USA, the EC and Australia

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of DuPont™ Fontelis® Fungicide, and approval of the new active constituent, penthiopyrad.

2 CHEMISTRY AND MANUFACTURE

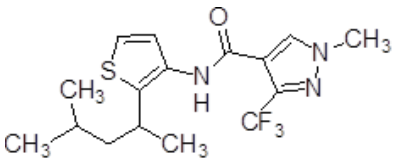
2.1 Active Constituent

Penthiopyrad is a new active constituent that inhibits mitochondrial function by disrupting complex II (succinate dehydrogenase) in the respiratory electron transport chain. It is to be used as a foliar spray for the control of fungal diseases in berries, pome fruit, stone fruits, tree nuts, bulb vegetables, brassica vegetables, cucurbit vegetables, fruiting vegetables, leafy vegetables, legumes, peanuts and root and tuber vegetables.

Sites of Manufacturing

FORMULATORS	STREET ADDRESS
1. DuPont de Nemours (France) S.A.I	DuPont de Nemours (France) S.A.I, Agricultural Products, 82, rue de Writtelsheim, BP9, F-68701 Cernay Cedex, France
2. E.I.du Pont de Nemours and Company	Valdosta manufacturing Center, 2509 Rocky Ford Road, Valdosta, GA 31601 USA
3. DuPont Brazil Ltda	Rodovia Presidente Duta, KM 280/A 27365-000, Barra Mansa-Rio De Janeiro, Brazil
4. E.I. DuPont India Pvt. Ltd.	Plot No. 11, G.I.D.C. Savli, Manjusar Distt: Vadodara, Gujarat, India

Chemical Characteristics of the Active Constituent

COMMON NAME (ISO):	Penthiopyrad
IUPAC NAME:	(*RS*)-*N*-[2-(1,3-dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide
CAS NAME:	*N*-[2-(1,3-dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide
CAS REGISTRY NUMBER:	183675-82-3
MANUFACTURER'S CODE:	MTF-753
MOLECULAR FORMULA:	$C1_6H_{20}F_3N3OS$
MOLECULAR WEIGHT:	359.4
STRUCTURE:	
PHYSICAL FORM:	Solid (crystalline)
COLOUR:	White
ODOUR:	None
MELTING POINT:	108.7°C
DENSITY:	1.256 g/ml (at 20°C)
WATER SOLUBILITY AT pH 7	1.375 mg/L
SOLUBILITY IN ORGANIC SOLVENTS:	Acetone: 557 g/L Dichloromethane: 531 g/L Ethyl acetate: 349 g/L Methanol: 402 g/L Ethanol: 234.5 g/L Xylene 42.7 g/L Toluene: 67.0 g/L n-Hexane: 0.75 g/L
PARTITION COEFFICIENTS (N-OCTANOL/WATER):	log P_{OW} = 4.36 at pH 4 log P_{OW} = 4.62 at pH 7 log P_{OW} = 4.54 at pH 10
VAPOUR PRESSURE AT 20°C:	2.96×10^{-6} Pa

APVMA Active Constituent Standard for Penthiopyrad Active Constituent

CONSTITUENT	SPECIFICATION	LEVEL
Penthiopyrad	White solid	Not less than 976 g/kg

2.2 Product

DuPont™ Fontelis® Fungicide

DISTINGUISHING NAME:	DuPont™ Fontelis® Fungicide
FORMULATION TYPE:	Suspension Concentrate (SC)
ACTIVE CONSTITUENT CONCENTRATION:	Penthipyrad 200 g/L

Physical and Chemical Properties of DuPont™ Fontelis® Fungicide

PHYSICAL FORM:	Liquid
COLOUR:	Off white
ODOUR:	Faint, ester-like
DENSITY:	0.9789 g/mL
PH (1% DILUTION):	pH 6.6
VISCSITY (BROOKFIELD,SPINDLE H1):	770.7 centipoise (mPas) at 30 rpms 505 centipoise at 80 rpms 425.5 centipoise at 135 rpms
FLASH POINT:	>105^{o}C
FLAMMABILITY:	Not flammable
EXPLOSIVE PROPERTIES:	Not explosive
OXIDISING PROPERTIES:	No oxidising properties
CORROSIVE HAZARD:	Not applicable
DIELECTRIC BREAKDOWN VOLTAGE:	Not applicable, formulation is not intended for use around electrical equipment
DANGEROUS GOODS CLASSIFICATION:	Not dangerous according to the Australian Code of Transport of Dangerous Goods by Road and Rail

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

Public Health Aspects & Toxicology

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

Penthiopyrad is a pyrazole carboxamide fungicide. The product, DuPont Fontelis Fungicide a suspension concentrate formulation containing 200 g/L penthiopyrad, is a fungicidal agent to be used to control fungal diseases in berries, pome fruit, stone fruits, tree nuts, bulb vegetables, bassica vegetables, cucurbit vegetables, fruiting vegetables, leafy vegetables, legumes, peanuts and root and tuber vegetables. The product will be in available in 50-100mL, 150-200mL, 500mL, 1L, 3L and 5L high-density polyethylene (HDPE) bottles with a screw cap. Application rates are 1.0 – 1.75 L/ha in water to a spray volume of 1000 L/ha using a conventional ground boom sprayer with either mechanical or by-pass agitation or by air-blast application. It is applied to crops up to three times per crop as part of either a preventative or curative program.

The submitted studies on the active constituent in rats showed that it is extensively and rapidly absorbed by the oral route (>83%) and excreted rapidly. The total absorbable dose *in vitro* for rat and human skin was 53% and 19% respectively. Penthiopyrad is of low acute oral, dermal and inhalational toxicity in rats. It was a not a skin irritant in rabbits but was considered a slight eye irritant in the same species. It was not a skin sensitiser in guinea pigs. In repeat dose studies, liver toxicity was common in mice, rats and dogs, with thyroid toxicity also observed in mice and rats. There were findings of an increased incidence of thyroid follicular epithelial adenomas in male rats, and hepatocellular carcinomas in male mice. Overall, OCS considers that the weak induction of thyroid follicular epithelial adenomas in male rats occurred via thyroid hormone pertubations and that the observed tumours are of limited relevance to humans. The OCS concluded that that the observed hepatocellular tumours probably occurred by a phenobarbital-like MOA, noting the questionable minimal incidence of hepatocellular carcinomas only in one sex, it is considered that the findings demonstrate a weak carcinogenic potential that is of limited relevance to humans. Consequently, penthiopyrad is not considered to be a carcinogenic hazard to humans.

Penthiopyrad was not a reproductive or developmental toxicant, and tested negative *in vitro* and *in vivo* in a battery of mutagenicity and/or genotoxicity studies. Additionally, the available data was not considered to demonstrate a neurotoxic or immunotoxic potential.

The product DuPont Fontelis Fungicide is of low acute oral, dermal and inhalational toxicity in rats. It is not a skin or eye irritant in rabbits nor a skin sensitiser in guinea pigs and mice.

Occupational Health and Safety

The main occupational use of the imported product will be by farmers and their workers. Workers may be exposed to the product when opening containers, mixing/loading, application, and cleaning up spills and equipment. The main route of exposure to the product will be dermal with inhalation exposure from the spray also possible.

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide was used to estimate exposure. Exposure to the product during mixing and loading and both ground boom and air-blast application were at an acceptable level when a single layer of clothing (cotton overalls or equivalent clothing) was worn with or without gloves.

Based on the risk assessment, a First Aid Instruction and Safety Directions have been recommended for the product label.

Conclusion

Based on an assessment of the toxicology, it was considered that there should be no adverse effects on human health from the use of DuPont Fontelis Fungicide when used in accordance with the label directions.

3.2 Evaluation of Toxicology

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

The toxicology assessment of penthiopyrad was conducted as part of a Global Joint Review (GJR) between scientists from the United States Environmental Protection Agency (US EPA), Health Canada Pest Management Regulatory Agency (PMRA), the United Kingdom Chemical Regulation Directorate (CRD) and the Office of Chemical Safety (OCS) within the Department of Health and Ageing. Since the assessment report relies significantly on international assessment collaboration between the agency partners, the OCS has adopted the NOAEL and LOAEL approach with scientific justification for the adoption of these NOAEL/LOAEL positions.

Chemical class

Penthiopyrad is a pyrazole carboxamide fungicide. The mode of pesticidal action is inhibition of succinate dehydrogenase in complex II of the mitochondrial respiratory chain, resulting in inhibition of spore germination, germ tubes, and mycelial growth.

Toxicokinetics/metabolism

Single and multiple dose oral absorption, distribution, metabolism and excretion of penthiopyrad have been evaluated in the Wistar rat. The single dose pharmacokinetic profile has also been investigated. A pilot single dose study at dose levels of 10 or 100 mg/kg bw was performed to provide preliminary information on the pharmacokinetics and routes of elimination. Only data to support the non-collection of respired volatiles and CO_2 in the pilot study is summarised in this section because the pilot study data on pharmacokinetic profile and routes of excretion were in agreement with the data from the main study.

Single orally administered doses of 10 or 100 mg/kg bw penthiopyrad in aqueous dispersion are rapidly (T_{max} values: 0.4 - 1.3hr) and extensively absorbed (> 83% AD) from the GI tract of the Wistar rat. The relative systemic exposure was dose-dependent in the range 10 - 100 mg/kg bw, as determined by the C_{max} and AUC ratios. Penthiopyrad was rapidly and widely distributed to body tissues with maximum tissue concentrations achieved within 1 hour of dosing, at which time, the concentrations in liver, fat, lymph nodes, adrenals, pancreas, kidneys and urinary bladder and GI tract are higher than those in plasma.

Extensive *in vivo* metabolism in the Wistar rat occurred at numerous positions within the molecule by thienyl ring oxidation and conjugation with glutathione, N-demethylation, alkyl side-chain hydroxylation, and oxidation to carboxylic acids, glucuronidation, thienyl ring opening and cleavage of the two ring structures. The most abundant metabolite in both urine and faeces was formed as the result of N-demethylation and oxidation of the terminal methyl moiety of the alkyl side chain to carboxylic acid. The intermediate demethylated and hydroxylated metabolites formed glucuronic acid conjugates that were mainly recovered in bile. The most abundant metabolites in bile were formed as a result of thienyl ring oxidation to 753-F-DO followed by conjugation with glutathione and catabolism of glutathione. N-demethylation and side chain hydroxylation probably occurred in parallel. Four metabolites containing the pyrazole moiety following cleavage from the thienyl moiety were excreted in both urine and faeces. The two acids (PCA and DM-PCA) are likely formed by amide hydrolysis from PAM and DM-PAM. The thienyl ring appears to be completely degraded and the radiocarbon incorporated into normal metabolic processes.

Excretion of penthiopyrad in Wistar rats is dose-independent and proceeded rapidly (74 – 85% of the administered dose), predominantly in bile but with appreciable amounts excreted in urine (5.0 - 22% of the administered dose). Excretion in faeces and urine was essentially complete within 48 hours after dosing. Elimination of penthiopyrad via respired volatiles and CO_2 was negligible. Residual tissue and carcass levels were very low at ≤0.10% and ≤0.41% of the administered dose, respectively. There were no clear sex- or dose-related differences in the extent of absorption or elimination, although C_{max} and AUC tended to be slightly higher in females than males. Similarly, there was no sex or dose-related differences in tissue distribution, tissue residues and the route and rate of elimination in Wistar rats.

The extent of oral absorption in Wistar rats was not affected by repeated dosing for up to 7 days, based on the consistency of the urinary and faecal excretion patterns after one, four and seven doses. Faecal excretion predominated (71.8 and 65.0% of the administered dose in males and females, respectively) and elimination was rapid and essentially complete within 48 hours of the final dose. Repeated dosing lead to a small increase of residues in adrenals, blood, fat, kidney, liver, lung, lymph nodes, ovaries, pancreas and thyroid compared to a single dose. In the plasma, radioactivity plateaued at up to 3.3 times the single dose value but subsequently cleared to levels below the limit of detection within 48 hours of the final dose. Concentrations of radioactivity decreased in all tissues after cessation of dosing. Four days after the last dose, the mean residues in the GI tract and its contents were 0.03% of the administered dose for both sexes, and mean carcass residues were 0.23 and 0.19% of the administered dose for males and females respectively. There was no evidence of the induction of specific metabolic processes following repeat dosing and there was no significant impact on the levels of major or minor metabolites following multiple dosing.

The only reliable dermal absorption data was from an *in vitro* study using rat and human skin. For penthiopyrad dilution to a field application concentration, the total absorbable dose at 24 hours post-treatment, calculated to include radioactivity from tape strips was 53% and 19% for rat and human skin, respectively. The *in vitro* value of 19% for human skin was considered appropriate for risk assessment purposes.

Acute toxicity studies

Penthiopyrad exhibits low acute oral and dermal toxicity in rats (LD_{50} values > 2,000 mg/kg bw). No deaths, adverse clinical signs or gross lesions at necropsy occurred following single oral or dermal doses of 2,000 mg/kg bw. Similarly, penthiopyrad is not acutely toxic to rats (4-hour LC_{50} value > 5.59 mg/L air) by nose-only inhalation exposure to aerosolized, respirable (MMAD ± GSD: 2.71 µm ± 2.96), dust particles. No deaths occurred at this exposure concentration. Transient decreased activity, hunched posture, ruffled fur and slight weight loss occurred after exposure, but persisted only to day 2. Penthiopyrad did not elicit a primary skin irritant response in any of the rabbits tested though it is a slight irritant to the eyes of rabbits. Penthiopyrad was not a skin sensitiser in the guinea pig maximization test.

Systemic effects

The oral short-term toxicity of penthiopyrad has been evaluated in 28-day and 13-week oral tstudies in the rat, mouse and dog, and a 28-day dermal study in the rat.

The liver was a common target organ in all 3 species after 28 days or 13 weeks treatment, but the thyroid gland in mice and the adrenal gland in dogs, were also target organs after 13 weeks treatment. After 28 days treatment, increased liver weight, associated with diffuse hepatocellular hypertrophy, was evident in mice and dogs, but increased liver weight in the rat was associated with micro/macro-vesicular fatty change and Kupffer cell proliferation. Increased plasma/serum concentrations of cholesterol and/or phospholipids, or triglycerides occurred in all species, and this finding may reflect adaptive changes in hepatic fat storage or transport. The dog also showed slight mucosal oedema in the gall bladder, and the rat showed reduced plasma bilirubin concentrations after 28 days treatment but there was no evidence of a cholestatic etiology.

In addition to diffuse hepatocellular hypertrophy, treatment for 13 weeks revealed further target organs in mice and dogs. Increased thyroid weight was evident in both mice and female dogs, but a histological correlate of follicular epithelial hypertrophy occurred only in mice. Adrenal cortical hypertrophy and cholecystitis in the gall bladder, associated with increased plasma bilirubin concentration, occurred in dogs treated at 811 / 864 mg/kg bw/d. In the rat, histomorphological lesions in the liver extended to enlargement, hypertrophy, hepatocellular degeneration and Kupffer cell proliferation after 13 weeks. Reduced plasma bilirubin concentrations were evident in the rat after 13-weeks of treatment.

Haematological perturbations also occurred at high dose levels in all three species after 28 and/or 90 days treatment and in the dog after 52 weeks. However, the changes occurred at high dose levels and were very mild and frequently did not present a consistent picture of anaemia.

Male rats treated at dose levels ≥ 100 mg/kg bw/d showed significantly decreased motor activity during a quantitative assessment. However, there were no effects at dose levels up to 663 mg/kg bw/d on a battery of functional observations performed towards the end of the 13-week treatment period.

In the 28-day dietary studies, a NOAEL of 142/149 mg/kg bw/d (males/females) was identified in the rat based on the occurrence of a dose related altered serum clinical chemistry and decreased body weight. A NOAEL of 100 mg/kg bw/d was identified in male mice based on increased plasma triglyceride concentration, reduced A/G ratio and increased liver weight, while a NOAEL of 330 mg/kg bw/d was identified in male mice based on increased relative and absolute liver weight. In dogs, a NOAEL of 27.1/29.1 mg/kg bw/d (males/females) was identified based on slight mucosal oedema of the gall bladder.

In a 4-week dermal study in the rat, a NOAEL of 1000 mg/kg bw/d was identified in both sexes based on the absence of local and systemic adverse findings at the top dose level administered.

In the 90-day dietary studies, a NOAEL of 40 mg/kg bw/d (males/females) was identified in the rat based on the occurrence of increased liver weight, along with histopathological alterations in the liver and haematological and clinical chemistry perturbations. A NOAEL of 100/102 mg/kg bw/d (males/females) was identified in mice based on the occurrence of increased BUN concentration and decreased body weight gains in males only and increased relative liver weight in both sexes. In dogs, a NOAEL of 76.7/80.9 mg/kg bw/d (males/females) was identified based on the occurrence of reduced body weight gain, clinical indicators of hepatic dysfunction, and histopathological alterations in the liver, gall bladder and adrenal gland.

Chronic toxicity & Carcinogenicity

Four long-term toxicity studies have been performed on penthiopyrad, a dog 52-week dietary study, a rat 52-week dietary toxicity study, and a 104-week and 78-week oncogenicity studies in the rat and the mouse, respectively. Three non-guideline studies have been undertaken to investigate the thyroid follicular cell proliferation potential of penthiopyrad in rats and hepatic enzyme induction potential in rats and mice. The investigative studies were designed to provide evidence to support the contention that excess incidences of thyroid adenoma in male rats and hepatic adenomas in male mice had non-genotoxic etiologies based on threshold mechanisms of action.

