Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active oxathiapiprolin in the Product DuPont Zorvec Enicade Fungicide

APVMA Product Number 68375

DECEMBER 2015

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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, Office of Chemical Safety (OCS), Department of Environment (DE), 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.

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 ZORVEC ENICADE 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 Friday 29 January 2016 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:

Case Management and Administration Unit
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PO Box 6182
Kingston ACT 2604

Phone: +61 2 6210 4701
Fax: +61 2 6210 4721
Email: enquiries@apvma.gov.au

Further information

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

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

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

1 INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of DUPONT ZORVEC ENICADE FUNGICIDE, and approval of the new active constituent, oxathiapiprolin.

An application was made by DU PONT (AUSTRALIA) PTY LTD to register the fungicide DUPONT ZORVEC ENICADE FUNGICIDE for the control of downy mildew disease in brassicas, cucurbits, leafy vegetables, bulb vegetables and poppies.

DUPONT ZORVEC ENICADE FUNGICIDE was registered in the United States in August 2015 for similar uses. Registration was also proposed in Canada in October 2015 and public consultation, similar to this APVMA process, is currently being completed.

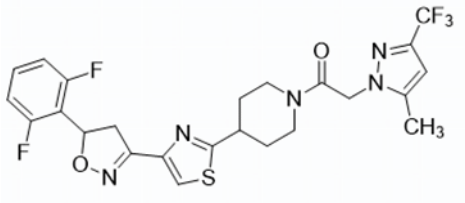
DUPONT ZORVEC ENICADE FUNGICIDE contains 100 g/L of the new active constituent oxathiapiprolin in an oil-based suspension concentrate (OD) formulation. Oxathiapiprolin is a piperidinyl-thiazole-isoxazoline fungicide which belongs to a new FRAC (Fungicide Resistance Action Committee) Mode of Action Group, U15. It effectively inhibits mycelial growth and zoospore release, encystment and mobility.

This submission has been assessed under a joint review / workshare arrangement where registrations for the same formulations and uses have been submitted concurrently in Australia, Canada, Mexico, Japan and the United States. Regulatory observers included South Korea, China and the Philippines.

2 CHEMISTRY AND MANUFACTURE

The purpose of this assessment is for registration of DUPONT ZORVEC ENICADE FUNGICIDE, containing 100 g/L oxathiapiprolin as an oil-based suspension concentrate (OD) formulation, for the control of downy mildew in a range of crops including bulb vegetables, brassicas vegetables, cucurbit vegetables, leafy vegetables and poppies.

The chemical active constituent oxathiapiprolin has the following properties:

COMMON NAME (ISO):	Oxathiapiprolin
CHEMICAL NAME:	1-(4-{4-[(5RS)-5-(2,6-difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}-1-piperidyl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]ethanone
CAS PRODUCT NAME:	1-[4-[4-[5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]ethanone
CAS REGISTRY NUMBER:	1003318-67-9
MANUFACTURER'S CODE:	DPX-QGU42
EMPIRICAL FORMULA:	C24H22F5N5O2S
MOLECULAR WEIGHT:	539.52
STRUCTURAL FORMULA:	

TECHNICAL GRADE OXATHIAPIPROLIN HAS THE FOLLOWING PHYSICAL AND CHEMICAL PROPERTIES:

PHYSICAL FORM:	Crystalline solid, powder
COLOUR:	Off-white
MELTING POINT:	~146°C
RELATIVE DENSITY:	1.4645 g/cm2
VAPOUR PRESSURE (PA, 20 °C):	1.141 × 10-6
OCTANOL/WATER PARTITION COEFFICIENT (LOG KOW, 20 °C):	3.6
SOLUBILITY IN WATER (G/L AT 20°C):	1.75 x 10-4
SOLUBILITY IN ORGANIC SOLVENTS (G/L AT 20°C):	Acetonitrile 129.9 Methanol 13.5 Acetone 162.8 Ethyl acetate 33.9 Dichloromethane 352.9 o-Xylene 5.8 n-Octanol 0.03 n-Hexane 0.01
SELF-HEATING/IGNITION:	Non-oxidising and not explosive

The APVMA has evaluated the chemistry aspects of oxathiapiprolin active constituent (manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable. Other compounds of toxicological significance are not expected to occur in oxathiapiprolin Technical Grade Active Constituent (TGAC) as a result of the raw materials and the synthetic route used.

On the basis of the data provided, and the toxicological assessment, it is proposed that the following APVMA Active Constituent Standard be established for oxathiapiprolin active constituent:

APVMA ACTIVE CONSTITUENT STANDARD

CONSTITUENT	SPECIFICATION	LEVEL
Oxathiapiprolin	Oxathiapiprolin	Not less than 950 g/kg

Based on a review of the data provided by the applicant, the APVMA proposes to be satisfied that the chemistry and manufacturing details of oxathiapiprolin are acceptable.

2.1 Formulated product

The chemistry aspects of the product, DUPONT ZORVEC ENICADE FUNGICIDE (physico-chemical properties, formulation process, quality control procedures, batch analysis results, stability, analytical methods and packaging) have been evaluated by the APVMA.