In the rat 52-week dietary study, very mild haematological perturbations occurred at 400 mg/kg bw/day comprising reduced haemoglobin concentration and red cell indices (MCV, MCH, MCHC). Since the effects

were minimal (≤ 5.6% lower than control values) and there was no evidence of reduced RBC counts or increased reticulocyte counts, they did not suggest anaemia and therefore are considered not to be biologically relevant. The liver, adrenal, thyroid gland and ovary were identified as target organs. Increased prothrombin time at 400 mg/kg/day and increased plasma enzyme activities and lipid concentrations at 100 or 400 mg/kg/day were suggestive of hepatic dysfunction. These effects occurred in the presence of increased liver weight and hepatocyte hypertrophy in both sexes, and periportal fat vacuolation, cell swelling and single cell necrosis in male rats only. Adrenal cortical lipid vacuolation and hypertrophy of the zona glomerulosa, diffuse follicular hypertrophy in the thyroid and ovarian interstitial cell hypertrophy were also apparent. The occurrence of reduced plasma bilirubin concentrations, consistent with a similar finding in the 28-day and 13-week studies, was considered not to be an adverse effect since there was no histological evidence of cholestasis.

A NOAEL of 25 mg/kg bw/day was identified in the rat 52-week dietary study for both sexes based on the occurrence of altered plasma chemistry profile, increased liver weight and histopathological alterations in the adrenal glands. In the dog 52-week dietary study, a NOAEL of 54.4/56/6 mg/kg bw/day was identified based on the occurrence of reduced body weight and body weight gain, haematological alterations, clinical indicators of hepatic dysfunction, and histopathological alterations in the liver, gall bladder and adrenal gland accompanied by increased organ weights.

In addition to liver, adrenal, thyroid and ovary effects identified in 13 and/or 52-week studies, further non-neoplastic effects seen in the rat 104-week study comprised increased incidences of alveolar macrophages and interstitial inflammation in the lungs of females and chronic progressive nephropathy in males.

The numbers of rats with neoplasms, the multiplicity of tumours and the latency period for tumour formation did not distinguish treated animals from the controls. There were no excess incidences of neoplasia in any tissue, with the exception of the male thyroid in which the incidence of follicular adenoma was slightly, but significantly, increased in males at the highest dose level, 250 mg/kg bw/day, surviving to termination. The incidence of follicular carcinoma was unaffected by treatment.

In the 78-week mouse carcinogenicity study, the lung was identified as a target organ for non-neoplastic alterations in which an increased incidence of alveolar foamy cells occurred at the highest dose level only (600 mg/kg bw/day). The thyroid follicular epithelial hypertrophy noted after 13 weeks of treatment was accompanied by further changes comprising altered colloid and lipofuscin deposits. Marked hepatomegaly at dose levels of 200 or 600 mg/kg bw/day was accompanied by increased incidences of hepatocellular adenoma, and adenoma + carcinoma in male mice surviving to termination.

Mechanistic studies – thyroid tumours

Two mechanistic studies were performed in the rat to investigate the effects of penthiopyrad on hepatic drug metabolising enzymes and cell proliferation. Enhanced hepatic cell proliferation was observed, as measured by PCNA immunohistochemical staining, during the early stages of treatment, and hepatic microsomal cytochrome P450 isozymes, peroxidase and UDP-glucuronososyltransferase (UDPGT) activities were increased, although the effect of penthiopyrad was milder than that of phenobarbital as a reference substance. Centrilobular hepatocellular hypertrophy and proliferation of smooth endoplasmic reticulum, as visualised under light and electron microscopy, respectively, also occurred in response to penthiopyrad, but it had no apparent effect on hepatic cell-to-cell communication as measured by the enumeration of gap

junction Cx32 protein spots. Enlarged liver in some animals and increased microsomal CYP4A1 activity occurred in response to 1000 ppm penthiopyrad, but there were no effects of treatment on any parameter at 100 ppm.

In the second study in the rat, penthiopyrad at dietary concentrations of 4000 and/or 16000 ppm elicited a pattern of effects comprising hepatocellular hypertrophy, increased liver weight, increased hepatic cytochrome P_{450} and UDPGT activities, reduced circulating thyroxine (T4) activity, up-regulation of the pituitary Prop-1 gene, increased plasma TSH activity, increased thyroid follicular cell proliferation, and thyroid follicular cell hypertrophy. The effects of treatment were fully reversible on withdrawal of treatment for 28 days. Based on these results it was postulated that penthiopyrad is a hepatic UDPGT inducer which enhances biliary excretion of T4, thereby lowering circulating T4 levels, which results in an increase in circulating TSH through negative feedback leading to thyroid follicular cell hypertrophy. Furthermore, prolonged follicular cell hypertrophy under the influence of increased TSH is considered to be a rational, non-genotoxic basis for the development of a slightly increased number of thyroid adenomas in the 104-week study. In addition, it is concluded that the effects of penthiopyrad on thyroid function, and thus on neoplasia in the long-term study, have a threshold below which thyroid neoplasia will not occur.

Furthermore, there are several important physiological and biochemical differences between rats and humans relating to thyroid function. The rat has a smaller reserve capacity of thyroid hormones and the half-life of T4 is very much shorter in rats than humans due to protein binding of T4 in humans. Inherent TSH levels in rats are markedly higher than in humans. Thus, humans are quantitatively less sensitive than rats to chemicals that reduce T4 and lead to increased TSH, and there is no increased risk of thyroid neoplasia if TSH is not increased. Further, there is no clear evidence that chemicals that reduce thyroid hormone levels in humans also increase susceptibility to thyroid neoplasia.

Thus, while noting the degree of uncertainty in relation to the apparent absence of thyroid follicular hyperplasia in the rodent database for penthiopyrad, the key biochemical events of induction of hepatic UDPGT activity, reduced circulating T4 and increased circulating TSH have all been shown to occur in response to penthiopyrad treatment, and the reversibility of these findings was observed following cessation of treatment. Furthermore, humans are considerably less susceptible to disruption of thyroid homeostasis leading to thyroid neoplasia than rats. Consequently, overall, OCS considers that the weak induction of thyroid follicular epithelial adenomas in male rats occurred by the postulated MOA (thyroid hormone pertubations) and that the observed tumours are of limited relevance to humans.

Mechanistic studies – liver tumours

A mechanistic study was performed in the mouse to investigate the effects of penthiopyrad on hepatic drug metabolising enzymes and cell proliferation in order to support a putative mechanism for the low incidence of hepatocellular adenoma reported in this species. The effects of penthiopyrad were compared with the effects of an established hepatic enzyme-inducer, phenobarbital. Phenobarbital administration produced a pattern of effects comprising increases in liver weight, microsomal protein and P_{450} content, microsomal ethoxycoumarin O-dealkylase (ECOD) and pentoxyresorufin O-dealkylase (PROD) activities, hepatic P_{450} Cyp1A, 2B and 3A isozyme content and hepatic BrdU labelling index, associated with histological evidence of centrilobular hepatic hypertrophy. A similar pattern of effects occurred in response to 600 mg/kg bw/day penthiopyrad, with the exception of increased microsomal protein content. Microsomal P_{450} content, specific

enzyme activities and hepatic P_{450} isozyme content were also increased in response to 200 mg/kg bw/day penthiopyrad, but to a lesser extent.

Cell proliferation in response to both penthiopyrad and phenobarbital was a transient phenomenon which may be described as an initial pulse of cell proliferation which had ceased within 14 days of the start of treatment. Though it is was proposed that non-genotoxic hepatocarcinogens such as phenobarbital may enhance hepatic cell proliferation, the enhanced proliferation ceases after a few days even if treatment is continued.

Thus, the postulated initial event induced by penthiopyrad, a transient pulse of mitogenic stimulation, was demonstrated to occur within 3 days of the start of treatment and to have ceased within 7 days. It was also demonstrated that the hepatic hypertrophy followed the increase in cell proliferation in most animals. OCS notes that although 2 of 6 mice showed hepatic hypertrophy concomitantly with increased cell proliferation at 3 days, 4 of the 6 mice developed histologically diagnosed hepatic hypertrophy within 4 or 11 days following mitogenic stimulation. However, the second key event, activation of CAR was not directly investigated in the mechanistic studies. Instead, it is proposed by the applicant that based on a CAR-mediated up-regulation of the genes encoding for microsomal enzyme induction, and specifically members of the P450CYP2B and 3A sub-families, it can be inferred that CAR activation occurred within 14 days of the start of treatment with penthiopyrad. Though OCS notes that enzyme induction was not evaluated earlier than 14 days after the start of treatment.

Furthermore, liver weight increases were shown to occur as early as 3 days after the start of treatment at 600 mg/kg bw/d. A dose of 300 mg/kg bw/d produced increased liver weight after 28 or 90 days treatment, while in the 78-week study marked increased in liver weight were seen at 200 mg/kg bw/d. The occurrence of hepatic hypertrophy largely mirrored the observed increases in liver weight in 14- to 90-day studies (and occurred at a lower incidence after 90-days treatment compared to 28-days), though hepatic hypertrophy did not occur at 300 mg/kg bw/d after 28- or 90-days treatment, and the very marked liver weight increases at 200 mg/kg bw/d in the 78-week study were not accompanied by either hepatic hypertrophy or hyperplasia. Further, altered hepatic foci which are frequently seen prior to hepatocellular tumours in rodents were not observed.

Thus, while it has been postulated that the hepatic tumours occurred by a phenobarbital-like MOA, for which extensive epidemiology is available indicating it is not a human carcinogen, the key event of CAR activation was not investigated and only inferred (i.e. specific hepatic enzyme induction) in the submitted mechanistic studies, and there is no histopathologically diagnosed hyperplasia or altered foci. Thus, a degree of uncertainty must be associated with the proposed MOA and, thus, OCS considers that it is only probable that the observed hepatocellular tumours occurred by a MOA that is not relevant to humans.

However, OCS notes that only the incidence of carcinomas at 200 (9.6%) and 600 mg/kg bw/d (11.5%) in males were just are outside the historical control range, while the incidence of adenomas was within the historical control range in both sexes and the incidence of adenomas plus carcinomas combined was at 600 mg/kg bw/d was the same as the historical control upper limit in males (36.5%) and within the historical control range in females. Consequently, OCS considers that the increased incidence of observed hepatocellular tumours (carcinoma) in one sex was minimal and notes if the incidences of co-occurring carcinomas and adenomas within individual animals were excluded the incidence of carcinomas fell back within the historical control range. Additionally, noting the absence of a dose response relationship for

preneoplastic lesions between 200 and 600 mg/kg bw/d and no effect on tumour latency, it was considered that the findings do not provide reliable evidence of a carcinogenic potential that would pose a risk to humans.

Consequently, overall, while it was concluded that that the observed hepatocellular tumours probably occurred by a phenobarbital-like MOA, noting the questionable minimal incidence of such tumours in one sex it is considered that the findings in male mice only demonstrate a weak carcinogenic potential that is of limited relevance to humans.

Genotoxicity

Penthiopyrad has been evaluated in a comprehensive battery of 6 genotoxicity assays comprising *in vitro* bacterial and mammalian gene mutation, *in vitro* mammalian cytogenetics, DNA repair and UDS (*in vivo* dosing followed by *in vitro* culture and assay) assays, and *in vivo* clastogenicity. The *in vitro* assays were performed with and without an exogenous metabolic activation system derived from rat liver pre-induced with phenobarbital and 5,6-benzoflavone.

In a 5-strain reverse mutation assay in *S. typhimurium* and *E. coli*, penthiopyrad was clearly negative at doses up to those producing cytotoxicity, in the presence and absence of metabolic activation. Similarly, it did not produce forward gene mutations at the tk-locus of mouse lymphoma cells at dose levels up to those producing a relative survival of 10 - 20%, in the presence and absence of metabolic activation.

Penthiopyrad was not clastogenic in an *in vitro* cytogenetics assay performed in Chinese hamster lung fibroblasts exposed for 6 and 24 hours at dose levels enabling cell survival of >50%. Although there was judged to be a positive response following a 6-hour exposure to 160 µg/mL, in the presence of metabolic activation, this dose was close to the lethal dose and produced approximately 60% cell death. Thus dose levels enabling cell survival of > 60% were not clastogenic either in the presence or absence of metabolic activation.

Furthermore, there was no evidence of clastogenicity in an *in vivo* mouse micronucleus study at total dose levels of up to 2000 mg/kg bw over 2 days at which there was clear evidence of exposure of the target bone marrow cell population as indicated by significantly reduced numbers of polychromatic erythrocytes in the total erythrocyte population.

There was no evidence of DNA-damaging potential in two different assay systems. In an *in vitro* DNA repair assay using *B. subtilis* H17 and M45 spores, there were no relevant differences in the growth inhibition zone diameters between the strains at doses up to 22650 or 11325 µg/disc without and with metabolic activation. In an *in vivo/in vitro* treatment UDS assay in rat hepatocytes, the incidences of cells in repair and the mean net nuclear grain counts in hepatocytes from rats treated orally at 1000 or 2000 mg/kg bw were comparable to negative control values, indicating no induction of unscheduled DNA synthesis.

Thus, penthiopyrad has no genotoxic potential at relevant doses in these assays at the DNA, gene and chromosome levels of genetic organization.

Reproductive & Developmental toxicity

Guideline pre-natal developmental oral (gavage) toxicity studies in rats and rabbits and a dietary 2-generation reproductive toxicity study in rats have been performed on penthiopyrad.

Penthiopyrad is not a reproductive toxicant in the rat 2-generation study at any parental dose level, the highest of which elicited slightly reduced body weight gain prior to mating in the F1 parental animals at the top dose level, and in intermediate dose F1 males. No functional reproductive and fertility effects or histopathological alterations in the reproductive organs occurred at the highest dose level employed. Therefore, the NOAEL for reproductive effects was established as 278 mg/kg bw/d for both sexes. In the parental and F1 generation high dose range of 278 - 480 mg/kg bw/d, increased liver, thyroid and adrenal weights were evident. Increased relative liver weight also occurred in females of both generations at 54.0 - 95.6 mg/kg bw/d. These correlated with histologically diagnosed hypertrophy of hepatocytes, thyroid follicular epithelium and adrenal cortex in both sexes of both parental generations. These effects, and the effect on F1 male pre-mating body weight gain, resulted in a parental NOAEL value of 11.0 mg/kg bw/d. Reduced pre-weaning weight gain occurred at the highest dose level only in both sexes and in both the F1 and F2 generations. At necropsy, shortly after weaning, these animals showed reduced thymus and/or spleen weights. No histomorphological lesions were apparent in spleen or thymus from these animals, and spleen weights in mature adult F1 generation animals did not show reduced weight. On the basis of these findings, the NOAEL for offspring effects was established as 54.0 mg/kg bw/d.

Penthiopyrad did not produce any effects in the rat on prenatal foetal growth and development at maternal dose levels up to 1000 mg/kg bw/d in a dose range-finding study. This high dose level was selected for the rat developmental toxicity on the basis of no unequivocal effects in a dose range-finding study. The only maternal clinical sign at this dose level was excess salivation which was considered not to be adverse. There was also a minimal and transient reduction in maternal weight gain at this dose level. Litter effects were confined to an increase in the number of early resorptions, leading to slightly reduced gravid uterus weight, litter weight and litter size. Excess salivation also occurred in a portion of females treated at 250 mg/kg bw/d, but there were no embryo-foetal effects at this dose level and the finding is not considered adverse. Therefore, maternal and embryo-foetal NOAEL values were established as 250 mg/kg bw/d, with the observed developmental findings being considered a secondary non-specific consequence of maternal toxicity.

In the rabbit developmental toxicity study, a maternal high dose level of 225 mg/kg bw/d produced one abortion. Despite the low incidence of this observation, it was considered to be treatment-induced on the basis of similar findings in the dose range-finding study in which dose levels of 500 or 1000 mg/kg bw/d each produced abortion incidences of 33% (though the poor health of the animals and deaths observed at these dose levels are noted). Foetal weight was slightly reduced at 225 mg/kg bw/d, but there was no evidence of retarded foetal development on detailed visceral and skeletal examinations. Other than slightly reduced foetal weight at 225 mg/kg bw/d, there were no effects on foetal growth and development. Therefore, maternal and foetal NOAEL values were established as 75 mg/kg bw/d, with the observed developmental findings being considered a secondary non-specific consequence of maternal toxicity.

These data indicate that penthiopyrad is not a morphological developmental toxicant in rats and rabbits, is not a reproductive toxicant in rats, and does not produce enhanced sensitivity to penthiopyrad on embryo-foetal and/or neonatal exposure.

Neurotoxicity

Acute and 13-week oral neurotoxicity studies and a developmental neurotoxicity study have been performed in the rat.

Administration of a single oral dose of 500 or 2000 mg/kg bw penthiopyrad produced a range of functional effects at the time of peak effect on the day of treatment. The transient effects included abnormal posture/gait, reduced motor activity and reduced body temperature. Whole body tremor also occurred in some animals treated at 2000 mg/kg bw. None of the functional neurobehavioural effects persisted beyond the day of treatment. There were no effects at any dose level on brain weight and dimensions, and no neurohistopathological alterations in the central and peripheral nervous systems at 2000 mg/kg bw. The acute NOAEL was determined as 125 mg/kg bw based on the occurrence of the transient functional effects.

In contrast to the acute study, penthiopyrad did not elicit either functional or histopathological evidence of neurotoxicity following 13-weeks treatment at dose levels up to the maximum tolerated dose of 712 mg/kg bw/d. The NOAEL in the study was determined as 177/170 mg/kg bw/d (males/females) based on decreased body weight gain 712/686 mg/kg bw/d (males/females).

In the developmental neurotoxicity study, dose levels up to 500 mg/kg bw/d were well-tolerated by the maternal animals. Transient neurobehavioural effects were observed in offspring at dose levels of 250 or 500 mg/kg bw/d. The effects occurred at one testing interval only and comprised an increased incidence of slight and occasional whole body tremors at 500 mg/kg bw/d and increased motor activity at 250 or 500 mg/kg bw/d. Quantitative assessments of sensory function and learning and memory in offspring were unaffected by treatment at all dose levels and there were no effects on brain weight, dimensions and morphometry of specific regions. No neurohistopathological alterations were evident in offspring at 500 mg/kg bw/d. Consequently, the NOAEL in offspring was determined as 100 mg/kg bw/d, based on increased motor activity and decreased body weight at 250 mg/kg bw/d.

The observed neurobehavioural effects were seen on the day of dosing only in the acute neurotoxicity study, and no functional or histopathological evidence of neurotoxicity were seen in the sub-chronic study. Similarly, transient neurobehavioural effects in offspring were seen in the absence of sensory function, learning, memory and neurohistopathological alterations. Further, the only other evidence of potential neurotoxicity was a decrease not an increase in motor activity in a 90-day dietary study in rats at 625 mg/kg bw/d, though mortality was also observed at this dose level. Consequently, it is considered that the observed transient clinical effects of penthiopyrad are likely an indication of a neuropharmacology effect rather than an indication of neuronal damage.

Immunotoxicity

Immunotoxicity studies are available for both rats and mice. In male rats, no evidence of immunotoxicity was observed up to the highest dose tested of 710 mg/kg bw/d in a 28-day dietary study, a dose level that that produced reduced body weight gain and food consumption, increased liver weight and a secondary reduction in spleen weight. However, decreased plaque forming ability was seen in males mice at the limit dose of 1000 mg/kg bw/d in a 28-day dietary study though there was no evidence of a decrease in splenic

β-cell numbers. In mice, the only other finding was decreased absolute and relative liver weight at 250 mg/kg bw/d and above.

Penthiopyrad was not immunotoxic in rats and it is considered that the singular finding in mice does not provide reliable and robust evidence of an immunotoxic potential.

Studies on metabolites

DM-PCA

The metabolite DM-PCA was of low acute oral toxicity in female Sprague Dawley rats. The LD_{50} was >2000 mg/kg bw with no mortalities or clinical signs of toxicity observed. While in a 13-week oral (gavage) study in Wistar rats reduced body weight and body weight gain was observed in males only at 1038 mg/kg bw/d with no treatment related adverse effects seen in females. Thus, the NOAEL was 258 mg/kg bw/d in males and 1200 mg/kg bw/d in females. DM-PCA was not mutagenic in bacterial strains and mammalian cells *in vitro* with and without metabolic actiation. The metabolite was not genotoxic in mammalian cells *in vitro* with and without metabolic activation.

PCA

The metabolite PCA was of low acute oral toxicity in female Sprague Dawley rats. The LD_{50} was >2000 mg/kg bw with no mortalities or clinical signs of toxicity observed. While in a 13-week oral (gavage) study in Wistar rats no treatment related effects were seen in either sex up to and including the limit dose of 1000 mg/kg bw/d. Thus the NOAEL in both males and females was 1000 mg/kg bw/d. PCA was not mutagenic in bacterial strains with and without metabolic activation. In an *in vitro* gene mutation assay in mammalian cells an increase in mutation frequency was seen in the continuous 24-hout treatment assay with metabolic activation at 483 µg/mL with lower frequencies seen at higher concentrations in the absence of cytotoxicity. Thus, this *in vitro* finding was considered a weakly positive response and of questionable biological plausibility. The metabolite was not genotoxic in mammalian cells *in vitro*, and in an *in vivo* micronucleus assay in mice up to and including administration of 2000 mg/kg bw/d for two days.

PAM

The metabolite PAM was of low acute oral toxicity in male and female Sprague Dawley rats. The LD_{50} was >300 and <2000 mg/kg bw in both males and females. All 3 males and all 3 female animals administered 2000 mg/kg bw died with death preceded by decreased activity, tremor and clonic convulsion. No deaths or clinical signs of toxicity were observed in animals administered 300 mg/kg bw. PAM was not mutagenic in bacterial strains with and without metabolic activation. The metabolite was mutagenic in mammalian cells *in vitro* at the non-cytotoxic concentration of 483 µg/mL in the continuous 24-hour treatment assay without metabolic activation, and was genotoxic in mammalian cells *in vitro* at the non-cytotoxic concentrations of 989 – 1931 µg/mL in the continuous 24-hour treatment assay without metabolic activation. PAM was not genotoxic in an *in vivo* micronucleus assay in mice up to and including the maximum tolerated dose of 500 mg/kg bw/day administered for two days.

753-A-OH

The metabolite 753-A-OH was of low acute oral toxicity in female Sprague Dawley rats. The LD_{50} was >2000 mg/kg bw with no mortalities or clinical signs of toxicity observed. 753-A-OH was not mutagenic in bacterial strains and mammalian cels *in vitro* with and without metabolic activation. Neither was it genotoxic in mammalian cells *in vitro* with and without metabolic activation.

753-T-DO

The metabolite 753-T-DO was not mutagenic in bacterial strains and mammalian cells *in vitro* with and without metabolic activation. Neither was it genotoxic in mammalian cells *in vitro* with and without metabolic activation.

3.3 Public Health Standards

Poisons Scheduling

In February 2012, the delegate to the Secretary to the Department of Health and Ageing made a delegate only decision on penthiopyrad. The Secretary's delegate recommended that penthiopyrad be included in Schedule 5 of the SUSMP with an exemption cut-off at 20% or less from poisons scheduling, and that this scheduling decision be implemented on 1 May 2012.

NOAEL/ADI /ARfD

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

The critical effect of penthiopyrad identified based on chronic toxicity studies is on the liver which was observed in mice, rats and dogs. Rats appeared to be the most sensitive species for penthiopyrad with increased liver weight seen in parental animals in an oral (gavage) rat 2-generation study at 54 mg/kg bw/d (the LOAEL). The corresponding NOAEL was 11 mg/kg bw/d.

No correction for oral absorption of penthiopyrad is necessary for use of this NOAEL value to establish an ADI, since the value is greater than 80%.

A default 100-fold safety factor (SF), consisting of SFs of 10 each for intraspecies and interspecies variation, was considered appropriate. The toxicological database for penthiopyrad included several long-term oral studies and carcinogenicity studies in the mouse and rat, and was considered complete. Since no sensitive population groups were identified during the course of this evaluation, no additional safety factor is required at this time. A default SF of 100 to account for for potential intraspecies (SF of 10) and interspecies (SF of 10) variation was therefore applied to the most sensitive NOAEL for the determination of an ADI level. The ADI is established at 0.1 mg/kg bw/d (rounding down) using the lowest NOAEL of 11 mg/kg bw/d from a 2-generation reproduction toxicity study in rats based on reduced body weight gain in F1 adult males, increased liver weight in P and F1 adult females and increased adrenal weight with increased incidence

cortical hypertrophy in F1 females at the next highest dose of 54 mg/kg bw/d, and applying a default SF 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 NOEL as a single or short-term dose which causes no effect in the most sensitive species of experimental animal tested, together with a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

An acute reference dose (ARfD) was established since penthiopyrad was considered likely to present an acute hazard to humans. Adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available.

The lowest appropriate NOAEL from single dose studies and short term studies is 75 mg/kg bw for both maternal and fetal toxicity from a rabbit developmental toxicity study based on abortion in one animal and slightly lower foetal weight at the next highest dose level (225 mg/kg bw). The ARfD is established at 0.75 mg/kg bw using a default safety factor (SF) of 100 to account for potential intraspecies (SF of 10) and interspecies (SF of 10) variation.

4 RESIDUES ASSESSMENT

4.1 Introduction

DuPont™ Fontelis® Fungicide is a suspension concentrate formulation containing the new active constituent penthiopyrad and is intended for control of grey mould and powdery mildew in strawberries, scab and powdery mildew in pome fruit, brown rot and scab in stone fruit and tree nuts, and powdery mildew and various rots, moulds and blights in cucurbit and non-cucurbit fruiting vegetables, bulb vegetables, root and tuber vegetables, leafy vegetables and brassica vegetables. As part of the residues assessment for penthiopyrad, 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 ^{14}C-labelled penthiopyrad in tomatoes, canola, wheat, cabbage, grapes, rotational crops (spinach/lettuce, wheat and radish), lactating goats and laying hens was provided.

Metabolism of penthiopyrad was consistent across the major crop groups of leafy vegetables (cabbage), oilseeds (canola), cereals (wheat), fruit (grapes) and fruiting vegetables (tomatoes). The main identified metabolic pathways are:

N-demethylation from the pyrazole moiety;

Hydroxylation of the pentyl side chain; and

Oxidation and opening of the thienyl ring yielding carboxylic acid and ketone functional groups, followed by cleavage at the N-thienyl linkage to yield pyrazolyl carboxamide and carboxylic acid fragments.

Penthiopyrad was the major residue component in cabbages, tomatoes, and grapes harvested 30 days after treatment with radio-labelled parent compound. In grapes harvested 60 days after treatment, 1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carboxamide (PAM) and 1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid (PCA) were becoming more prominent, although parent compound was still present. In wheat forage, hay and straw, parent compound was the largest component of the residue, although PCA and PAM were significant, particularly in straw. In wheat grain, the metabolic profile was more complicated, with parent, PAM and PCA all being present at similar levels. In canola, there were many metabolites present at low levels, with few of them positively identified. PAM and PCA were both present. In rotational studies, only PCA and 3-trifluoromethyl-1*H*-pyrazole-4-carboxamide (DM-PAM) were identified at harvest (in spinach and lettuce leaves), and the highest level observed was only 0.012 mg/kg

With a few exceptions (mainly root vegetables), penthiopyrad was by far the dominant residue in all samples from the residue trials.

Parent compound is therefore a suitable target compound for residues analyses to determine compliance with MRLs. Given the significantly higher levels of parent compound found in most of the residue trials (often parent levels were around 10x those of the metabolite), it is not proposed to include any of the metabolites in the residue definition for risk assessment purposes. A residue definition of parent compound only is therefore proposed for penthiopyrad in plant commodities.

The metabolic pathways for penthiopyrad in lactating goats, laying hens and rats are very similar. The key pathways are hydroxylation of the pentyl side chain, oxidation of the thienyl ring, followed by cleavage of the N-thienyl linkage to yield the carboxamide metabolite PAM, and conjugation of the oxidised thienyl moiety with cysteine.

In the lactating goat metabolism studies, PAM was the largest component of theresidue in edible tissues and milk, with penthiopyrad occurring only in trace amounts in liver, kidney and fat. PCA was found in significant quantities in some tissues. PAM was a major component of the residue in the acid hydrolysis fraction, formed by decomposition of the various conjugates. In the hen metabolism studies, PAM was the largest proportion of the residue in most matrices, with parent compound, PCA and DM-PAM also forming significant components of the residue in some matrices.

In the cattle and hen feeding studies, PAM was the only residue observed in eggs and milk, while penthiopyrad was the residue that occurred most often and in the highest concentrations in hen tissues. In cattle tissues, PAM was the most prevalent residue, followed by penthiopyrad. Given that penthiopyrad and PAM are the most commonly observed penthiopyrad-derived residues in milk, eggs and tissues, it is proposed that a residue definition of the sum of penthiopyrad and PAM be adopted for penthiopyrad in animal commodities.

4.3 Analytical methods

Determination of penthiopyrad residues in plant commodities

A number of analytical methods were developed and validated for penthiopyrad and metabolites in plant commodities. The method used for the residues trials involved extraction of homogenised samples with acetonitrile/water, followed by evaporation of the organic solvent and acidification of the aqueous residue to hydrolyse conjugates, before partition with ethyl acetate. The ethyl acetate phase is evaporated and the residue reconstituted in methanol/water for analysis by LC/MS/MS.

The method was validated in a range of commodities, including high water content (lettuce, potatoes, cucumber, wheat forage, melon pulp and rind, radish, pea vines and pea and bean seed), dry commodities (wheat grain and straw, dried beans, raisins, prunes, almond hulls, dry apple pomace, and pea hay), high acid content (apple fruit and juice, grapes, grape juice, peach, plum and sweet cherry), oily matrices (pecan nutmeat, peanut oil and nutmeat, and canola seed and oil), and showed good recoveries (70-120%) and repeatability (RSD <20%). A limit of quantitation of 0.01 mg/kg was achievable in most tested matrices.

Determination of residues of penthiopyrad in animal tissues

The analytical method for determination of penthiopyrad and its metabolites in animal tissues, eggs and milk involved extraction of samples with acetone/water, followed by evaporation of the organic solvent, acidification of the aqueous residue and clean-up of the sample by partition with ethyl acetate. The combined ethyl acetate phase was then evaporated and the extract reconstituted in methanol/water for analysis by LC/MS/MS. The method accuracy and precision was good, with recoveries in the range 70-120% and relative standard deviations <20% being achieved for both penthiopyrad and the metabolite PAM at fortifications of 0.01 and 1 mg/kg in eggs, chicken liver, muscle, and fat, milk, and bovine liver, kidney, muscle and fat. The limit of quantitation was o.o1 mg/kg in animal commodities.

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

4.4 Residue definition

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

COMPOUND	RESIDUE DEFINITION
Penthiopyrad	*Commodities of plant origin:* Penthiopyrad *Commodities of animal origin:* sum of penthiopyrad and 1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-ylcarboxamide, expressed as penthiopyrad

4.5 Storage stability

Stability over 18 months storage at -20 °C was tested for residues of penthiopyrad and five metabolites in a range of samples covering high water content (lettuce and potato), high water and high acid content (apple, grape and grape juice), dry commodities (raisins, dried grape pomace, dry beans, and wheat straw, forage and grain) and oily samples (canola seed and oil).

Some low recoveries in stored samples were observed in the stability study; these were either associated with similar low procedural recoveries and/or were followed by good recovery at subsequent time points. Residues of penthiopyrad and the metabolites were found to be stable when stored at -20 °C for at least 18 months in lettuce, apple, potato, grape, grape dried pomace, grape juice, raisins, dried beans, wheat grain, wheat straw and wheat forage, oilseed rape seed, and rapeseed oil.

4.6 Residue trials

Fruiting vegetables (other than cucurbits)

Use of penthiopyrad in non-cucurbit fruiting vegetables (both field and greenhouse crops) is proposed with an application rate of 350 g ai/ha, a re-treatment interval of 7-10 days, a maximum seasonal rate of 1050 g ai/ha and a maximum of two consecutive applications, before switching to a fungicide from a different mode of action group. A nil harvest withholding period is proposed.

The proposed use pattern in non-cucurbit fruiting vegetables was mainly supported by a package of US/Canadian trials (20 in tomatoes, 11 in capsicum and 9 in chilli peppers) conducted with three applications at 350 g ai/ha (1x the proposed individual and seasonal application rate), at a re-treatment interval of 7 days.

Residues of penthiopyrad in US/Canadian tomatoes on the day of the last application were 0.11, 0.16, 0.17, 0.18, 0.20, 0.21, 0.24, 0.25, 0.26, 0.28, 0.30, 0.36, 0.42, 0.43, 0.44, 0.46, 0.50, 0.76, 1.5, and 1.7 mg/kg (STMR = 0.29 mg/kg). In capsicum, the residues were 0.15, 0.18 (2), 0.19, 0.20, 0.21 (2), 0.22, 0.23, 0.75, and 0.91 mg/kg (STMR = 0.21 mg/kg), while in chilli peppers, residues were 0.18, 0.22, 0.36, 0.37, 0.55, 0.60, 0.91, 1.0, and 1.7 mg/kg (STMR = 0.55 mg/kg).

An MRL of 5 mg/kg is proposed for penthiopyrad in fruiting vegetables, other than cucurbits, in conjunction with a nil withholding period.

European fruiting vegetable trials included one application at 200 g ai/ha followed by a second at 600 g ai/ha, giving a lower total rate than that proposed for Australia. On the day of the last application, residues of penthiopyrad in European greenhouse grown tomatoes were 0.24, 0.30, 0.31, 0.49, 0.76, 0.85, and 1.1 mg/kg (STMR = 0.49 mg/kg). In field grown European tomatoes, residues on the day of the last application were 0.11, 0.18, 0.29, 0.35, and 0.85 mg/kg (STMR = 0.29 mg/kg), indicating higher residues in protected crops. In greenhouse grown European capsicum, residues on the day of the last application were 0.18, 0.52, 0.64, and 0.69 mg/kg. The European residue results are generally lower than the American results, reflecting the lower application rate. The European results are supportive of the proposed Australian MRL.

Fruiting vegetables, cucurbits

Use of penthiopyrad in cucurbit fruiting vegetables (both field and greenhouse crops) is proposed with an application rate of 350 g ai/ha, a re-treatment interval of 7-14 days, a maximum seasonal rate of 700 g ai/ha and a maximum of two consecutive applications before switching to a fungicide from a different mode of action group. A harvest withholding period of 1 day is proposed.

26 trials were conducted in Europe in cucumber and zucchini, half under cover and half in the field. In these trials, two applications of penthiopyrad were made at a target interval of 5 days, the first at approximately 200 g ai/ha (0.57x the proposed Australian rate) and the second at approximately 600 g ai/ha (1.7x the proposed Australian rate), giving a seasonal rate of 800 g ai/ha (1.14x the rate proposed for Australia). In USA and Canada, 10 trials were conducted in cucumber, 9 in summer squash, and 8 in muskmelon. In these trials, four applications of 250 g ai/ha were made at 5-day intervals, giving individual application rates of 0.71x rate proposed for Australia, and a 1.4x seasonal rate 1.4x. Two trials were conducted in Australia

for zucchini with three applications of 350 g a/ha, at 1x that proposed rate and at 1.5x proposed seasonal rate.

The combined cucurbit data set is 0.01, 0.015, 0.034, 0.042, 0.05, 0.051, 0.053, 0.056, 0.068, 0.075, 0.076, 0.08, 0.082, 0.083, 0.089, 0.093, 0.094, 0.098, 0.11 (2), 0.12 (3), 0.13 (6), 0.15, 0.16 (3), 0.17 (2), 0.18, 0.19 (2), 0.20, 0.21, 0.23, 0.24, 0.25, 0.27, 0.28, 0.29 (2), 0.30 (2), 0.35 (2), 0.37, 0.38, 0.46, and 0.48 mg/kg (STMR = 0.13 mg/kg) for cucumbers, melon and zucchini harvested 1 day after the last application.

It is proposed to establish an MRL of 1 mg/kg for penthiopyrad in fruiting vegetables (cucurbits).

Bulb vegetables

For bulb vegetables, the proposed application rate is 350 g ai/ha with a 7-14 day re-treatment interval, a maximum of three applications per crop and a maximum of two consecutive applications. A 3-day harvest withholding period is proposed.