DUPONT ZORVEC ENICADE FUNGICIDE HAS THE FOLLOWING PROPERTIES:

FORMULATION TYPE:	Oil-based suspension concentrate (OD)
APPEARANCE:	Off-white liquid
ACTIVE CONSTITUENT CONCENTRATION:	Oxathiapiprolin 100 g/L
SPECIFIC GRAVITY:	0.987 g/mL at 20 ºC
PH:	6.5 (1% dilution in water)
SURFACE TENSION:	26.1 mN/m undiluted
VISCOSITY:	550 mPa.s at 25 RPM rotational speed 362 mPa.s at 100 RPM rotational speed
PERSISTENT FOAM:	3 mL (after 1 min)
WET SIEVE TEST:	0.006% residue on a 75 micron sieve
POURABILITY:	Residue: 2.48% Rinsed residue: 0.26%
SAFETY PROPERTIES:	Not explosive; No oxidising properties; Not flammable; Not corrosive to the PE/EVOH containers
PACK SIZES	1 L or 5 L
PACKAGING MATERIAL	Polyethylene with ethylene vinyl alcohol (PE/EVOH)
PRODUCT STABILITY	The product should remain within specifications for at least 2 years under normal conditions in PE/EVOH packaging

The product DUPONT ZORVEC ENICADE FUNGICIDE will be manufactured overseas and imported into Australia in 1 or 5 litre polyethylene with ethylene vinyl alcohol (PE/EVOH) containers.

Based on a review of the data provided by the applicant, the APVMA proposes to be satisfied that the chemistry and manufacturing details of DUPONT ZORVEC ENICADE FUNGICIDE product are acceptable.

3 TOXICOLOGICAL ASSESSMENT

The purpose of this assessment is for registration of DUPONT ZORVEC ENICADE FUNGICIDE, containing 100 g/L oxathiapiprolin as an oil-based suspension concentrate (OD) formulation, for the control of downy mildew in a range of crops including bulb vegetables, brassicas vegetables, cucurbit vegetables, leafy vegetables and poppies.

The toxicological database provided for oxathiapiprolin was extensive and comprised a full contemporary suite of acute and repeat dose toxicity studies in mice, rats and dogs as well as *in vitro* and *in vivo* genotoxicity studies, reproductive and developmental studies, neurotoxicity and immunotoxicity studies. Studies have also been conducted on the major metabolites of oxathiapiprolin.

3.1 Evaluation of toxicological data

Toxicokinetics and metabolism

Following a single low (10 mg/kg bw) or high (200 mg/kg bw) dose in rats, oxathiapiprolin was rapidly absorbed (t_{max} 0.25–3 hr), widely distributed into organs and tissues, and slowly ($t_{1/2}$ 40–51 hrs) but almost completely eliminated (partially via biliary elimination) with no evidence of bioaccumulation. The vast majority of the administered dose was excreted in the faeces (>82% dose), and a small portion in the urine by 48 hours after administration. The un-metabolised oxathiapiprolin (up to 87% dose) was the primary component recovered from the faeces, together with other metabolites mainly resulting from hydroxylation followed by oxidation or dehydration. In repeat low dose (10 mg/kg bw) metabolism studies, metabolism and elimination profiles were similar to those observed after single dose administration.

Overall, oxathiapiprolin was moderately (up to approximately 50%) and rapidly absorbed at low doses, widely distributed throughout the body and moderately metabolised. Oxathiapiprolin was rapidly excreted via the faecal pathway, with the majority of excreted faecal material identified as unchanged parent compound.

Percutaneous absorption

Based on the data from dermal absorption studies on a undiluted 100 g/L OD oxathiapiprolin formulation (similar to DUPONT ZORVEC ENICADE FUNGICIDE) and a 1/142 dilution (0.7 g/L), the estimated dermal absorption values *in vitro* were 0.916% and 2.68% in humans, and 3.22% and 12.6% in rats. Dermal absorption for rats in vivo were 1.79% and 3.06% respectively for the two test solutions.

Consistent with the principles described in the OECD Guidance Notes on Dermal Absorption (OECD 2011), dermal absorption of oxathiapiprolin in humans was estimated as 0.51% and 0.65% respectively, by adjusting the rat *in vivo* dermal absorption by the ratio of the human to the rat *in vitro* dermal absorption.

Acute toxicity

Oxathiapiprolin was of low acute oral (LD_{50} >5000 mg/kg bw), dermal (LD_{50} >5000 mg/kg bw) and inhalational (LC_{50} >5100 mg/m^3) toxicity, was a non-irritant to the skin and eye in rabbits, and was not a skin sensitiser in guinea pigs (Magnusson and Kligman Maximization method).

The product DUPONT ZORVEC ENICADE FUNGICIDE was of low acute oral (LD_{50} >5000 mg/kg bw), dermal (LD_{50} >5000 mg/kg bw) and inhalational (LC_{50} >5080 mg/m^3) toxicity in rats, and was not an eye irritant in rabbits, but was a slight skin irritant in rabbits and a skin sensitiser in guinea pigs (Magnusson and Kligman Maximization method).

Repeat-dose toxicity

In short-term (28 day) oral studies in mice, rats and dogs, and a short-term dermal study in rats using oxathiapiprolin at up to 1000 mg/kg bw/day or higher (i.e. the limit dose), no treatment related deaths or adverse changes in body weight, body weight gain, clinical signs, haematology (including coagulation), clinical chemistry parameters, urinalysis, gross findings, organ weights or histopathology were observed during the studies. The NOAEL was the highest tested dose level (1000 mg/kg bw/day or higher) in all studies.

In subchronic toxicity studies, oxathiapiprolin was administered in the diet to mice, rats and dogs for 90 days at concentrations up to 1000 mg/kg bw/day (the limit dose) or higher. No deaths were observed. No adverse changes in body weight, body weight gain, food consumption, food efficiency, clinical signs, functional observational battery assessments, locomotor activity, ophthalmology evaluations, haematology, clinical chemistry parameters, gross findings, organ weights or histopathology were observed during these studies.

In long-term toxicity studies, oxathiapiprolin was administered in the diet to mice (18–month), rats (2-year) and dogs (1–year) at concentrations approaching 1000 mg/kg bw/day (i.e. the limit dose). No deaths occurred during the study. No adverse changes in body weight, body weight gain, food consumption, food efficiency, clinical signs, ophthalmology evaluation, haematology (including coagulation), clinical chemistry, urinalysis, gross findings, organ weights, or histopathology were observed during the study. The NOAEL was set at the highest dose level tested (735/957 mg/kg bw/day in M/F mice, and >1000 mg/kg bw/day or higher in other studies) in all studies, based on a lack of findings at any dose tested.

Genotoxicity and carcinogenicity

Oxathiapiprolin has been examined in a range of *in vitro* and *in vivo* genotoxicity assays, including endpoints of gene mutation and chromosomal damage. *In vitro*, oxathiapiprolin was negative for mutagenicity in bacteria (Ames test) and mammalian cells (HGPRT locus, Chinese hamster CHO-K1 cells) with and without metabolic activation. In the *in vitro* mammalian chromosome aberration assay using human peripheral blood lymphocytes, oxathiapiprolin did not induce chromosomal aberrations with and without metabolic activation.

In vivo, oxathiapiprolin was found to be non-clastogenic in the mouse bone marrow micronucleus assay in male and female mice, with the study being conducted up to and including the limit dose.

Oxathiapiprolin was administered in the diet to mice for 18-month and to rats for 2–years at concentrations up to 1000 mg/kg bw/day or higher (735/957 mg/kg bw/day in M/F mice). No deaths occurred during the study. No neoplastic lesions were detected in any organs or tissues in either species. Hence, oxathiapiprolin did not show carcinogenic potential in mice or rats.

Reproductive/developmental toxicity

In a 2–generation reproduction study (and a range-finding study) in rats administered up to and above the limit dose (>1000 mg/kg bw/day) of oxathiapiprolin, no parental toxicity was seen and no effect was seen on reproductive parameters. However, there was a slight but significant increase in the mean age to achieve preputial separation in F1 and F2 males at the highest dose of 1228/1278 mg/kg bw/day (F1 and F2 generation respectively). This singular effect of a delay in preputial separation, associated with decreases in pup body weight at this dose level exceeding the limit dose of 1000 mg/kg bw/day, as recommended in OECD (2001) [Test Guideline 416], occurred without other evidence of reproductive/developmental toxicity across the series of Guideline-compliant studies. The NOAEL for offspring toxicity is 411/430 mg/kg bw/day) based on an increased interval to preputial separation at 1228/1278 mg/kg bw/day.

No evidence of developmental toxicity potential was seen in an oral (gavage) developmental toxicity study in rats or in rabbits, and androgenic potential of oxathiapiprolin was negative in a series of *in vivo* and *in vitro* studies. Therefore, while acknowledging the occurrence of the preputial separation finding, the available data suggests that oxathiapiprolin should not being considered a hazard for reproductive or developmental toxicity.

Neurotoxicity

Sprague Dawley (SD) rats in groups of 12/sex/dose received oxathiapiprolin at 0, 200, 1000 or 2000 mg/kg bw as a single oral gavage dose. No treatment-related effects on survival, clinical signs, body weight or gain, food consumption, functional observation battery or motor activity parameters, gross pathology, or neuropathology were observed up to the high dose of 2000 mg/kg. The NOAEL for systemic toxicity and neurotoxicity was 2000 mg/kg bw based on no effects seen.

Immunotoxicity

Oxathiapiprolin was administered to female CD-1 mice (10/dose) at 0 (control), 200, 800, 3500, or 7000 ppm (0, 38, 151, 645, or 1432 mg/kg bw/day) for 28 days. There were no adverse effects on body weight or nutritional parameters in female mice at any dose level. No treatment-related mortality or clinical signs of systemic toxicity were observed. No test substance-related effects were observed on gross pathology, absolute and relative brain, spleen, and thymus weights, or humoral immune response. Expected decreases in spleen and thymus absolute/relative weights and on anti-sRBC response (decreased serum IgM levels) were observed in the positive control group. The immunotoxicity NOAEL for female mice was 7000 ppm (1432 mg/kg bw/day), based on no effects seen at the highest dose level tested.