A group of 11 trials in dry bulb onions, and 6 trials in green onions was conducted in the USA and Canada. The GAP for the US/Canadian trials involved three applications of penthiopyrad at 350 g ai/ha, at approximately 7 day intervals.

Residues of penthiopyrad in bulb onions (dry) 3 days after the last application were 0.01, 0.018, 0.06, 0.061, 0.064, 0.066, 0.14, 0.16, 0.38, and 0.45 mg/kg. Residues of penthiopyrad in green (spring or Welsh type) onions 3 days after the last application were 0.21, 0.24, 0.55, 1.0 (2), and 1.8 mg/kg.

An MRL of 1 mg/kg is recommended for penthiopyrad in bulb onions in conjunction with a 3-day harvest withholding period. MRLs of 5 mg/kg are supported for penthiopyrad in spring onions, Welsh onions and shallots, in conjunction with a 3-day harvest withholding period.

Leafy vegetables

Use of penthiopyrad in non-brassica leafy vegetables is proposed with an application rate of 350 g ai/ha, a re-treatment interval of 7-10 days, and a maximum seasonal rate of 1050 g ai/ha and a maximum of two consecutive applications before switching to a fungicide from a different mode of action group. A 3-day harvest withholding period is proposed. In brassica leafy vegetables, the proposed application rate is 350 g ai/ha with a 7-14 day re-treatment interval, a maximum of three applications per crop and a maximum of two consecutive applications. A nil harvest withholding period is proposed.

A series of trials was conducted in the USA and Canada (11 trials in celery, 12 trials in head lettuce, 12 trials in leaf lettuce and 10 trials in spinach) in accordance with the proposed use pattern in leafy vegetables for Australia, with three applications of 350 g ai/ha being made at a target interval of 7 days. Trials in mustard greens were conducted with three applications of penthiopyrad at target intervals of 7 days. The first application was at a target rate of 150 g ai/ha, with applications 2 and 3 at 450 g ai/ha. In the turnip trials (where leaves were harvested), two applications of 450 g ai/ha were made 7 days apart, giving an individual application rate of 1.3x that proposed and a seasonal rate 0.86x that proposed. A single Australian trial in leaf lettuce was presented, in which four applications of 350 g ai/ha were made.

At the proposed withholding period of 3 days, residues of penthiopyrad were <LOD, 0.37, 0.4, 0.43, 0.44, 0.59, 0.62, 1.6, 2.3, 2.9, 3.4, and 3.9 mg/kg in head lettuce, 1.1, 1.2 (2), 1.8, 1.9, 2.1, 4.8, 4.9 (2), 5.7, 7.4, 7.8, and 11 mg/kg in leaf lettuce, and 0.85, 1.2, 1.5, 2.0, 2.8, 2.9, 3.2, 10, 13, and 17 mg/kg in spinach.

At the proposed nil withholding period for brassica leafy vegetables, residues of penthiopyrad in mustard greens were 8.8, 9.0, 9.3, 9.5, 11, 16, 18, 26, and 32 mg/kg, while residues in turnip leaves (see section 3.6.6) were 4.5, 5.3, 7.3, 13, 20, and 27 mg/kg.

An MRL of 10 mg/kg is proposed for penthiopyrad in head lettuce. An MRL of 50 mg/kg is proposed for leafy vegetables (except head lettuce and brassica leafy vegetables). An MRL of 70 mg/kg is proposed for brassica leafy vegetables. These MRLs will allow for variation in residue levels in different crops across the groups which may be harvested at various growth stages.

Brassica vegetables

In brassica vegetables, the proposed application rate is 350 g ai/ha with a 7-14 day re-treatment interval, a maximum of three applications per crop and a maximum of two consecutive applications. A nil harvest withholding period is proposed.

An extensive residue study was conducted in the USA and Canada for penthiopyrad in brassica vegetables (10 trials in head cabbages, 7 trials in broccoli and 3 trials in cauliflower). Three applications of penthiopyrad were made at 7-day intervals, with the first application of 150 g ai/ha and the second and third of 450 g ai/ha each, giving a seasonal rate the same as proposed for Australia. On the day of the last application, residues of penthiopyrad were 1.0, 1.1, 1.4, 1.8, 2.0 (2), and 2.5 mg/kg in broccoli, 0.12, 0.56, and 0.59 mg/kg in cauliflower, and 0.026, 0.11, 0.20, 0.28, 0.29, 0.57, 1.1, 1.4, 1.5, and 2.3 mg/kg in cabbage.

A group MRL of 7 mg/kg is recommended for penthiopyrad in brassica vegetables.

Root and tuber vegetables

Use of penthiopyrad in root vegetables is proposed with an application rate of 350 g ai/ha, a re-treatment interval of 7-14 days, and a maximum seasonal rate of 700 g ai/ha and a maximum of two consecutive application before switching to a fungicide from a different mode of action group. A harvest withholding period of 7 days is proposed.

22 US/Canadian trials were conducted in potato. Penthiopyrad was applied using three different treatment regimes. The first was three foliar applications of 350 g ai/ha at 7-day intervals post flowering (i.e. close to harvest). The second was one application of 350 g ai/ha in furrow at the time of planting and two foliar 350 g ai/ha applications 7 days apart close to harvest. The third regime was two foliar applications 7 days apart earlier in the season, i.e. around flowering, and a third application closer to harvest. One trial in potatoes was conducted in Australia, in which four applications of 350 g ai/ha were made.

34 trials were conducted in the USA and Canada in carrot, radish and sugar beet. Penthiopyrad was applied twice 7 days apart at a target application rate of 450 g ai/ha, representing individual and seasonal application rates approximately 1.3x those proposed for Australia.

Residues of penthiopyrad in potato tubers 7 days after last application after treatment in accordance with the treatment regimes 1 and 2 were <0.01 (25), 0.01 (3), 0.011, 0.012, 0.013, 0.015, 0.016 (3), 0.018, 0.02, 0.021 (2), 0.022, 0.029, 0.037, 0.038, and 0.058 mg/kg. An MRL of 0.1 mg/kg is proposed for penthiopyrad in potatoes, in conjunction with a 7-day harvest withholding period.

Residues of penthiopyrad in sugar beet roots 7 days after the last application were 0.016, 0.018, 0.019, 0.039, 0.058, 0.091 (2), 0.17, 0.18, 0.19, 0.22, and 0.35 mg/kg. Residues of penthiopyrad in radish roots 0-1 day after the last application were ND, 0.17, 0.23, 0.34, 0.93, and 1.2 mg/kg. Residues of penthiopyrad in carrot roots on the day of the last application were 0.021, 0.027, 0.05, 0.06, 0.086, 0.088, 0.13, 0.17, and 0.43 mg/kg. An MRL of 2 mg/kg is therefore recommended for root vegetables other than potatoes.

Strawberries

The proposed use pattern in strawberries is a maximum of three applications per season, and a maximum of two consecutive applications at 350 g ai/ha (or dilute foliar spraying at 35 g ai/100 L), with a 7-10 day re-treatment interval and a nil harvest withholding period.

Nine trials were conducted in the USA and Canada, plus one in Australia. In these trials, three applications of 350 g ai/ha were made at 7-day intervals, which is consistent with the proposed Australian use pattern. On the day of the last application, residues of penthiopyrad in strawberries were 0.40, 0.49, 0.68, 0.69, 0.74, 0.86, 0.90, 1.4, 1.5, and 2.2 mg/kg (STMR = 0.80 mg/kg). An MRL of 5 mg/kg for penthiopyrad in strawberries is recommended for strawberries in conjunction with a nil harvest withholding period.

Pome fruit

The proposed use pattern for penthiopyrad in pome fruit is dilute foliar application at a maximum spray concentration of 25 g ai/100 L with a re-treatment interval of 7-21 days, and a 28 day harvest withholding period. A maximum of three applications per season is proposed, with no more than two consecutive applications of penthiopyrad.

Six Australian trials were conducted (4 apple, 2 pear), in which penthiopyrad was applied three times at a target interval of 7 days, with three spray concentrations (15, 25 and 50 g ai/100 L, 0.6x, 1x and 2x the proposed rate). 18 trials were conducted in pome fruit in Europe, with application at spray concentrations of 15 and 22 g ai/100 L. Three applications were made at a target interval of 7 days. 24 trials were conducted in the USA and Canada, with applications being made three times 7 days apart at a target application rate of 300 g ai/ha. Spray volumes ranged from 600-1800 L/ha, giving a spray concentration range of 16.7-50 g ai/100 L.

For trials at least 0.7x the proposed GAP, the combined data set for penthiopyrad in pome fruit 28 days after the last application is <0.003 (2), <0.01, 0.032, 0.037, 0.04 (2), 0.044, 0.05, 0.06 (2), 0.065, 0.076, 0.08 (3), 0.10, 0.11 (3), 0.12 (4), 0.13 (2), 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, 0.20, 0.23 (3), 0.25, and 0.26 (2) mg/kg (STMR = 0.11 mg/kg). An MRL of 0.5 mg/kg is therefore recommended for penthiopyrad in pome fruit in conjunction with a 28-day harvest withholding period.

Stone fruit

A package of 32 trials (13 in peaches, 10 in plums, 4 in sweet cherries and 5 in tart cherries) was conducted in the USA and Canada, in which penthiopyrad was applied three times at a target interval of 7 days at a target rate of 300 g ai/ha, with spray volumes ranging from 600-2000 L/ha, with most trials being around 1000 L/ha.

Residues of penthiopyrad in peaches (whole fruit including stone) on the day of the last application were 0.22, 0.27, 0.36, 0.49, 0.53, 0.58, 0.59 (2), 0.64, 0.67, 0.71, 0.82, and 1.5 mg/kg (STMR = 0.59 mg/kg). Residues in whole plums on the day of the last application were 0.048, 0.058, 0.084, 0.09, 0.097, 0.12, 0.13, 0.21, 0.30, and 0.80 mg/kg (STMR = 0.11 mg/kg). Residues in whole cherries on the day of the last application were 0.40, 0.47, 0.97, 1.0, 1.2, 1.3 (2), 1.6, and 1.8 mg/kg (STMR = 1.2 mg/kg). An MRL of 5 mg/kg is recommended for penthiopyrad in stone fruit, in conjunction with a nil harvest withholding period.

Tree nuts

The proposed use pattern for penthiopyrad in tree nuts is a maximum of three applications per season, and a maximum of two consecutive applications by dilute foliar spraying at 30 g ai/100 L, with a 7-14 day re-treatment interval and a 14-day harvest withholding period.

Twelve residue trials (6 each in almonds and pecans) were conducted in the USA. In these trials, penthiopyrad was applied three times at 7-day intervals at 300 g ai/ha. The spray volumes used ranged from 600-1500 L/ha, giving a range of spray concentrations from 20-50 g ai/100 L.

Residues of penthiopyrad in pecan nutmeat 14 days after the last application were <0.01 (6) mg/kg). Residues in almond nutmeat were <0.01 (4), 0.01, and 0.045 mg/kg. Residues in almond hulls were 0.72, 1.2, 1.9, 2.3, and 2.7 (2) mg/kg. An MRL of 0.1 mg/kg is recommended for penthiopyrad in tree nuts, in conjuction with a 14-day harvest withholding period. An MRL of 7 mg/kg is recommended for penthiopyrad in almond hulls.

4.7 Processing studies

Apples

An apple processing study showed that residues did not concentrate in apple juice, canned apple, frozen apple slices or apple sauce. Processing factors of 6.6, 10, and 12 were determined for dry apple pomace. The calculated HR-P for dry apple pomace is 0.26 mg/kg (HR) x 12 = 3.12 mg/kg, while the STMR-P is 1.32 mg/kg (0.11 mg/kg x 12). An MRL of 5 mg/kg is therefore recommended for apple pomace (dry).

Plums

A plum processing study showed that penthiopyrad concentrates slightly in prunes, with processing factors of 1.32 and 1.50 being calculated. This gives an HR-P of 2.7 mg/kg for dried stone fruit.

Tomatoes

The tomato processing study showed that penthiopyrad does not concentrate in juice or canned tomatoes, while concentrating slightly in puree (processing factors of 1.5-2.2) and catsup (ketchup; processing factors of 0.95-1.9), moderately in paste (processing factors of <0.06-3.8) and significantly in pomace (processing factors of 26, 41 and 43 for dry pomace).

The calculated HR-P for tomato pomace (dry) is 47.3 mg/kg (1.1 mg/kg x 43). An MRL of 70 mg/kg is therefore proposed for penthiopyrad in tomato pomace (dry).

Potatoes

A potato processing study showed that residues of penthiopyrad do not concentrate in commercial potato products (peeled or unpeeled French fries, potato flakes, boiled peeled or unpeeled potatoes, unpeeled microwaved potatoes, crisps, or steam- or abrasion-peeled potatoes).

Animal feeds

Evaluation of the processing studies for grapes showed that penthiopyrad residues could concentrate in apple pomace and tomato pomace (see the above discussion on processing), while the tree nuts trial showed that significant residues could be expected in almond hulls. The following entries in Table 4 of the MRL Standard were recommended: almond hulls: 7 mg/kg, apple pomace, dry: 5 mg/kg and tomato pomace, dry: 100 mg/kg.

Crop rotation

Field crop rotation studies were conducted in Europe (Spain and the UK), and the USA and Canada. In the USA and Canada, penthiopyrad was applied either four times at 250 g ai/ha at approximately 5-day intervals or three times at 350 g ai/ha at approximately 7-day intervals, giving total seasonal rates of 1000 or 1050 g ai/ha. Both of these regimes closely match the proposed use pattern of three applications of 350 g ai/ha proposed for most vegetable crops in Australia. Lettuce, radish and wheat were planted at plant back intervals of 7-30, 60 or 300-365 days after the last application. In the European trials, two applications of penthiopyrad were made at 400 g ai/ha, giving a seasonal rate of 800 g ai/ha, 0.76x the proposed maximum seasonal rate for Australia. Lettuce, spinach, radish, wheat and barley were sown at plant back intervals of 30, 60, 120 and 365-402 days after the last application.

With the exception of one sample of radish root in Canada planted 8 days after the last application and one radish and one spinach sample in the UK planted 62 days after the last application, no residues of parent compound were found above the LOQ in any rotational crops. The highest residue seen in radish root was 0.024 mg/kg, while the highest residue in spinach was 0.011 mg/kg. Both of these results are well below the proposed MRLs of 2 and 50 mg/kg for root vegetables and leafy vegetables respectively.

Establishment of plant back intervals or MRLs in relation to rotational crops is therefore not proposed. The risk of residues in rotational crops is expected to be low.

4.8 Animal commodity MRLs

Mammalian livestock

In a lactating cattle feeding study, cattle were dosed with penthiopyrad at average dose levels of 8.4, 24.1 and 74.6 ppm, or 0.15, 0.48 and 1.65 mg/kg bw/day, for 28 days. Three animals were included in each group, plus two extra animals in the high dose group for generation of depuration data. Milk sampling took place on Days -3, -1, 1, 3, 6, 9, 12, 15, 18, 21, 24, 28 or 29, 30 and 35. A larger sample was taken on day 23 for separation into milk and cream. All cattle except the depuration animals were slaughtered within 24 hours of the final dose, while the depuration animals were slaughtered 3 and 7 days after the last dose. Samples of muscle, liver, kidney, subcutaneous fat, mesenteric fat and renal fat were taken immediately after slaughter.

Penthiopyrad and the metabolites (*RS*)-*N*-[2-(1,3-dimethyl-3-hydroxybutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide (753-A-OH) and PCA were not found in milk at any dose level. The metabolite PAM was only found at levels of up to 0.02 mg/kg in milk from the high dose group. Residues of PAM were found at up to 0.01 mg/kg (the LOQ) in skim milk and cream from the high dose animals.

All residues in tissue were at or below the LOQ for the low dose group, while residues of penthiopyrad up to 0.03 and 0.02 mg/kg were found in liver and fat for the high dose group. PAM was found at up to 0.02 mg/kg in muscle for the high dose group, up to 0.01 and 0.02 in fat for the mid and high dose groups, up to 0.02 and 0.06 mg/kg in the mid and high dose groups in liver, and up to 0.01 and 0.03 mg/kg in the mid and high dose groups in kidney.

Clearance of penthiopyrad residues from tissues and milk was rapid. In the depuration phase, residues of all analytes were below the LOQ of 0.01 mg/kg in samples from cows dosed at the 10x rate and slaughtered 3 and 7 days after the others in the 10x dose group, with the exception of one detection of PAM in kidney (0.01 mg/kg) in the first cow slaughtered (after 3 days depuration).

The maximum dietary intake of penthiopyrad by cattle consuming treated feeds containing penthiopyrad residues 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	Almond hulls	10	2	2.7	90	6	0.3	0.012
By-products	Apple pomace	20	4	3.12	100	12.5	0.624	0.025
By-products	**Tomato pomace**	**10**	**2**	**47.3**	**100**	**94.6**	**9.46**	**0.19**
B-yproducts	Potato process waste	5	1	0.25	12	2.08	0.104	0.004

Roots and tubers	Potato culls	10	2	0.058	20	0.58	0.029	0.001
Roots and tubers	Carrot culls	5	1	0.43	12	3.58	0.179	0.007
Roots and tubers	**Turnip roots**	**10**	**2**	**0.35**	**15**	**4.67**	**0.233**	**0.009**
TOTAL (highest residue by-product feed plus highest residue root and tuber feed, which are indicated in bold type)						99.3	9.69	0.199

The calculated dietary burden is 9.7 mg/kg in feed, or 0.2 mg/kg bw/day for both beef and dairy cattle. In the lactating cattle feeding study, cattle were fed penthiopyrad daily for 28 days at average doses of 8.4, 24.1 and 74.6 mg/kg in feed, corresponding to 0.15, 0.48 and 1.65 mg/kg bw/day.