Other toxicology data

A series of *in vitro* and *in vivo* genotoxicity studies were conducted on various metabolites identified in the pharmacokinetic studies, with negative results reported in each case. Hence, none of the metabolites are considered to be genotoxic.

3.2 Public health standards

Poisons scheduling

The Advisory Committee on Chemicals Scheduling (ACCS) have considered the OCS recommendations to the Chemicals Scheduling Delegate of the Department of Health that consideration be given to a listing in Appendix B of the Poisons Standard for Oxathiapiprolin. The Delegate's interim decision is expected to be published in February 2016 at the TGA website (www.tga.gov.au/committee/advisory-committee-chemicals-scheduling-accs).

ADI

The ADI for humans is the level of intake of a chemical that can be ingested daily over an entire lifetime without appreciable risk to health. It is calculated by dividing the overall NOAEL for the most sensitive toxicological endpoint from a suitable study (typically an animal study) by an appropriate safety factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans, intra-species variation, and the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

The toxicological database for oxathiapiprolin included several long-term oral and carcinogenicity studies in the mouse and rat (including a two-generation reproduction study), as well as a 12–month study in beagle dogs, and was considered complete. From the available long-term studies, the most appropriate NOAEL was found in the two-generation reproduction study in rats, where delayed sexual maturation (as measured by an increased interval to preputial separation) was noted in each generation of male offspring at a dose considered to be above the standard limit dose as recommended in the test guidelines.

Based on the evaluated toxicology information, the ADI is established at 4.1 mg/kg bw/d based on a NOAEL of 411 mg/kg bw/d in a two generation reproduction rat study and applying a 100 fold safety factor (consisting of a 10–fold safety factor for both intra- and inter-species variation).

ARfD

The acute reference dose (ARfD) is the estimate of the amount of a substance in food or drinking water, expressed on a milligram per kilogram body weight basis, that can be ingested over a short period of time, usually in 1 meal or during 1 day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

An ARfD was not established since oxathiapiprolin was considered unlikely to present an acute hazard to humans, noting that no toxicologically significant acute findings were seen in any animal studies.

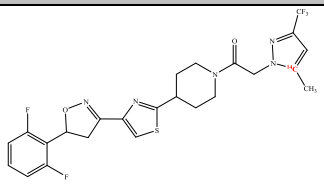
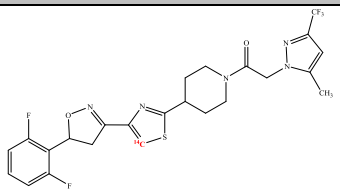
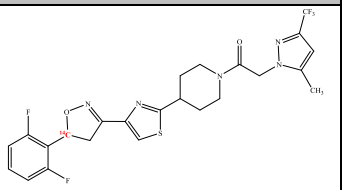
4 RESIDUES ASSESSMENT

The purpose of this assessment is for registration of DUPONT ZORVEC ENICADE FUNGICIDE, containing 100 g/L oxathiapiprolin as an oil-based suspension concentrate (OD) formulation, for the control of downy mildew in a range of crops including bulb vegetables, brassicas vegetables, cucurbit vegetables, leafy vegetables and poppies.

As part of the residues assessment for oxathiapiprolin, plant and animal metabolism studies, supervised residue trials, processing studies, and trade aspects were considered.

4.1 Metabolism

Metabolism data for ^{14}C-labelled oxathiapiprolin in lettuce, potatoes, grapes, rotational crops (lettuce, wheat and turnip), rats, lactating goats and laying hens were provided. The ^{14}C-labelled oxathiapiprolin structures used in these metabolism studies were:

CHEMICAL NAME	STRUCTURE		
1-(4-{4-[(5*RS*)-5-(2,6-Difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}-piperidin-1-yl)-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazole-1-yl]ethanone	 [^{14}C-5-Pyrazole]-oxathiapiprolin	 [^{14}C-5-Thiazole]-oxathiapiprolin	 [^{14}C-5-Isoxazoline]-oxathiapiprolin

In the plant metabolism studies, where the compound was applied by foliar treatment, parent compound was by far the most significant residue (in lettuce, potato foliage (tubers contained insufficient residue for extraction), grape foliage and grape berries, residues of parent compound ranged from 0.165–7.242 mg eq/kg, or 35.9–82.0% of TRR). Except for the cleavage products IN-E8S72 (3-trifluoromethyl-1*H*-pyrazole-5-carboxylic acid) and IN-WR791 (2-(5-methyl-3-trifluoromethyl-1*H*-pyrazol-1-yl)acetic acid) in grape berries, at 0.044–0.062 mg eq/kg (13.3–14.4% of TRR) and 0.057-0.069 mg eq/kg (15.1–18.6% of TRR) respectively, no component of the residue other than parent exceeded 10% of the TRR in the foliar application metabolism studies.

By far the most prevalent residue component in the field residue trials was parent compound, with comparatively few detections of metabolites. Where metabolites were detected, in almost all cases, the levels were below the LOQ, apart from IN-E8S72 (one spinach sample contained 0.026 mg/kg) and IN-WR791 (one broccoli sample contained 0.01 mg/kg and one summer squash sample contained 0.014 mg/kg).

In the confined crop rotation metabolism studies, a number of components exceeded 10% of the TRR and/or 0.01 mg eq/kg in edible matrices; these were the metabolites IN-WR791, IN-E8S72, IN-SXS67, IN-RZB20, and IN-RZB21/IN-RZD74.

The residue behaviour in the field rotational cropping residue studies was different from the primary field residue studies, reflecting the different metabolic pathways observed after soil application when compared with foliar application. Residues of metabolites, particularly IN-E8S72 and IN-SXS67 occurred more frequently than parent, though at relatively low levels. After scaling to the proposed seasonal application rate, no residues of parent compound would be expected to be found above the LOQ, while mostly, they would be undetectable.

All currently proposed use patterns for oxathiapiprolin involve foliar application, and in studies involving foliar application, only parent compound residues are of significance. Finite residues have been observed for the metabolites IN-WR791, IN-E8S72, and IN-SXX67 in rotational crops. However, no toxicological concerns have been raised for the soil and rotational crop metabolites IN-WR791, IN-E8S72 and IN-SXS67, and regulators in the USA and Canada are not proposing to include these compounds in the residue definition. It is therefore proposed to establish a residue definition of parent compound only in plant commodities, for both compliance and dietary risk assessment.

In the goat and hen metabolism studies, parent compound was found in most matrices, usually at levels above 10% of the TRR. The metabolites IN-RAB06, IN-E8S72, IN-Q7D41 exceeded 10% of the TRR only in goat milk/hen liver, goat kidney and goat/hen fat respectively. Parent compound is therefore the best marker residue for analysis of animal tissues, milk and eggs.

Feeding studies are not available for oxathiapiprolin in cattle or poultry. It is however noted that none of the crops proposed for registration (bulb vegetables, brassica vegetables, cucurbits, leafy vegetables and poppies) are significant animal feeds.

A residue definition of parent compound only in animal commodities is therefore proposed for both compliance and dietary risk assessment.

Analytical methods

Determination of oxathiapiprolin residues in plant commodities

For generation of residue data, an LC-MS/MS method was developed and validated for analysis of oxathiapiprolin parent compound and the metabolites IN-E8S72, IN-WR791, IN-RDG40, IN-Q7H09, IN-SXS67, IN-RZB20, and IN-RZD74 in crop matrices. Samples were extracted with water/acetonitrile/formic acid. The method LOQ was 0.01 mg/kg for each analyte. Mean recoveries in a wide range of plant commodities were within the range 70–120%. The efficiency of extraction of incurred residues from samples from the lettuce, wheat and grape metabolism studies was confirmed. The German official multiresidue method (DFG S19) was successfully validated for parent compound and the metabolites listed above (with the exception of oily matrices and the metabolite IN-SXS67), while the QuEChERS method was successfully validated for determination of parent compound in a range of plant matrices.

Determination of residues of oxathiapiprolin in animal tissues

The applicant developed and validated an LC-MS/MS method for determination of residues of parent compound, and the metabolites IN-RAB06, IN-RLB67, IN-RDG40, and IN-Q7H09 in animal tissues, milk and eggs. Samples were extracted initially by homogenisation with acetonitrile/hexane, the hexane was discarded and the samples re-extracted twice with acetonitrile/water (hexane was also added for fatty samples, and then

discarded after extraction). The combined extracts were analysed by LC-MS/MS. The method LOQ was 0.01 mg/kg for each analyte. Acceptable recoveries (70–120%) were achieved for all analytes in eggs, milk, cream, and beef fat, muscle, liver and kidney. The German official multiresidue method was also successfully validated for the matrix/analyte combinations listed above.

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

Residue definition

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

COMPOUND	RESIDUE DEFINITION
Oxathiapiprolin	Oxathiapiprolin

Storage stability

The stability of oxathiapiprolin and the metabolites IN-Q7H09, IN-RDG40, IN-E8S72, IN-RZB20, IN-RZD74, and IN-SXS67 was tested in wheat forage, straw and grain, tomatoes, potatoes, grapes, dry beans, soybeans, and dry grape pomace (covering a wide range of matrix types). Homogenised samples were fortified with a known amount of a mixed standard solution (usually at a target concentration of 0.10 ppm per analyte). The samples were stored in a freezer at -20 ± 10 °C for up to 18 months and analysed for parent compound and the metabolites at intervals of 0, 3, 6, 12 and 18 months using the LC-MS/MS method described above. Concurrent recoveries were determined using freshly fortified samples at each analysis interval.

All analytes were stable in all matrices, with the recoveries for the stored samples at 18 months ranging from 73–120% after correction for the concurrent recovery.

4.2 Residue trials

Bulb vegetables

The proposed GAP for oxathiapiprolin in bulb onions is 2 × 35 g ac/ha foliar applications with a 10–day re-treatment interval and a 10–day harvest withholding period.

In Australian, New Zealand and US trials, after 4 × 35 g ac/ha applications at intervals of 4–10 days, residues at a 10–day withholding period in bulb onions were <0.005 (6), <u>≤0.01</u> (0.004), and <0.01 (0.009) mg/kg (STMR = 0.01 mg/kg).

An MRL of 0.02 mg/kg is proposed for oxathiapiprolin in bulb onions, with a harvest withholding period of 10 days.