No residues of penthiopyrad or the three metabolites PCA, PAM or 753-A-OH were found in whole milk, skim milk or cream at the low or mid dose level. These doses bracket the expected concentration of penthiopyrad in feed. Therefore, quantifiable residues of penthiopyrad or the metabolites are not expected to be found in milk, and an MRL at the LOQ (0.01 mg/kg) is proposed for milk.

In muscle and fat, residues of the penthiopyrad and the three metabolites were not found in any sample at the low dose level. For the mid dose level, residues of PAM only were found at the LOQ in mesenteric fat (no residues were quantified in muscle or the other fat compartments at this feeding level). Given that the mid dose feeding level (24.1 mg/kg in feed and 0.48 mg/kg bw/day) considerably exceeds the calculated dietary burden for cattle, finite residue of penthiopyrad are not expected in meat, and an MRL of at the LOQ (0.01 mg/kg) is proposed for mammalian meat.

In liver and kidney, residues of penthiopyrad and the three metabolites were below the LOQ in all samples from the low dose group. In the mid dose group, residues of penthiopyrad, PCA and 753-A-OH were below the LOQ in all cases. Residues of PAM for the mid dose group reached a maximum of 0.02 mg/kg in liver and 0.01 mg/kg in kidney. Scaling these values for the expected maximum dose of 0.2 mg/kg bw/day or 9.7 mg/kg in feed means that residues of PAM would be expected to be less than the LOQ in both liver and kidney. An MRL at the LOQ is therefore recommended for mammalian edible offal.

Poultry

Apple and tomato pomace and almond hulls are not commonly used as feeds for poultry. Therefore, there is unlikely to be a significant dietary burden of penthiopyrad in poultry feed as a result of registration of products containing penthiopyrad. As a consequence, it is proposed to establish MRLs for penthiopyrad in poultry meat, poultry edible offal, and eggs at 0.01 mg/kg, which is the validated limit of quantitation for penthiopyrad 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) (*0.01 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).

4.9 Spray drift

Spray drift modelling shows the risk of drift from orchard or boom sprayer applications onto adjacent pasture resulting in detectable residues of penthiopyrad in meat or dairy products is very low. No-spray zones related to international trade are not required.

4.10 Bioaccumulation potential

Penthiopyrad has an octanol/water partition coefficient ($log_{10}P_{OW}$) of 4.6 at 20 °C and pH 7 (there is little variation over a pH range of 4-10). However, residues are not designated as fat soluble given the cattle feeding study showed no tendency of penthiopyrad to partition into milk fat or body fat.

4.11 Estimated dietary intake

The chronic dietary intake risk for penthiopyrad has been assessed. The ADI for penthiopyrad is 0.1 mg/kg bw/day, based upon a NOEL of 11 mg/kg bw/day and a 100-fold safety factor. The NEDI calculation is made in accordance with WHO Guidelines[2] and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for penthiopyrad, is equivalent to 6% of the ADI. DIAMOND Modelling[3] of chronic dietary exposure is also performed on new chemicals. The DIAMOND model estimated the chronic dietary exposure of penthiopyrad as 8% of the ADI for the general population.

The acute reference dose (ARfD) for penthiopyrad is 0.75 mg/kg bw, based on a NOEL of 75 mg/kg bw, and a safety factor of 100. The NESTI calculations are made in accordance with the deterministic method used by the JMPR[5] 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 21% of the ARfD. It is concluded that the acute dietary exposure is acceptable.

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

2 Guidelines for predicting dietary intake of pesticide residues, WHO, 1997.
3. DIAMOND: The DIamond Modelling Of Nutritional Data is a computer dietary modelling program based upon statistical software that is used by FSANZ.

4.12 Recommendations

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

Table 1: MRL for food

COMPOUND	FOOD		MRL (MG/KG)
ADD: Penthiopyrad	VL 0054	Brassica leafy vegetables	70
	VB 0040	Brassica vegetables	7
	MO 0105	Edible offal (mammalian)	*0.01
	PE 0112	Eggs	*0.01
	VC 0050	Fruiting vegetables, cucurbits	1
	VO 0045	Fruiting vegetables, other than cucurbits	5
	VL 0050	Leafy vegetables [except brassica leafy vegetables and lettuce, head]	50
	VL 0482	Lettuce, Head	10
	MM 0095	Meat (mammalian)	*0.01
	ML 0106	Milks	*0.01
	VA 0385	Onion, Bulb	1
	VA 0387	Onion, Welsh	5
	FP 0009	Pome fruit	0.5
	VR 0589	Potato	0.1
	PO 0111	Poultry, edible offal of	*0.01
	PM 0110	Poultry meat	*0.01
	VR 0075	Root and tuber vegetables [except potato]	2
	VA 0388	Shallot	5
	VA 0389	Spring onion	5
	FS 0012	Stone fruit	5
	FB 0275	Strawberry	5
	TN 0085	Tree nuts	0.1

*MRL set at the limit of quantitation.

Table 3: Residue Definition

COMPOUND	RESIDUE DEFINITION
ADD: Penthiopyrad	*Commodities of plant origin:* Penthiopyrad *Commodities of animal origin:* sum of penthiopyrad and 1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-ylcarboxamide, expressed as penthiopyrad

Table 4: MRL Standard – Animal Feed

COMPOUND	ANIMAL FEED COMMODITY		MRL (MG/KG)
ADD: Penthiopyrad		Almond hulls	7
	AB 0226	Apple pomace, dry	5
		Tomato pomace, dry	100

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

HARVEST WITHHOLDING PERIOD

Strawberries, brassica vegetables, brassica leafy vegetables, fruiting vegetables (other than cucurbits), stone fruit: Not required when used as directed.

Cucurbit vegetables: Do not harvest for 1 day after application.

Onions, spring onions, shallots, leafy vegetables (other than brassica leafy vegetables): Do not harvest for 3 days after application.

Root and tuber vegetables: Do not harvest for 7 days after application.

Tree nuts: Do not harvest for 14 days after application.

Pome fruit: Do not harvest for 28 days after application.

GRAZING WITHHOLDING PERIOD

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 that have a potential for detectabel residues of penthiopyrad and are also major export commodities, are pome and stone fruit.

The total exports of Australian apricots in 2010/2011 were worth US$1.468 million (Australian Bureau of Statistics). The largest markets were the United Arab Emirates, Hong Kong and France.

Total cherry exports in 2010/2011 were worth A$12.995 million, with the largest markets being Taiwan ($3.138 million), Hong Kong ($3.060 million), and Thailand ($1.852 million).

Total peach and nectarine exports in 2010/2011 were worth A$12.656 million, with the largest markets being Hong Kong ($5.167 million), the United Arab Emirates ($2.653 million), and Singapore ($1.598 million).

Plum exports in 2010/2011 were A$9.213 million, with the largest markets being Hong Kong ($5.471 million), Singapore ($1.565 million) and the UK ($0.876 million).

Apple exports in 2010/2011 were worth US$5.924 million, with the largest markets being Indonesia ($2.346 million), Papua New Guinea ($1.393 million), and the UK ($0.978 million).

Pear and quince exports in 2010/2011 were worth A$7.465 million, with the largest markets being Canada ($2.468 million), New Zealand ($2.046 million), and New Caledonia ($0.529 million).

5.2 Overseas registration status

Codex MRLs not have been established for penthiopyrad. The residues aspects of penthiopyrad are yet to be considered by the Joint Meeting on Pesticide Residues (JMPR) in September.

Penthiopyrad products are registered in the USA, Canada and Japan. Some MRLs are established for pome and stone fruit (see table below).

The following relevant overseas MRLs have been established or proposed:

Penthiopyrad pome and stone fruit MRLs

COUNTRY/STATUS	COMMODITY	TOLERANCE, mg/kg (EXPIRY DATE)	REFERENCE
USA (established)	Pome fruit	0.5	Electronic Code of Federal Regulations, Title 40: Protection of Environment, Part 180.658 (Penthiopyrad tolerances for residues)
	Stone fruit	4	

COUNTRY/STATUS	COMMODITY	TOLERANCE, mg/kg (EXPIRY DATE)	REFERENCE
Canada (proposed)	Pome fruit	0.5	Proposed Maximum Residue Limit PMRL2012-5, Penthiopyrad, Pest Management Regulatory Agency, 6 March 2012
	Stone fruit	4	
EU (proposed)	Pome fruit	0.5	
	Peaches	2	
	Plums	1.5	
	Cherries	4	

The residue definition for penthiopyrad in plant commodities is parent only for the European Union, USA and Canada.

The following overseas animal commodity MRLs /tolerances have been proposed:

Penthiopyrad overseas animal commodity MRLs

COUNTRY	COMMODITY	TOLERANCE, mg/kg (EXPIRY DATE)	REFERENCE
USA (established)	Cattle, goat, horse and sheep, fat	0.03	Electronic Code of Federal Regulations, Title 40: Protection of Environment, Part 180.658 (Penthiopyrad tolerances for residues)
	Cattle, goat, horse and sheep, meat	0.03	
	Cattle, goat, horse and sheep, meat by-products	0.09	
	Milk	0.02	
Canada (proposed)	Meat byproducts of cattle, goats, horses and sheep	0.09	Proposed Maximum Residue Limit PMRL2012-5, Penthiopyrad, Pest Management Regulatory Agency, 6 March 2012
	Meat and fat of cattle, goats, horses and sheep	0.03	
	Meat and fat of poultry	0.02	
	Meat byproducts of poultry	0.02	
	Meat and fat of pigs	0.02	
	Meat byproducts of pigs	0.02	
	Eggs	0.02	

	Milk	0.02	

The animal commodity residue definition in the USA and Canada is the same as proposed for Australia, the sum of penthiopyrad and the metabolite 1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-ylcarboxamide expressed as penthiopyrad.

5.3 Potential risk to trade

Finite MRLs are proposed for pome and stone fruit. The pome fruit MRL is the same as the MRLs proposed or established for the USA, Canada and the European Union. The stone fruit MRL is higher than those established or proposed for the USA, Canada and the European Union, although residue levels following use in accordance with the proposed GAP are expected to be similar.

Most export destinations for pome fruit and stone fruit do not currently have MRLs for penthiopyrad. Pome and stone fruit exports are therefore at possible risk as a result of the proposed use of penthiopyrad in Australian fruit.

Detectable residues of penthiopyrad are not expected to be found in poultry commodities as the stockfeeds of interest for this application (apple pomace, tomato pomace and almond hulls) are not commonly fed to poultry. The lactating cattle feeding study, together with calculations of the expected dietary burden for cattle show that detectable residues of penthiopyrad are not expected in milk, meat, offal or fat of mammalian livestock, and MRLs are proposed at the limit of quantitation.

5.4 CONCLUSIONS

Pome fruit

The available residues trial data show that pome fruit when treated with penthiopyrad may contain residues when harvested (range of residues from supervised Australian, America and Canadian apple and pear residues trials (n = 39) was <0.01-0.26 mg/kg; STMR = 0.11 mg/kg. Residues of penthiopyrad may have an impact on the export of Australian pome fruit to the major importing countries. The APVMA welcomes comment on whether penthiopyrad residues will unduly prejudice Australian trade in pome fruit.

Stone fruit

The available residues trial data show that stone fruit from orchards treated with penthiopyrad may contain residues when harvested (range of residues from supervised American and Canadian peach, plum and cherry residues trials (n = 32) was 0.048-1.8 mg/kg; STMR = 0.56 mg/kg. Residues of penthiopyrad may have an impact on the export of Australian stone fruit to the major importing countries. The APVMA welcomes comment on whether penthiopyrad residues will unduly prejudice Australian trade in stone fruit.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Health hazards

Penthiopyrad (CAS: 183675-82-3) is not currently listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA 2011). With the available toxicology information, OCS has not classified penthiopyrad as a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). No human health risk phrases will be required for this new active constituent.

Based on the product toxicology information and concentrations of penthiopyrad in the product (20%), DuPont Fontelis Fungicide is not classified as a hazardous substance in accordance with the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004). Thus, no human health risk phrases have been assigned.

6.2 Formulation, packaging, transport, storage and retailing

The active constituent penthiopyrad will be manufactured overseas. The product DuPont Fontelis Fungicide will be manufactured overseas and imported into Australia in 50-100mL, 150-200mL, 500mL, 1L, 3L and 5L high-density polyethylene (HDPE) bottles with a screw cap.

6.3 Use pattern

The product DuPont Fontelis Fungicide is a suspension concentrate formulation containing 200 g/L penthiopyrad which is to be mixed with water and applied as a spray to control fungal diseases in berries, pome fruit, stone fruits, tree nuts, bulb vegetables, bassica vegetables, cucurbit vegetables, fruiting vegetables, leafy vegetables, legumes, peanuts and root and tuber vegetables.

The product is to be used in autumn, spring and summer for a maximum of 3 applications per season. It is proposed to be used at a rate of 1.0 – 1.75 L/ha in water to a spray volume of 1000 L/ha using a conventional ground boom sprayer with either mechanical or by-pass agitation or by air-blast application. It is applied to crops up to three times per crop as part of either a preventative or curative program.

6.4 Exposure during use

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

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used to estimate exposure. The toxic endpoint of concern and identified NOAEL is derived from repeat dose study in animals, and in this instance a margin of exposure (MOE) of 100 or above is acceptable.

The MOE takes into account both interspecies extrapolation, intra-species variability and the seriousness of the critical health effect of concern. The MOEs for mixing and loading, and both ground boom and air-blast application are acceptable when the operator is wearing a single layer of clothing (cotton overalls or equivalent clothing) with or without gloves. Though OCS notes that in the interest of best practice the applicant has recommended PPE for all mixing, loading and application activities (cotton overalls or equivalent clothing buttoned to the neck and wrist and a washable hat).

6.5 Exposure during re-entry

Based on calculations using the ARTF Occupational Post-Application Risk Assessment Calculator Version 1 EPA Policy 003.1, after use of the product (at the proposed use pattern and use rate) no entry statement is required. Though OCS notes that in the interest of best practice the applicant has recommended waiting until the spray had dried before entering treated areas.

6.6 Recommendations for safe use

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

6.7 Conclusion

The registration of DuPont™ Fontelis® Fungicide containing penthiopyrad at 200 g/L for the control of fungal diseases in berries, pome fruit, stone fruits, tree nuts, bulb vegetables, bassica vegetables, cucurbit vegetables, fruiting vegetables, leafy vegetables, legumes, peanuts and root and tuber vegetables is supported.

DuPont™ Fontelis® Fungicide can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product Material Safety Data Sheet.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

DuPont has applied for the approval of a new active constituent penthiopyrad in conjunction with registration of the end use product DuPont™ Fontelis® Fungicide containing 200 g ac/L.. The product will be marketed for the control of certain diseases in bulb vegetables, legume vegetables, brassica vegetables, peanuts, cucurbits, fruiting vegetables, root and tuber vegetables, leafy vegetables, berries and pome/stone fruit and nut trees. Fontelis® will be applied at a rate of up 1200 g ac/ha three times per season with a minimum interval between treatments of 7 days.

7.2 Environmental Fate

Degradation in Soil

Aerobic Degradation

The route of degradation of penthiopyrad labelled separately in pyrazole (P-label) and thienyl (T-label) rings was studied in the dark under aerobic conditions in three European, two American and one Japanese soil. The studies were extended beyond the 120 days recommended in OECD test guideline 307 (161 days for the soils Oakville, Senozan, Gartenacker and Bruisyard; 360 days for the North American soil and 196 days for the Japanese soil), in order to gather information on the fate of the metabolites.

DM-PCA was the major metabolite, which tended to increase steadily with time and reached nearly 10% after one year in the US study and ranged from 3.3 to 28.0% after 6 months in the other studies. Radiolabelled carbon dioxide steadily increased with time from both pyrazole and thienyl ring labels and accounted from 0.6 to 22.1% of AR (P-label) and from 1.2 to 26% of AR (T-label) at the end of the studies. The mineralisation of the T-label was consistently higher than the P-label reflecting the greater instability of this portion of penthiopyrad after cleavage.

The metabolites, 753-T-DO and 753-A-OH were found between 5 and 10% AR. Other metabolites, PAM, PCA, 753-F-DO, M12 and M11, were present at less than 5% of AR. At the end of some of the studies several metabolites were still increasing in concentration, while >50% of the parent was unchanged.

The DT50 and DT90 values are summarised below:

- Penthiopyrad DT50 and DT90 were 65.3 to 356 and 217 to >1000 days, respectively.
- DM-PCA DT50 and DT90 were 36 to 168 and 121 to 558 days, respectively.

Anaerobic Degradation

The route of degradation in the dark under anaerobic conditions at 20°C was studied in one American soil. In the initial aerobic phase penthiopyrad degraded but once anaerobic conditions were established, the degradation rate slowed down significantly. The main component was unchanged parent and the only major (>5% AR) metabolite was DM-PCA which accounted for 2.7% at the end of the aerobic phase and 7.1% at

the end of the study. Metabolites PAM, PCA, 753-F-DO and 753-T-DO were present, but at levels <3%, peaking at study end. CO_2 was also produced, peaking at 3.1% at study end. No acceptable DT50 or DT90 could be calculated

Photolysis

The route of degradation on soil surfaces of ^{14}C-penthiopyrad (P and T labels applied as a mixture) in the presence of artificial sunlight was studied in one American soil. There was no significant degradation in the dark control but rapid degradation in the presence of light. The major photo-degradates were PAM and PCA which reached peaks of 47 and 36% of AR (adjusted for single-labelled systems) at days 10 and 7 respectively and declined slowly to the end of the study at 15 days when radiolabelled carbon dioxide was the major degradation product (25.8 to 51.6% of AR). Several minor and transient metabolites were detected, with 753-F-DO and M11 and unknowns M1 and M8 being the only ones to exceed 3% AR. This contrasts to the aerobic degradation studies, where the main degradation product was DM-PCA (up to 28% AR), with PAM and PCA of secondary importance (up to 3.0% AR each). CO_2 formation was also lower for the aerobic degradation study (up to 13.3% AR). No new degradation products were formed in the photolysis study relative to the aerobic and anaerobic degradation studies.

The DT50 values are summarised below:

- Penthiopyrad DT50 was 2.8 to 5.5 days.
- PAM DT50 was 7.4 to 24.7 days.
- PAC DT50 was 7.8 to 14.8 days.