The proposed GAP for oxathiapiprolin in bulb vegetables other than bulb onions is 3 × 35 g ac/ha foliar applications with a 10–day re-treatment interval and a 10-day harvest withholding period.

In trials conducted in the USA and Canada, residues of oxathiapiprolin in green onions at 4–6 days after 4 × 35 g ac/ha applications were 0.24, 0.34, 0.36, 0.41, and 0.49 mg/kg (STMR = 0.36 mg/kg).

An MRL of 1 mg/kg is therefore proposed for oxathiapiprolin in bulb vegetables [except bulb onions], in conjunction with a 10–day harvest withholding period.

Brassica vegetables

The proposed GAP for oxathiapiprolin in brassica vegetables is 3 × 35 g ac/ha foliar applications with a 7–day re-treatment interval and a nil harvest withholding period.

In trials conducted in cabbage, cauliflower and broccoli in the USA and Canada, residues of oxathiapiprolin on the day of the last of 4 × 35 g ac/ha applications made at intervals of 4–6 days were 0.045, 0.065, 0.071, 0.082, 0.086 (2), 0.092, 0.096, 0.12, 0.14, 0.17 (2), 0.18, 0.22, 0.24, 0.25, 0.30, 0.32, 0.46, and 0.84 mg/kg (STMR = 0.155 mg/kg).

An MRL of 2 mg/kg is proposed for oxathiapiprolin in brassica vegetables, in conjunction with a nil harvest withholding period.

Fruiting vegetables, cucurbits

The proposed GAP for oxathiapiprolin in cucurbit vegetables is 3 × 35 g ac/ha foliar applications with a 7–day re-treatment interval and a 1–day harvest withholding period.

Residue trials for oxathiapiprolin were conducted in Europe, the USA and Canada in field and protected crop cucumbers, summer squash, zucchini, and melons.

At a harvest interval of 0 or 1 day, the combined cucurbit data set matching GAP (3 or 4 applications at 30–35 g ac/ha at re-treatment intervals of 2–8 days) is 0.006, 0.007, 0.008, 0.009, 0.011 (2), 0.013 (2), 0.014 (2), 0.015, 0.016, 0.017, 0.021, 0.022, 0.024, 0.027, 0.028, 0.029, 0.032 (2), 0.033, 0.035 (3), 0.040 (2), 0.042, 0.043, 0.044 (2), 0.045 (2), 0.055, 0.057, 0.059, 0.062, 0.074, 0.081, 0.083, 0.087, 0.089, 0.096, and 0.13 (3) mg/kg (STMR = 0.035 mg/kg).

Based on the combined data set, a group MRL of 0.2 mg/kg is proposed for oxathiapiprolin in fruiting vegetables, cucurbits, in conjunction with a 1–day harvest withholding period.

A proportion of the trials in cucurbits were conducted in protected cropping systems, and these trials did not indicate a significant difference in the residue levels found in trials from field and protected crops.

Leafy vegetables

The proposed GAP for oxathiapiprolin in leafy vegetables is 3 × 35 g ac/ha foliar applications with a 7–day re-treatment interval and a 3–day harvest withholding period.

Residue data in head and leaf lettuce, spinach, mustard and Chinese cabbage generated in Australia, the USA and Canada were provided.

The combined Australian, US and Canadian data set for head lettuce, at a 3–day harvest withholding period after 4 × 35 g ac/ha applications at re-treatment intervals of 2–8 days, is <0.005, 0.017, 0.024, 0.092, 0.13 (2), 0.18, 0.20, 0.26, 0.31, 0.32, 0.55, 0.62, 0.69, 0.82, and 1.0 mg/kg (STMR = 0.23 mg/kg).

Based on the combined head lettuce data set, an MRL of 2 mg/kg is proposed for oxathiapiprolin in head lettuce, in conjunction with a 3–day harvest withholding period.

The leaf lettuce and spinach data sets were combined for the purpose of estimating an MRL for leafy vegetables other than head lettuce: 0.20, 0.28, 0.40, 0.55, 0.58, 0.77, 0.82, 0.94 (2), 1.1, 1.3, 1.4 (2), 1.5 (2), 1.6, 1.7, 1.8, 2.0, 2.1, 2.7, 2.9, 3.1, 3.4 (2), 4.0, 6.9, and 8.5 mg/kg (STMR = 1.5 mg/kg).

Based on this combined data set, it is proposed to establish an MRL of 15 mg/kg for oxathiapiprolin in leafy vegetables, except head lettuce, in conjunction with a 3–day harvest withholding period. An MRL of 15 mg/kg is also proposed for cardoon, a leafy vegetable listed on the label and which is not covered by the Codex leafy vegetables (VL) group.

All trials were conducted in field grown leafy vegetable crops. However, it is noted that the cucurbit residue data set did not show significantly different residues in crops grown in protected systems compared with crops grown in the field. Therefore, the proposed MRL for leafy vegetables is considered to be adequate to cover residues in leafy crops grown in protected systems.

Poppies

The proposed GAP in poppies is 1 × 35 g ac/ha application with a 6–week PHI.

Six trials in poppies were conducted in Tasmania. After 1 or 2 × 35 g ac/ha applications, at a harvest interval of 39–57 days, residues of oxathiapiprolin were <0.005 (5) mg/kg. It is also noted that after 1 or 2 × 70 g ac/ha applications (2× the proposed individual application rate), residues of oxathiapiprolin were likewise <0.005 (5) mg/kg.

An MRL of *0.01 mg/kg is therefore proposed for oxathiapiprolin in poppy seed, in conjunction with a 6–week harvest withholding period.

4.3 Crop rotation

Field rotational crop studies were conducted in Europe, the USA and Canada. After scaling to the proposed maximum seasonal application rate (105 g ac/ha), no residues of parent compound (the only compound proposed for inclusion in the residue definition) would be expected to be found above the LOQ, while mostly, parent oxathiapiprolin would be undetectable. Scaled for the proposed maximum rate, the highest residue of parent compound expected in rotational food crops is <0.003 mg /kg (LOD), with only one detection above the LOQ being made in a food crop (radish). In rotational animal feeds, the highest residue of parent compound expected (after scaling for the proposed maximum application rate) is 0.015 mg/kg, in soybean forage. This is not of concern for animal feeding.

As only parent compound is proposed for inclusion in the residue definition, and residues of parent compound are expected to be below the LOQ and mostly below the LOD in rotational crops, it is not proposed to establish MRLs for crops planted in rotation with primary crops treated with oxathiapiprolin.

4.4 Animal commodity MRLs

None of the crops (bulb vegetables, brassica vegetables, cucurbits, leafy vegetables and poppies) proposed for application of oxathiapiprolin are significant animal feeds, although vegetable wastes can be fed to livestock in small amounts (up to 5% of the diet). The livestock dietary burden calculated using the OECD Feed Calculator for beef and dairy cattle and laying and broiler hens in Australia and the lactating goat metabolism study indicate that quantifiable residues of oxathiapiprolin are unlikely to be found in milk, eggs, offal or meat.

It is proposed to establish MRLs for oxathiapiprolin in mammalian meat (in the fat), mammalian offal, milk, poultry meat (in the fat), poultry offal, and eggs at the LOQ, which is 0.01 mg/kg.

4.5 Spray drift

The proposed label prohibits aerial application. Modelling of the spray drift using the standard APVMA scenario for high level ground boom application with a medium droplet size shows that the average spray deposition over a 300–metre paddock downwind of the application area would result in a concentration of 0.083 mg ac/kg dry weight in pasture (assuming pasture of a density of 1500 kg dry matter per hectare).

Although a feeding study was not supplied, in the goat metabolism study, after dosing at 14.2–14.3 ppm in feed, the highest total residue was 0.857 mg eq/kg (in liver). Scaling for a feed concentration of 0.083 mg ac/kg oxathiapiprolin would mean that even the TRR in the milk and tissues of livestock grazing downwind of the treatment area would be expected to be <LOQ. No buffer zones are required for protection of international trade.

4.6 Bioaccumulation potential

The octanol-water partition coefficient ($\log_{10}K_{OW}$ value) for oxathiapiprolin is 3.6 at 20 °C, with no dependence on pH.

In the goat metabolism study, residues of oxathiapiprolin parent compound were higher in subcutaneous fat than in muscle, and higher in perirenal fat than in kidney. In the poultry metabolism study, detectable levels of oxathiapiprolin were found in fat, while levels of total residue in muscle were too low to warrant extraction. It is therefore proposed that mammalian and poultry meat MRLs be established ‘in the fat’ (at the LOQ, which is 0.01 mg/kg).

4.7 Risk assessment conclusions

Estimated dietary intake

The chronic dietary intake risk for oxathiapiprolin has been assessed. The ADI for oxathiapiprolin is 4.1 mg/kg bw/day, based upon a NOAEL of 411 mg/kg bw/day and a 100–fold safety factor. The NEDI calculation is made in accordance with WHO (1997) and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for oxathiapiprolin, is equivalent to <0.1% of the ADI. HARVEST Modelling[2] of chronic dietary exposure is also performed on new chemicals. The HARVEST model estimated the chronic dietary exposure of oxathiapiprolin as <0.1% of the ADI for the general population.

An acute reference dose (ARfD) has not been established for oxathiapiprolin due to the lack of an identified acute toxicological hazard.

It is concluded that the dietary exposure to oxathiapiprolin is low and the risk from residues in food is acceptable when DUPONT ZORVEC ENICADE FUNGICIDE is used according to label directions.

[2] HARVEST is a computer dietary modelling program based upon statistical software that is used by FSANZ.