Field Dissipation

The following field studies were carried out:

- Six bare soil field studies for US and Canada, with an additional one field study on cropped soil at each of two of these sites;
- Four bare soil field dissipation studies for sites in Europe;
- Two field dissipation studies on turf in the US.

US and Canada bare field and cropped soil

Six terrestrial field dissipation studies were initiated on bare soil under field conditions in the United States and Canada in 2006 using penthiopyrad formulated as a suspension concentrate (200 g/L SC) containing 200 g of active substance per litre. Two additional cropped plots were prepared at the Washington (WA) and Missouri (MO) sites. For the California (CA), Georgia (GA), Ontario (ON), and Saskatchewan (SK) sites, two broadcast applications of the test substance were applied to the test plots in 2006 at the target rate of 400 g ac/ha at an interval of 15 days. A single broadcast application of the test substance was applied to the test plots at the target rate of 200 g ac /ha for WA and 100 g ac/ha for the MO site. Soil samples were taken at intervals up to 10 months. Penthiopyrad degraded at all sites to form several metabolites. The major metabolites (>10% or > 5% at two consecutive time points) were DM-PCA, with PAM and PCA. Metabolites 753-A-OH, 753-F-DO and 753-T-DO were also detected at lower levels.

By the study end, <5% unchanged parent remained at all bare soil sites, while <10% was present at the cropped sites, indicating that there is little potential for further primary metabolite formation after the end of the study.

Data from the replicate plots as replicate observations (un-averaged) were used to calculate the DT50 and DT90 values. The results are summarised below:

- Penthiopyrad DT50 and DT90 were 2.2 to 33.3 and 7.2 to 110.7 days, respectively.
- DM-PCA DT50 and DT90 were 12.6 to 2815 and 41.9 to 9352 days, respectively.
- PAM DT50 and DT90 were 0.9 to 130.2 and 2.9 to 432.4 days, respectively.
- PCA DT50 and DT90 were 2.0 to 16.8 and 6.6 to 55.3 days, respectively.

Turf US Field Trials

Terrestrial field dissipation studies were conducted on turf-covered fields located in Georgia and New York, USA in 2007 using penthiopyrad formulated as a suspension concentrate (SC) containing 200 g ac/L. At the Georgia site, the test substance was applied as two broadcast applications at the target rate of 750 g ac/ha each, with a 14-day interval, for a total of 1500 g ac/ha. At the New York site, the test substance was applied as three broadcast applications at the target rate of 500 g ac /ha each, with a 14-day interval, for a total of 1500 g ac/ha.

Turf, thatch and soil samples were taken at intervals over approximately 195 days in Georgia and 208 days in New York following test substance application. Soil cores were collected to a maximum depth of 90 cm.

By comparison, in 2006 a bare soil field dissipation trial was also conducted at a nearby test site in Georgia, with a similar soil. The DT50 value for penthiopyrad in bare soil at this test site was 2.6 days (FOMC) to 4.7 days (SFO).

At both sites, penthiopyrad parent partitioned from the turf into the thatch and soil layers. Penthiopyrad degraded at both sites to form several metabolites. The major metabolite was DM-PCA. Metabolites PAM, PCA, 753-A-OH, 753-F-DO and 753-T-DO were also detected.

The total residue data (sum of all matrices and depths) was used to determine the rate of dissipation for penthiopyrad for the whole system, using non-FOCUS kinetics. Kinetic calculations of dissipation rate (DT50 and DT90) for penthiopyrad in the turf system was determined. The results are summarised below:

- The DT50 was 1.5 to 10.9 days in turf to thatch;
- The DT50 was 20.5 to 64.7 days in thatch;
- The DT50 was 102 days in soil; and
- The DT50 and DT90 were 12.7 to 39.8 and 42.3 to 132 days in total system, respectively.

Soil Dissipation Studies: Bareground EU Field Trials

Four terrestrial field dissipation studies were initiated on bare soil under field conditions in Europe in 2006 using penthiopyrad formulated as a suspension concentrate (200 g/L SC). The test substance was applied as a single broadcast application at the target rate of 800 g ac/ha, which is the highest proposed total application rate for penthiopyrad per year for the European Union. Soil samples were taken at intervals over approximately 12 to 15 months at the test sites to a depth of 90 cm.

Penthiopyrad degraded at all sites to form several metabolites. The major metabolites were DM-PCA, with PAM and PCA. Metabolites 753-A-OH, 753-F-DO and 753-T-DO were also detected at minor amounts. The amount of parent remaining at study end was <3% of the total applied amount at three sites and <10% of applied at one site. This implies that there is little likelihood of primary metabolites increasing further after study end. Penthiopyrad and metabolite residues were not generally found below 30 cm depth, although small amounts of residues (usually DM-PCA) were found up to 90 cm depth.

Dissipation rates were calculated by the applicant using first-order multi-compartment kinetics (FOMC) because this model rendered a better fit visual fit and more random residual distribution for the residue decline data than non-linear first-order kinetics (SFO). Penthiopyrad DT50 and DT90 were 0.4 to 8.9 and 20.7 to 168.3 days, respectively.

Adsorption and Desorption

Soil adsorption/desorption studies were performed for the evaluation of the mobility in soil of penthiopyrad and its metabolites PCA, DM-PCA, PAM, 753-A-OH and 753-T-DO.

Adsorption/desorption studies were conducted with ^{14}C-labelled (penthiopyrad and DM-PCA) and unlabelled (PCA, PAM, 753-A-OH and 753-T-DO) test items at different concentrations on various soil types covering a range of different soil properties (pH, organic carbon content and textural classification) using the batch equilibrium method. The experiments were conducted at room temperature and the samples were submitted to HPLC analysis for the determination of the test item concentrations. The batch-equilibrium studies consisted of three parts:

1. Preliminary test: to determine the optimal soil-to-solution ratio, the equilibration time for the adsorption and the amount adsorbed at equilibrium.
2. Screening test: to determine the distribution coefficients Kd and Koc.
3. Advanced test: to determine the Freundlich adsorption/desorption isotherms and the influence of concentration on adsorption to soil.

Penthiopyrad

In the adsorption/desorption study of ^{14}C-penthiopyrad (^{14}C-MTF-753), one US and four European soil types were tested. Based on the results of the preliminary test and screening test, a soil/solution ratio of 1:5 and equilibration times of 24 hours (adsorption) and 48 hours (desorption) were used for the determination of the Freundlich adsorption/desorption isotherms. Five test item concentrations covering two order of magnitude (0.299, 0.084, 0.026, 0.008 and 0.003 mg/L) were used.

Desorption equilibrium was reached after about 2 hours in all five soils. Determined K_{FOC} values ranged from 546 to 919, while Freundlich isotherms for desorption ranged from 710 to 1352. It is concluded that penthiopyrad is slightly mobile in soil and that the mobility is dependent on soil % OC and clay content.

DM-PCA

This study included a combined investigation of the degradation rate of DM-PCA in soil, a batch-equilibrium test to determine potential for adsorption/desorption and was also used to investigate time-dependent (sorption supportive information only).

In the adsorption/desorption study of ^{14}C-DM-PCA a soil/solution ratio of 1:1 and an equilibration time of 24 hours (adsorption and desorption) were used for the determination of the Freundlich adsorption/desorption isotherm. Four soils were tested, with DM-PCA concentrations covering two orders of magnitude.

The mean values for the Freundlich adsorption/desorption isotherm coefficients K_{FOC} and K_{des}, F_{OC} were 7 mL/g and 26 mL/g, respectively. The higher Freundlich isotherm coefficients for desorption indicate a partially irreversible sorption process. DM-PCA is very mobile in soil.

PCA

The applicant used three methods to estimate the adsorption coefficient for PCA: batch equilibrium, HPLC and estimation with the KOCWIN program.

In the batch equilibrium adsorption study of PCA, non-radiolabelled soil/solution ratios of 1:1 and 1:5 and an equilibration time of 4 hours were used for the determination of the Freundlich adsorption coefficients, with PCA concentrations covering two orders of magnitude (0.1, 0.5, 1.0, 5.0 and 10 µg/g).

The mean value for the Freundlich adsorption isotherm coefficients K_{Foc} was 8.1 (range 1.7 to 16.5), which indicate that PCA was poorly adsorbed to the four soils tested. The K_d values obtained could not be correlated to any of the soil properties.

Because of the difficulties with the soil K_{oc} study with PCA, additional estimations of K_{oc} for PCA and DM-PCA were made from structure with the US EPA KOCWIN Program and by comparison of retention times on reverse phase HPLC. The results of the estimation from structure showed that the Koc values were comparable for PCA and DM-PCA (22.7 and 11.3 mL/g using the log Kow method and 25.86 and 16.12 L/kg using the MCI method).

In order to estimate the adsorption coefficient in soil for PCA using HPLC, combined reference solutions were prepared containing five reference materials, one at pH 7 and another at pH 2. The log K_{oc} of the test item was found to be -3.7 at pH 6.8 and 0.5 at pH 2.1, which is equal to a K_{oc} value of 0.0002 and 3.5 mL/g, respectively.

The results indicate that PCA was better retained on the column than DM-PCA, and would therefore adsorb to soil more than DM-PCA. This conclusion is supported by the Koc results obtained from the physical property estimation method, as the estimated Koc value for PCA was higher than the value for DM-PCA.

The HPLC retention timed and KOCWIN programme methods have therefore been used to support the theory that PCA is more strongly adsorbed than DM-PCA. It was concluded that PCA is very mobile.

PAM

In the adsorption study of PAM a soil/solution ratio of 1:1 and an equilibration time of 24 hours were used for the determination of the Freundlich adsorption coefficients in four soils, with PAM concentrations covering two orders of magnitude.

The mean value for the Freundlich adsorption isotherm coefficient K_{Foc} was 9.1 (range 6.5 to 12.2 mL/g). By comparing the K_d values obtained (0.1-0.5) with the soil properties it was suggested by the applicant that there was some correlation between PAM adsorption and the soil organic carbon content.

753-A-OH

In the adsorption study of 753-A-OH carried out on four soils, a soil/solution ratio of 1:1 and an equilibration time of 24 hours were used for the determination of the Freundlich adsorption coefficients with 753-A-OH concentrations covering two orders of magnitude (0.1, 0.5, 1.0, 5.0 and 10 µg/g).

The mean value for the Freundlich adsorption isotherm coefficients K_{Foc} was 93.3 (range 45.3 to 211.0 mL/g). By comparing the K_d values obtained (0.5-3.7) with the soil properties it was suggested by the applicant that there is a weak correlation between 753-A-OH adsorption and the soil organic carbon content. It was concluded that 753-A-OH is mobile to moderately mobile.

753-T-DO

In the adsorption study of 753-T-DO a soil/solution ratio of 1:20 and an equilibration time of 4 hours were used for the determination of the Freundlich adsorption coefficients in four soils, with 753-T-DO concentrations covering two orders of magnitude (0.1, 0.5, 1.0, 5.0 and 10 µg/g).

The mean value for the Freundlich adsorption isotherm coefficient K_{Foc} was 484 (range 460.6 to 509.7 mL/g). The applicant states that, by comparing the K_d values obtained (6.0-32.8) with the soil properties a strong correlation between 753-T-DO adsorption and the organic carbon content and was observed. It is concluded that 753-T-DO is of moderate mobility in soil.

Degradation in Aquatic Systems

Hydrolysis

The results show that the degradation of penthiopyrad at 50˚C was less than 10% after 5 days. It can be concluded that the estimated half-life time is greater than one year under representative environmental conditions (25˚C). Therefore, penthiopyrad is considered to be hydrolytically stable.

Aqueous Photolysis

The photodegradation of penthiopyrad at 25˚C during continuous irradiation for 15 days was investigated in a phosphate buffer solution (pH 7.0), resulting in a target concentration of 2.10 mg/L penthiopyrad. This

solution was irradiated using a Suntest CPS, Original Hanau apparatus, to simulate outdoor summer sunlight.

No significant photodegradation of the parent molecule occurred during 15 days of continuous irradiation with artificial sunlight at 25˚C in pH 7.0 buffer solution, showing that penthiopyrad was photolytically stable.

Ready Biodegradability

The ready biodegradability of penthiopyrad was determined under aerobic conditions by following the biochemical oxygen demand (BOD) by means of manometric methods over the 28 days the test was conducted according to OECD Guideline for Testing of Chemicals No. 301 F (1992). Penthiopyrad was not biodegradable under the test conditions.

Aerobic Conditions

The route of degradation of penthiopyrad labelled separately in pyrazole (P-label) and thienyl (T-label) rings (a single sample per label of the test item representing duplicates per aquatic system) was studied in the dark under aerobic conditions at 20°C in two aquatic systems: river (sandy loam sediment, 0.87% OC, water pH 7.05 and sediment pH 7.39 at start of incubation) and pond (silt loam sediment, 3.40% OC, water pH 7.65, sediment pH 6.96 at start of incubation).

In both aerobic aquatic systems (river and pond), penthiopyrad steadily dissipated from the water phase to the sediment. The majority of the radioactivity in the sediment was extractable and this extractable radioactivity increased over time, reaching a maximum on day 56. The amount of non-extractable radioactivity in the sediment increased continuously with time with bound residues reaching maximum levels of 12% and 11% AR in the river and pond systems, respectively, on day 185.

Levels of parent in sediment are >10% by day 14 for both systems. Dissipation of parent is slightly faster in the river system (mean of 55.5% remaining in the total river system and 65.6% remaining in the total pond system at study end). Low mineralization of both labels of the test item was observed. Radioactive carbon dioxide amounted to less than 3 or 5% AR for river or pond system.

DT50 values for the river system were 10.9 days for water using the two compartment model and 295 days for the sediment using SFO, with a DT50 value of 242 days for the whole system using SFO kinetics. DT50 values for the pond system were 8.9 days for water using the two compartment model and 559 days for the sediment using SFO, with a DT50 value of 296 days for the whole system using SFO kinetics. The DT50 values have been extrapolated beyond the end of the study (185 days).

Besides the parent compound, numerous degradation products were detected, including six that were identified as PAM, PCA, DM-PCA, 753-F-DO, 753-T-DO and 753-A-OH. Metabolites seem to be present at higher levels in the river system than in the pond system and there are more major metabolites in the river system.

PCA was the major degradation product in both aquatic systems (maximum 11.9% AR on day 185 for the total river system – mostly in the water phase). DM-PCA and 753-A-OH were present in amounts approaching or exceeding 5% AR in both total systems. In the river system, most metabolites appear to be

starting to plateau at study end, including PCA and 753-A-OH, although DM-PCA may still be increasing. There were no major metabolites in sediment for either system.

The results of the degradation studies in the two aquatic systems show that the pathway that leads to degradation of penthiopyrad is the same observed in the soil degradation studies. There are no major metabolites in sediment, with metabolites present in higher concentrations in water, particularly towards the end of the study.

Anaerobic Conditions

The degradation under anaerobic conditions at 20°C in the dark was investigated in an aquatic system (pond) silty clay loam, sediment 3.3% OC, sediment pH 7.95, water pH 8.01 at start of incubation). Penthiopyrad was the main component in the total anaerobic pond system, slightly decreasing from 102.3% on day 0 to 99.0% at the end of the study (100 days). Up to five minor degradation products, characterized as PAM, PCA, DM-PCA, DM-753 and 753-T-DO, were detected only in traces. None of them individually exceeded 2.7% AR in the total anaerobic system. A very low mineralisation (less than 1% AR) and no significant bound residues (max. 3.0% AR on day 100) were observed.

Penthiopyrad steadily dissipated from the anaerobic water phase to the sediment via adsorption. After 100 days, almost all applied radioactivity was present as unchanged parent (99% roughly partitioned as 20:80 split in water: sediment). The degradation in the overall system was so slow that a meaningful DT50 could not be calculated.

Fate and Behaviour in Air

The vapour pressure and Henry's Law Constants of penthiopyrad as measured by the applicant are 2.93 x 10^{-6} Pa and 7.66 x 10^{-3} Pa m^3 mol^{-1} respectively. Neither penthiopyrad nor any of its principal degradation products have significant volatility.

The applicant has submitted a theoretical calculation of the potential for photo-oxidation of penthiopyrad in the atmosphere using the computer modelling software, "Atmospheric Oxidation Program (AOPWIN v.1.9)". A rate constant of 82.902 x $10^{-12}$$cm^3$/$molecule^{-1}$/$sec^{-1}$ was calculated for reaction with OH radicals. This corresponded to a first order DT50 of 0.129 days when based on an OH concentration of 1.5 x 10^6 cm^3 on a 12-hour basis. Penthiopyrad is not persistent in air.

Environmental Effects

Avian

The acute LD50 value for the northern bobwhite is >2250 mg/kg bw and the dietary LC50 is > 5790 mg/kg diet for the northern bobwhite and the mallard.

The reproduction toxicity NOEC is 1520 mg ac/kg diet for the mallard, there were no treatment-related effects observed upon any adult parameter, but the analysis detected statistically and biologically significant treatment-related reductions in eggs and eggs set at the highest treatment level.

The LD50 to the zebra finch in an acute test could not be determined due to regurgitation at every dose level; therefore, an ED50 (effect dose) is calculated as regurgitation followed a general dose response pattern, the ED50 is estimated to be 335 mg ac/kg bw. The acute LD50 values for the northern bobwhite exposed to the product is >2266 mg/kg bw.

Based on these tests penthiopyrad is practically non-toxic to the bobwhite quail and mallard duck at the acute and sub-dietary levels, but some toxicity was seen with the acute test on the zebra finch.

Fish

The LC50 values for fathead minnow, rainbow trout, common carp and bluegill sunfish are 290, 386, 572 and 1242 µg ac/L, respectively, based on mean-measured concentrations of the active constituent, indicating penthiopyrad is toxic to very toxic to fish.

The 96 hour LC50 values for the metabolites DM-PCA (rainbow trout), PCA (zebra fish), and PAM (rainbow trout) are greater than 99.19, 96.7, and 100.3 mg/L, respectively, based on mean-measured concentrations. The 96 hour LC50 rainbow trout value for the 753-A-OH metabolite is greater than 9300 µg/L and the 96 hour LC50 rainbow trout value for the metabolite 753-T-DO is 5004 µg/L. The latter two metabolites are considered to be harmful and toxic, respectively which is classified as very toxic.

The chronic toxicity of penthiopyrad was tested on the early life stage of the fathead minnow over 28 days and the NOEC based on growth (total length and dry weight) and mean-measured concentrations was determined to be 100 µg ac/L, which is classified as very toxic.

The low whole fish bioconcentration factors (BCF) values of 155-186 (low and high doses) indicate that penthiopyrad does not bioaccumulate in rainbow trout (*Oncorhynchus mykiss*).

The acute LC50 values for rainbow trout, fathead minnow, sheepshead minnow exposed to the product were 356, 309 and 2634 µg ac/L, respectively, based on mean-measured concentrations of the product. This is a similar toxicity range to the active constituent.

Aquatic Invertebrates

The EC50 value for *Daphnia magna* was 2531 µg ac/L, based on immobilisation and the mean-measured concentrations of the active constituent and indicating penthiopyrad to be toxic. The 48-hour EC50 values for immobilisation of *Daphnia magna* exposed to the metabolites DM-PCA, PCA, PAM were determined to be greater than 99.19, 91.75, and 100.5 mg/L, respectively, based on mean-measured concentrations classified as practically non-toxic. The 48-hour EC50-value for immobilisation of *Daphnia* exposed to the metabolites 753-A-OH and 753-T-DO was determined to be more than 8700 and 4479 µg/L, respectively (at worst toxic).

The chronic toxicity to *Daphnia magna* was determined in a 21-day reproduction study under flow-through conditions. The NOEC, based on reproduction and mean-measured concentrations, was determined to be 471 µg ac/L, classified as toxic.

The 48-hour EC50 values for immobilisation of *Daphnia magna* exposed to the SC product were between 59.6 and 157 µg/L for unfed *Daphnia* and >1660 µg/L for fed *Daphnia*. The EC50 values for immobilisation of older *Daphnia magna* exposed to the SC product was > 1530 µg/L for 14/28 days old *Daphnia*. The 21 day

chronic NOEC value for survival, growth and reproduction of *Daphnia magna* exposed to the SC product was 10.60µg/L. All values are based on mean-measured concentrations. The SC formulation was considered to be toxic to very toxic to *Daphnia*.

Algae and Aquatic Plants

The toxicity of penthiopyrad was evaluated for the algal species *Pseudokirchneriella subcapitata, Skeletonema costatum, Anabaena flos-aquae and Navicula pelliculosa*. The results were calculated in terms of both the geometric mean-measured and initial measured concentrations (where specified). The 72 hour toxicity study with *Pseudokirchneriella subcapitata* determined the EC50 for growth rate was estimated to be > 4060 µg ac/L. For the 96 hour toxicity studies with *Pseudokirchneriella subcapitata, Skeletonema costatum, Anabaena flos-aquae and Navicula pelliculosa*, the 96 hours EC50 for cell density (the most sensitive endpoint) were 1533 µg ac/L (geometric mean-measured), 1200 µg ac/L (geometric mean-measured), >1660 µg ac/L (initial measured) (>1240 µg ac/L geometric mean-measured), and >1470 µg ac/L (initial measured) (>1429 µg ac/L geometric mean-measured), respectively. The growth rate EC50 for the 96 hour toxicity studies with *Pseudokirchneriella subcapitata* and *Skeletonema costatum* were estimated to be >2000 µg ac/L (geometric mean-measured) and > 1576 µg ac/L (geometric mean-measured), respectively. Thus penthiopyrad is at worst toxic to algae.

The metabolites DM-PCA, PAM, and 753-A-OH all had estimated EC50 values for *Desmodesmus subspicatus* (DM-PCA) and *Pseudokirchneriella subcapitata* (PAM and 753-A-OH) greater than the highest concentration that was tested (>85.5 mg/L, 100.4 mg/L, and >8430 µg/L, respectively). The metabolites PCA and 753-T-DO had estimated EC50 values for *Pseudokirchneriella subcapitata*, based on cell density, of 83 mg/L and 790 µg/L (geometric mean-measured), respectively. The EC50 values for growth rate for the metabolites PCA and 753-T-DO were >94.1 mg/L and 1100 µg/L (geometric mean-measured), respectively. The metabolites 753-T-DO is only one with significant algae toxicity, in fact it is more toxic than parent.

The toxicity of penthiopyrad to the aquatic vascular plant *Lemna gibba* resulted in an estimated EC50 > 1205 µg ac/L, the highest concentration tested showing penthiopyrad is at worst toxic to aquatic algae.

Sediment Dwelling Organisms

The chronic toxicity of penthiopyrad to Chironomus riparius was assessed in a static study over an exposure period of 28 days. The 28-day LC_{50} of penthiopyrad for survival was 67.8 mg ac/kg, based on the nominal test concentrations. The 28-day NOEC and LOEC values, based on the reduced emergence rate of adults were determined to be 50 and 100 mg ac/kg, respectively.

Marine & Other Organisms

In an acute toxicity test with the saltwater mysid under static-renewal conditions the 96-hour LC50 was estimated to be >1700 µg ac/L. In an acute toxicity test with the eastern oyster under flow-through conditions the 96-hour EC50 for shell deposition was estimated to be 1200 µg ac/L. These are all classified as toxic.

The acute LC/EC50 values for saltwater mysid and eastern oyster exposed to the product were 2345 and >233 µg ac/L, respectively, based on mean-measured concentrations of the product, all indicating toxicity.

Terrestrial Invertebrates

Penthiopyrad technical 48 hour LD50 values were greater than 500 µg ac/bee, for both acute oral and acute contact toxicity, indicating it is very slightly non-toxic. This is also the case when tested as the proposed SC formulation, as opposed to the EC formulation, which is noted as slightly toxic to bees.

Non-target Arthropods

There was little toxicity to *Aphidius rhopalosiphi* on glass plates but *Typhlodromus pyri* was much more sensitive in Tier I tests. Under laboratory conditions, the 48 hour LR50 and the 7-day LR50 values of Penthiopyrad 20 SC formulation were 3504.5 g ac/ha and 327.1 g ac/ha to *Aphidius rhopalosiphi* and *Typhlodromus pyri*, respectively. Extended laboratory testing with dried residues on leaves indicates much lower toxicity except for the EC formulation to *Typhlodromus pyri*.

The SC formulation showed lower toxicity to predatory mites under field test conditions and little toxicity to the predatory bug (*Orius laevigatus*) and to the green lacewing (*Chrysoperla carnea*) in extended laboratory tests.

Earthworms

In an acute toxicity test with Eisenia fetida, the 14-day LC50 value was determined to be >1000 mg ac/kg soil dry weight, the highest concentration tested. The 14-day LC50 values for the metabolites DM-PCA, PCA and PAM were all determined to be greater than 1000 mg/kg soil dry weight, the highest concentration tested. All these substances are classified as very slightly non-toxic.

In a sublethal toxicity test with penthiopyrad the NOEC for mortality, growth, reproduction and feeding activity of the earthworm Eisenia fetida was determined to be ≥ 48 mg ac/kg soil dry weight, which was the highest concentration tested. In addition, the overall NOEC values for the metabolites DM-PCA, PCA and PAM were all determined to be ≥ 48, 50 and 50 mg/kg soil dry weight, respectively, which are the highest concentrations tested.

The NOEC in a toxicity test with Penthiopyrad 200 g/L SC for mortality and growth of the earthworm Eisenia fetida was equal to 31.3 mg/kg soil dry weight.

Soil Microbial Activity

Penthiopyrad did not affect the short-term respiration and nitrogen turnover in a soil treated up to 1000 mg ac/kg dry soil (equivalent to an application rate of 750 kg ac/ha). The formulations Penthiopyrad 200 g/L SC and EC also did not affect these parameters at 20 and 36 L/ha, respectively. However, tests of the metabolites DM-DCA, PCA and PAM were indeterminate for nitrogen transformation as they were not carried out for long enough (> 28 d) or at too high a limit dose (100 mg/kg to carbon mineralisation).

Micro-organisms

The effects of Penthiopyrad 20 SC and its metabolite DM-PCA on the breakdown of organic matter in litterbags were assessed under field conditions. While at the higher rate the treated decomposition was >20% lower after 1 year (no greater than 10% allowed) it was concluded that penthiopyrad and DM-PCA did

not cause any long-term adverse impacts on organic matter decomposition at the lower treated rate (combined 800 g ac/ha and 165 g DM-PCA/ha).

Terrestrial Plants

There were adverse effects on seedling emergence (ryegrass (*Lolium perenne*) and tomato (*Lycopersicon esculentum*) were the most sensitive species), and vegetative vigour (wheat (*Triticum aestivum*) and soybean (*Glycine max*) were the most sensitive species). Although no test species had an inhibition of greater than 25% for any endpoint, there was, however, significant reduction of emergence and survival (14%) for ryegrass and growth (dry weight) and 20% reduction for tomato for the seedling emergence study, and a 20% and 8% reduction in growth (dry weight) for wheat and soybean, respectively, for the vegetative vigour study.

The NOEC for both the seedling emergence and vegetative vigour studies were < 1563 g ac/ha for ryegrass (emergence and survival), tomato, and wheat (growth – dry weight). Definitive NOECs were not obtained for these species exhibited statistically significant reductions at the limit concentration relative to the negative control (and/or pooled or formulation controls).

Risk Assessment

Fontelis® will be applied at a maximum rate of up 350 g ac/ha applied up to three times per season with a minimum interval between treatments of 7 days interval between applications. This equates to a maximum seasonal application rate of 1050 g ac/ha.

The major potential risk to the environment was penthiopyrad potential to accumulate in soil and water from multiple applications. In spite of conservative modelling, likely to over predict the exposure, acceptable risk to all organisms except for aquatic organisms from spray drift.

Birds

The risk quotients were acceptable under the worst case scenarios for each case. Thus, the risk to bird is acceptable.

Aquatic Organisms

The risk to water and sediment dwelling organisms from spray drift was found to be acceptable if downwind no-spray zones were implemented. Moreover, acceptable risk to aquatic organisms was found from run-off water entering environmental waters.

Terrestrial Organisms

The risk quotients were acceptable under the worst case scenarios for earthworms, non-target arthropods, plants, and soil non-target micro-organisms. Thus, the risk to terrestrial organisms is acceptable.

Mandatory No-spray zones

On the basis of the information provided, DSEWPaC recommends that the APVMA be satisfied that the proposed use of DuPont™ Fontelis® fungicide for the control of certain fungal diseases in certain fruit and vegetable crops would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment provided the following recommendations for non-spray downwind buffer zones are implemented.

For ground application: Boom equipment –

Vegetables (including strawberries)

> "**DO NOT** apply if there are aquatic or wetland areas including aquacultural ponds within **10 metres** downwind from the application area."

For ground application: Airblast equipment -

Berries

> "**DO NOT** apply if there are aquatic or wetland areas including aquacultural ponds within **10 metres** downwind from the application area."

Pome/stone fruit orchards

> "**DO NOT** apply if there are aquatic or wetland areas including aquacultural ponds within **80 metres**, downwind from the application area."

Tree nuts

> "**DO NOT** apply if there are aquatic or wetland areas including aquacultural ponds within **100 metres**, downwind from the application area."

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed Use Pattern

It is proposed that DuPont™ Fontelis® Fungicide (200g/L penthiopyrad as a suspension concentrate) be used for the control of a range of fungal diseases in various vegetable, fruit and nut crops. It will be used at the rate of 1.75 L/ha for all diseases of broadacre vegetable crops, at 175ml/100L for strawberries, for tree crops and stone fruit the rate is 150 ml/100 L and at 75 mL/100L as protectant or 125 mL/100 L as a curative application for pome fruit. As a protectant spray it is applied before disease is apparent and then after a 7-14 interval.

8.2 Summary of Evaluation of Efficacy and Crop Safety

The application is supported by a data package of 108 trial results. These trials were conducted globally in USA, Mexico, Canada, Spain, Brazil and Australia. All overseas trial conditions were comparable with Australian conditions and were conducted by external bodies which all used a strict format provided by the applicant. This ensured that all trials were of a high standard, used four replicates of all treatments, applied the candidate formulation at label rates, documented well the spray application and disease rating details and included usually two industry standard fungicides.

All trials included the application of cover spray schedules of 2-10 applications of Fontelis® at a range of rates, including label rates, at 7-14 days intervals. As spray applications were made to near leaf runoff, the volume of spray varied considerably, depending on the bulk of the crop, from 150L/ha for field crops up to 2500L/ha for pome and stone fruit. The size of plots varied with the crop from single-tree plots to 10-35 sq m plots for field crops. Assessments were for percentage infection and disease severity on plant parts (leaves, stem, fruit, blossom or whole plant (usually sampled 5-20 days after a spray application).

Results from four USA trials on Botrytis in strawberry showed that high levels of control was achieved in all trials at the proposed label rate and that the level of control achieved was equal to that of the industry fungicide. Results from a single trial on powdery mildew of strawberry showed moderate control under extreme disease pressure and this was superior to that achieved with an industry standard fungicide. In three of the four strawberry cultivars tested there were no symptoms of phytotoxicity observed. In the fourth cultivar while there was a dose related response to Fontelis® of leaf reddening and flecking, however it was not severe and had no effect on fruit quality.

Results from 10 Australian trials on apple and pears showed that at the proposed label rate, Fontelis® acts as a protectant against Powdery Mildew and Black Spot, providing high levels of control statistically equivalent or superior to, six Australian industry standard fungicides. At the higher label rates Fontelis® was also effective as an eradicant fungicide. Similar results were also obtained in 18 overseas trials. Six trials on apple Black Spot averaged 89% control on leaves for DuPont™ Fontelis® Fungicide equivalent to the industry standard. Two trials on pear Black Spot averaged 100% control on leaves, equivalent to the industry standard. In all trials no symptoms of phytotoxcicty occurred on nine cultivars of apple and two of pear.

Data on stone fruit disease control were provided from trials in USA (18), Canada (2), and Australia (2). These trials, on apricot, cherry, nectarine and peach adequately demonstrated that at the proposed label

rate, Fontelis® provided a high level of control of Monilinia Blossom Blight and Monilinia Brown Rot and Scab, and that this control was equivalent to that provided by several industry standard fungicides. In all the trials, Fontelis® averaged 82% control of Brown Rot, 83% control of Blossom Blight and 87% control of Scab. No symptoms of phytotoxicity were observed in these trials on any stone cultivar.

Trial data from six efficacy trials (USA) in almonds confirmed that Fontelis® Fungicide, at label rates, provided a high level of control of Blossom Blight and Brown Rot, equivalent to several industry standard fungicides. No symptoms of phytotoxicity were observed on any of the almond cultivars tested.

Four trials in the USA confirmed the efficacy of DuPont™ Fontelis® Fungicide for the control of Botrytis and Purple Patch in onions, equivalent to industry standards. No symptoms of phytotoxicity were observed on any of the onion cultivars tested.

Data from three USA efficacy trials on Brassica (cabbage) showed that Fontelis®, at the proposed label rate, provided high levels of control of White Mould, equivalent to two industry standard fungicides. No symptoms of phytotoxicity were observed on any cabbage cultivar .These results were considered sufficient to support control of this disease in all Brassicas listed.

Seventeen trials conducted in Australia, Canada, USA and Spain demonstrated the efficacy of DuPont™ Fontelis® Fungicide for the control of Powdery Mildew, Grey Mould (Botrytis) and Gummy Stem Blight in zucchini, pumpkin, cumcumber, melon and water melon. High levels of control by DuPont™ Fontelis® Fungicide were recorded in all these trials, equivalent to industry standard fungicides. Over all trials, control a week after spraying was 93% for Powdery Mildew, 82% for Gummy Stem Blight and 65 – 81% for Grey Mould. No symptoms of phytotoxicity were observed on any of the cucurbit cultivars in these trials. This data was considered sufficient to support all nine cucurbit RLP claims.

Data from 11 trials conducted in Australia, USA, Mexico and Spain were provided, demonstrating the efficacy of Fontelis® against Powdery Mildew, Grey Mould and Early Blight in tomato, chilli and bell pepper. High levels of control by Fontelis® were recorded in all these trials, equivalent to industry standard fungicides. No symptoms were observed on any cultivar in these trials. Extension of the RLP claims to include all five fruiting vegetables is supported by this data.

Eight trials in lettuce were conducted in USA, Spain and Canada to demonstrate the efficacy of Fontelis® against Grey Mould and Sclerotinia. High levels of control were achieved by Fontelis® with the level of control achieved equivalent to that achieved by several industry standard fungicides. No symptoms were observed on any cultivar in these trials. Extension of the RLP claims to include all nine leafy vegetables is supported by this data.

Data were provided from seven trials conducted on carrots and potato in USA and Canada. These trials demonstrated that Fontelis® provided a high level of control of Early Blight and Powdery Mildew that was equivalent or superior to that obtained with several industry standard fungicides. Slight phytotoxic symptoms were recorded after a Fontelis® application in two trials on potato cv. Narland. Symptoms were transient and were not recorded after other applications. In the other trials no symptoms were recorded with applications of Fontelis® at up tp 875 g ai/ha, well above label rate. Based on this data, extending the claims to include control of these two diseases on all 10 root vegetables is supported.

Crop Safety

The information presented indicate that Fontelis® is safe to use on the nominated vegetable, fruit and nut crops when used as directed. Only transient symptoms of phytotoxicity were recorded on only two plant cultivars in all supporting trials. Therefore, Fontelis® can be considered of low phytotoxicity and no label warnings needed.

Resistance Management

Penthiopyrad belongs to the pyrazole carboxamide sub-group of the succinate dehydrogenase inhibitor (SDHI group of fungicides. The Fungicides Resistance Action Committee (FRAC), a specialist technical group of CropLife International, has classified penthiopyrad's pesticidal mode of action as inhibition of succinate dehydrogenase in complex II of the mitochondrial respiratory chain, resulting in inhibition of spore germination, germ tubes and mycelial growth. CropLife Australia's Fungicide Resistance Management Review Group has designated penthipyrad as a Group 7 fungicide. The proposed use pattern is subject to a CropLife anti-reistance strategy. Restraints included on the proposed label are consistent with the current CropLife Australia resistance management strategy for Group 7 fungicides.

8.3 Conclusion

The trial data presented substantiates the claims on the proposed label for Fontelis®. The directions for use, restraints, situations, pests and advice or critical comments on crop safety, application techniques, withholding periods, resistance warnings all appears to be appropriate.

Therefore, in terms of evidence for the efficacy of the product and its safety to target and non-target species, the application by DuPont Australia Pty Ltd for the registration of for DuPont™ Fontelis® Fungicide is supported when used in accordance with the proposed label instructions and Good Agricultural Practice (GAP).

9 LABELLING REQUIREMENTS

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

ACTIVE CONSTITUENT: 200 g/L PENTHIOPYRAD

GROUP	7	FUNGICIDE

For the control of certain fungal diseases in fruit, nut and vegetable crops as per the Directions for Use

IMPORTANT: READ THIS LEAFLET BEFORE USE

DIRECTIONS FOR USE

RESTRAINTS:
DO NOT apply if rainfall is expected within 1 hour of application.
DO NOT use on hydroponic crops.
DONOT apply by air.

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 when wind speed is less than 3 or more than 20 km per hour are measured at the application site.
DO NOT direct the spray above trees 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 the **mandatory no-spray zones** shown in Table 1 below.

Table 1: No-spray Zones for Protection of the Aquatic Environment	
FOR GROUND APPLICATION: BOOM APPLICATIONS	
Wind Speed Range at Time of Application	**Downwind mandatory No-Spray Zone**
3 to 20 kilometres per hour	10 metres
FOR GROUND APPLICATION: AIRBLAST APPLICATION	
3 to 20 kilometres per hour	Pome/Stone fruit orchards – 80 metres Tree nuts – 100 metres

EXPORT STATEMENT: Growers should note that suitable Maximum Residue Levels (MRLs) or import tolerances may not be established in all markets for produce treated with Fontelis® fungicide. If you are growing produce for export, please check with DuPont for the latest information on MRLs and export tolerances before using this product.

For use in all States where appropriate for the crop and/or disease.

TREE AND FRUIT CROPS

CROP	PEST	RATE	WHP	CRITICAL COMMENTS	
Apply by dilute or concentrate spraying equipment. Apply the same total amount of product to the target crop whether applying this product by dilute or concentrate spraying methods. Refer to Application section of the label. Thorough fruit coverage is essential. Use in accordance with CropLife Fungicide Resistance Management Strategy guidelines.					
Strawberry	Grey mold (Botrytis) (*Botrytis cinerea*) Powdery mildew (*Sphaerotheca* spp.)	175 mL/100 L 1.75 L/ha	Nil	Begin applications prior to disease development and continue on a 7 to 10 day interval. Use shorter interval when disease pressure is high. **DO NOT** apply more than two (2) sequential applications of Fontelis™ fungicide or other Group 7 fungicides before switching to a fungicide with a different mode of action. Maximum seasonal use rate is 5.25 L/ha.	
Pome fruit including; Apples Nashi pears Pears	Apple black spot (Scab) (*Venturia inaequalis*) Apple powdery mildew (*Podosphaera leucotricha)* Pear scab (*Venturia pirina*)	**Dilute spraying:** 75 mL/100 L **Concentrate spraying:** Refer to **Mixing/ Application** section	28 days	**Protectant program:** Begin applications prior to disease development and continue on a 7 to 21 day interval depending on the targeted diseases. Application interval for Apple black spot (Scab) and Pear scab is 7 to 10 days. Application interval for Powdery mildew is 14 to 21 days.	**Resistance Management Strategy:** The use of Fontelis® fungicide is subject to a CropLife Australia Resistance Management Strategy. **DO NOT** apply more than two (2) sequential applications of Fontelis® fungicide or other Group 7 fungicides before switching to a fungicide with a different mode of action. **DO NOT** apply more than a total of three applications of Fontelis® fungicide or other Group 7 fungicides per season. Refer to **Resistance Management Strategy** in General Instructions for further details. **DO NOT** use a concentration factor greater than 3X, for concentrate application.
	Apple black spot (scab) (*Venturia inaequalis*) Pear scab (*Venturia pirina*)	**Dilute spraying:** 100 or 125 mL /100 L **Concentrate spraying:** Refer to **Mixing/ Application** section		**Curative program:** DuPont™ Fontelis® will provide curative control for 3 days after commencement of an infection period. Use higher rate under heavy disease pressure. New infections commencing within 10 days of spraying **DO NOT** require re-treatment. Infections occurring more than 10 days after a curative spray application will require another curative spray. If changing to another fungicide after using Fontelis® fungicide, spray within 10 days depending upon weather conditions. If continuing with Fontelis® fungicide on a protectant programme retreatment is not needed for 10 to 14 days.	

CROP	PEST	RATE	WHP	CRITICAL COMMENTS
Stone fruits including; Almond Apricots Cherries Nectarines Peaches Plums Prunes (fresh)	Brown rot (Blossom blight) (*Monilinia* spp.) Scab (Freckle) (*Cladosporium carpophilum,- Venturia carpophila)*	150 mL/100 L	Nil	Begin applications prior to disease development and continue on a 7 – 14 day interval. Use higher rate and shorter interval when disease pressure is high. The use of Fontelis® fungicide is subject to a CropLife Australia Resistance Management Strategy. **DO NOT** apply more than two (2) sequential applications of Fontelis® fungicide or other Group 7 fungicides before switching to a fungicide with a different mode of action. **DO NOT** apply more than a total of three applications of Fontelis® fungicide or other Group 7 fungicides per season. Refer to **Resistance Management Strategy** in General Instructions for further details. **DO NOT** use a concentration factor greater than 3X, for concentrate application.
Tree nuts including; Chestnut Filbert (Hazelnut)	Brown rot (Blossom blight) (*Monilinia* spp.)	150 mL/100 L	14 days	Begin applications prior to disease development and continue on a 7 to 14 day interval. Use shorter interval when disease pressure is high. The use of Fontelis® fungicide is subject to a CropLife Australia Resistance Management Strategy. **DO NOT** apply more than two (2) sequential applications of Fontelis® fungicide or other Group 7 fungicides before switching to a fungicide with a different mode of action. **DO NOT** apply more than a total of three applications of Fontelis® fungicide or other Group 7 fungicides per season. Refer to **Resistance Management Strategy** in General Instructions for further details **DO NOT** use a concentration factor greater than 3X, for concentrate application.

VEGETABLE CROPS

CROP	PEST	RATE	WHP	CRITICAL COMMENTS	
Onions Shallots Spring onions	Botrytis blight and Neck rot (*Botrytis* spp.) Purple blotch (*Alternaria porri*)	1.75 L/ha	3 days	Begin applications prior to disease development and continue on a 7 to 14 day interval. **DO NOT** make more than 2 sequential applications of Fontelis® fungicide before switching to a fungicide with a different mode of action. Maximum seasonal use rate is 5.25 L/ha.	
Brassica vegetables including; Broccoli Brussels sprout Cabbage Cauliflower	White mould (Sclerotinia stem rot) (*Sclerotinia* spp.)		Nil		
Brassica leafy vegetables including; Buk choy Chinese broccol (Gai lum/Gai lan/Kai lan), Chinese cabbage (Pet sai / Wombok / Haksukai) Choy sum Gai choy / Am soy Kai choy Kale Mibuna Leafy mustard including Indian mustard and Mustard spinach (Komatsuma), Pak choy Tat soy					
Cucurbit vegetables including (field and protected crops); Bitter melon Chokos Cucumber Gherkin Marrow Melons Pumpkin Squash Zucchini	Grey mould (*Botrytis cinerea*) Powdery mildew (*Sphaerotheca fuliginea*, *Erysiphe cichoracearum*)		1 day	Begin applications prior to disease development and continue on a 7 to 14 day interval. Use shorter interval when disease pressure is high.	**DO NOT** apply more than two (2) sequential applications of Fontelis® fungicide or other Group 7 fungicides before switching to a fungicide with a different mode of action. Maximum seasonal use rate is 3.5 L/ha.
	Gummy stem blight (*Didymella bryoniae*)			Begin applications prior to disease development and continue on a 7 - 10 day interval. Use shorter interval when disease pressure is high.	

CROP	PEST	RATE	WHP	CRITICAL COMMENTS
Fruiting vegetables including (field and protected crops) including: Egg plants Capsicums (Pepper) Chillies Tomatillo Tomatoes (field + greenhouse)	Early blight (*Alternaria solani*) Grey mould (*Botrytis cinerea*) Powdery mildew *(Leveillula taurica)*	1.75 L/ha	Nil	Begin applications prior to disease development and continue on a 7 to 10 day interval. Use shorter interval when disease pressure is high. **DO NOT** apply more than two (2) sequential applications of Fontelis® fungicide or other Group 7 fungicides before switching to a fungicide with a different mode of action. Maximum seasonal use rate is 5.25 L/ha.
Leafy vegetables including; Chinese cabbage Endive Fennel Kale Cress Lettuce Mustard Silverbeet Spinach	Sclerotina rot (Lettuce drop) *(Sclerotinia* spp.*)* Grey mould (*Botrytis cinerea*) Powdery mildew (*Erysiphe cichoracearum*)		3 days	
Root and Tuber vegetables including: Beetroot Carrots Celeriac Galangal Parsnips Potatoes Radish Swedes Sweet potato Turnips	Early blight (Target spot, Leaf spot) (*Alternaria* spp.) Powdery mildew (*Erysiphe* spp.)		7 days	Begin applications prior to disease development and continue on a 7- to 14-day interval. Use shorter interval when disease pressure is high. **DO NOT** apply more than two (2) sequential applications of Fontelis® fungicide or other Group 7 fungicides before switching to a fungicide with a different mode of action. Maximum seasonal use rate is 3.5 L/ha.

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

WITHHOLDING PERIODS

HARVEST

BRASSICA VEGETABLES, BRASSICA LEAFLY VEGETABLES, FRUITING VEGETABLES (OTHER THAN CUCURBITS), STONE FRUIT, STRAWBERRIES: NOT REQUIRED WHEN USED AS DIRECTED.

ONIONS, SPRING ONIONS, SHALLOTS, LEAFLY VEGETABLES (EXCEPT BRASSICA LEAFY VEGETABLES): DO NOT HARVEST FOR 3 DAYS AFTER APPLICATION.

CUCURBIT VEGETABLES: DO NOT HARVEST FOR 1 DAYS AFTER APPLICATION.

TREE NUTS: DO NOT HARVEST FOR 14 DAYS AFTER APPLICATION.

POME FRUIT: DO NOT HARVEST FOR 28 DAYS AFTER APPLICATION.

ROOT AND TUBER VEGETABLES: DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION.

GRAZING

DO NOT GRAZE OR CUT FOR STOCK FOOD.

GENERAL INSTRUCTIONS

DuPont™ Fontelis® fungicide is a broad-spectrum fungicide, recommended for control of foliar and soil-borne plant diseases, and has preventive, curative, and locally systemic activity. DuPont™ Fontelis® must be applied in a regularly scheduled protective spray program in rotation with other fungicides. See the Directions for use table for specific crop/disease recommendations.

FUNGICIDE RESISTANCE WARNING

For fungicide resistance management DuPont™ Fontelis® fungicide is a Group 7 fungicide.

Some naturally occurring fungal biotypes resistant to Fontelis® fungicide and other Group 7 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungi population if Fontelis® fungicide and other Group 7 fungicides are used repeatedly. The effectiveness of Fontelis® fungicide on resistant individuals could be significantly reduced. Since the occurrence of resistant individuals is difficult to detect prior to use DuPont accepts no liability for any losses that may result from the failure of Fontelis® fungicide to control resistant fungi.

DuPont™ Fontelis® fungicide may be subject to specific resistance management strategies. To help prevent the development of resistance to Fontelis® fungicide, use Fontelis® fungicide in accordance with the current Fungicide Resistance Management (IRM) strategy for your region. For further information contact your farm chemical supplier, consultant, local Department of Agriculture or Primary Industries, or local DuPont Representative.

MIXING

Fill spray tank to ¼ to ½ full of water. Measure the amount of Fontelis® fungicide required for the area to be sprayed. Add Fontelis® fungicide directly to the spray tank with the agitation engaged. Mix thoroughly to disperse the fungicide. Once dispersed, the material must be kept in suspension at all times by continuous agitation. Use mechanical or hydraulic means, **DO NOT** use air agitation, premix or slurry.
If spray solution is left standing, ensure thorough re-agitation of the spray mix until fully resuspended. **DO NOT** allow spray mix to sit overnight, as resuspension may be difficult.

SURFACTANT/WETTING AGENT

Use of a surfactant/wetting agent is not required.

APPLICATION

Use a sprayer fitted with high flow rate nozzles to apply the highest practical spray volume. Use sufficient water to obtain thorough coverage of plants, with a minimum 110 L/ha.
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. For orchard/vineyard sprayers avoid directing spray above trees and always turn-off outward pointing nozzles at row ends and outer rows.

Dilute Spraying

- Use a sprayer designed to apply high volumes of water up to the point of run-off and matched to the crop being sprayed.
- Set up and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient water to cover the crop to the point of 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

1. Dilute spray volume as determined above: For example 1500 L/ha
2. Your chosen concentrate spray volume: For example 500 L/ha
3. The concentration factor in this example is : 3 times (i.e. 1500 L divided by 500 L = 3)
4. If the dilute label rate is 150 g/100 L, then the concentrate rate becomes 3 x 150, that is, 450 g/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 information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow industry Best Practices.

Compatibility

DuPont™ Fontelis® is compatible with many commonly used fungicides, liquid fertilisers, herbicides, insecticides, and biological control products. 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. DuPont™ Fontelis® is compatible with Altacor®, Avatar®, mancozeb, Polyram* and Systhane*.

The crop safety of all potential tank-mixes, including additives and other pesticides, on all crops has not been tested. Before applying any tank-mix 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.

DuPont™ Fontelis® contains a percentage of mineral oil in the formulation which may predispose oil sensitive products such as Captan* to crop damage if they are not applied according to the restrictions referring to summer oils on their label.

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 (Fontelis®), emulsifiable concentrates, adjuvants and surfactants, soluble fertilisers.

Spray Equipment Cleanout

Prior to application, start with clean, well-maintained application equipment. Immediately following application, thoroughly clean all spray equipment to reduce the risk of forming hardened deposits which might become difficult to remove. Drain spray equipment. Thoroughly rinse sprayer and flush hoses, boom, and nozzles with clean water.

Clean all other associated application equipment. Take all necessary safety precautions when cleaning equipment. **DO NOT** clean near wells, water sources or desirable vegetation. Dispose of waste rinse water in accordance with local regulations.

PROTECTION OF CROPS, NATIVE AND OTHER NON-TATGET PLANTS
IMPORTANT: Not all crops within a crop group, and not all varieties, cultivars or hybrids of crops, have been individually tested for crop safety. To test for crop safety, apply the product in accordance with the label instructions to a small area of the target crop to ensure that a phytotoxic response will not occur, especially where the application is a new use of the product by the applicator.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Very toxic to aquatic life. **DO NOT** contaminate streams, rivers or waterways with the chemical or used containers.

STORAGE AND DISPOSAL
KEEP OUT OF REACH OF CHILDREN.
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.

RE-ENTRY
DO NOT allow entry into treated areas until the spray has dried. When prior entry is necessary, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), chemical resistance gloves and footwear. Clothing must be washed after each day's use.

SAFETY DIRECTIONS
When opening the container, preparing and using the product wear cotton overalls (or equivalent clothing) buttoned to the neck and wrist and a washable hat. Wash hands after use. After each day's use wash 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 http://www.hortscience.com.au).

NOTICE TO BUYER
To the extent permitted by the Competition and Consumer Act (2010) or any relevant legislation of any State or Territory (the "Legislation") all conditions and warranties and statutory or other rights of action, whether arising in contract or tort or whether due to the negligence of DuPont or Seller, which buyer or any other user may have against DuPont or Seller are hereby excluded provided however that any rights of the buyer pursuant to non excludable conditions or warranties of the Legislation are expressly preserved. DuPont hereby gives notice to buyer and other users that to the extent permitted by the Legislation it will not accept responsibility for any indirect or consequential loss of whatsoever nature arising from the storage, handling

or use of this Product. Where permitted by the Legislation DuPont's liability shall in all circumstances be limited to the replacement of the product, or a refund of the purchase price paid therefor.
The Product must be used and applied strictly in accordance with the label instructions and other directions for use. It is impossible to eliminate all risks associated with the use of this product. Such risks may arise from factors such as weather conditions, soil factors, off-target movement, unconventional technique, presence of other materials, the manner of use or application, or other unknown factors, all of which are beyond the control of DuPont or the Seller. Buyer accepts these risks.

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ABBREVIATIONS

ac	active constituent
AD	Administered Dose
AUC	Area under the concentration curve
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
BrdU	Bromodeoxyuridine
bw	bodyweight
CAR	Constitutive Androstane Receptor
C_{max}	Maximum concentration
CO_2	Carbon dioxide
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
ESI	Export Slaughter Interval
EUP	End Use Product

g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GI	Gastro-intestinal
GLP	Good Laboratory Practice
GSD	Geometric Standard Deviation
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
K_d	Soil partition co-efficient
kg	kilogram
K_{oc}/K_{Foc}	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

MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OM	Organic Matter
PCNA	Proliferating Cell Nuclear Antigen
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
STMR	Supervised Trials Median Residues
STMR-P	STMR corrected for processing

SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T_{max}	Time to achieve maximum conentration
TSH	Thyroid Stimulating Hormone
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
UDP	Uridine Diphosphate
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 a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	repels water
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

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

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