Recommendations

The following amendments to the MRL Standard are recommended in relation to the proposed use of DUPONT ZORVEC ENICADE FUNGICIDE:

TABLE 1

COMPOUND		FOOD	MRL (mg/kg)
ADD:			
	Oxathiapiprolin		
VB	0040	Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead brassicas	2
VA	0035	Bulb vegetables [except Onion, Bulb]	1
		Cardoon	15
MO	0105	Edible offal (Mammalian)	*0.01
PE	0112	Eggs	*0.01
VC	0045	Fruiting vegetables, Cucurbits	0.2
VL	0053	Leafy vegetables [except Lettuce, Head]	15
VL	0482	Lettuce, Head	2
MM	0095	Meat (mammalian) [in the fat]	*0.01
ML	0106	Milks	*0.01
VA	0385	Onion, Bulb	0.02
SO	0698	Poppy seed	*0.01
PO	0111	Poultry, edible offal of	*0.01
PM	0110	Poultry meats [in the fat]	*0.01

TABLE 3

COMPOUND	RESIDUE
ADD:	
Oxathiapiprolin	Oxathiapiprolin

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

HARVEST WITHHOLDING PERIODS:

BRASSICA VEGETABLES	NOT REQUIRED WHEN USED AS DIRECTED
CUCURBIT VEGETABLES	DO NOT HARVEST FOR 1 DAY AFTER APPLICATION
BRASSICA LEAFY VEGETABLES, LEAFY VEGETABLES	DO NOT HARVEST FOR 3 DAYS AFTER APPLICATION
BULB VEGETABLES	DO NOT HARVEST FOR 10 DAYS AFTER APPLICATION
POPPIES	DO NOT HARVEST FOR 6 WEEKS AFTER APPLICATION

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

The purpose of this assessment is for registration of DUPONT ZORVEC ENICADE FUNGICIDE, containing 100 g/L oxathiapiprolin as an oil-based suspension concentrate (OD) formulation, for the control of downy mildew in a range of crops including bulb vegetables, brassicas vegetables, cucurbit vegetables, leafy vegetables and poppies.

5.1 Commodities exported and main destinations

The proposed use patterns for DUPONT ZORVEC ENICADE FUNGICIDE (bulb vegetables, brassica vegetables, cucurbit fruiting vegetables, leafy vegetables and poppies) do not involve major export commodities. The applicant has proposed the following risk mitigation statement which is considered appropriate and acceptable:

Growers should note that suitable Maximum Residue Levels (MRLs) or import tolerances may not be established in all markets for produce treated with Zorvec Enicade 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.

Meat and dairy products are major export commodities.

The significant export markets for animal commodities are listed in Overseas Trade (Part 5B) of the APVMA Data Guidelines[3]. Total exports of dairy products in 2013–14 were worth $2.70 billion, with key export destinations including Japan, Singapore, China, Indonesia, Malaysia, Thailand, the Philippines, Korea, and Russia. Total exports of beef and veal were worth $6.27 billion in 2013–14, with the major destinations including Japan, the USA, Korea, China, Taiwan, the EU, the Middle East, and Russia. Total exports of lamb and mutton were worth $2.22 billion in 2013–14, with the key destinations including the USA, China, the Middle East, the European Union, and Japan.

Finite residues are not expected to be found in animal commodities. MRLs of *0.01 mg/kg are proposed for oxathiapiprolin in mammalian meat [in the fat], milk, poultry meat, poultry edible offal and eggs.

5.2 Overseas registration status

The residues aspects of oxathiapiprolin have not been considered by the Joint Meeting on Pesticide Residues (JMPR).

The following relevant Australian and overseas MRLs for plant commodities have been established or proposed:

[3] apvma.gov.au/node/1017

OXATHIAPIPROLIN PLANT COMMODITY MRLS

COUNTRY	RESIDUE DEFINITION	COMMODITY	MRL (mg/kg)
Australia (proposed)	Oxathiapiprolin	Brassica vegetables	2
		Bulb vegetables [except onion, bulb]	1
		Cardoon	15
		Fruiting vegetables, cucurbits	0.2
		Leafy vegetables [except lettuce, head]	15
		Lettuce, head	2
		Onion, bulb	0.02
		Poppy seed	*0.01
Canada (proposed)	Oxathiapiprolin	Brassica vegetables	1.5
		Bulb onion	0.04
		Dried tomatoes	3
		Fruiting vegetables, cucurbits	0.2
		Fruiting vegetables, other than cucurbits	0.5
		Ginseng roots	0.15
		Green onion	2
		Leafy greens	15
		Peas, edible pods and seeds	1
		Peas, succulent shelled seeds	0.05
		Tuberous and corm vegetables	0.01
USA	Oxathiapiprolin	All other foods	0.1
		Brassica vegetables	1.5
		Bulb onion	0.04
		Dried tomatoes	3
		Fruiting vegetables, cucurbits	0.2

COUNTRY	RESIDUE DEFINITION	COMMODITY	MRL (mg/kg)
		Fruiting vegetables, other than cucurbits	0.5
		Ginseng roots	0.15
		Grapes	0.7
		Green onion	2
		Leafy greens	15
		Peas, edible pods and seeds	1
		Peas, succulent shelled seeds	0.05
		Tuberous and corm vegetables	0.01

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

OXATHIAPIPROLIN ANIMAL COMMODITY MRLS

COUNTRY	RESIDUE DEFINITION	COMMODITY	MRL (mg/kg)
Australia (proposed)	Oxathiapiprolin	Edible offal (mammalian)	*0.01
		Eggs	*0.01
		Meat (mammalian)	*0.01
		Milks	*0.01
		Poultry, edible offal of	*0.01
		Poultry meat	*0.01
Canada (proposed)	Oxathiapiprolin	Milk	0.01
		Meat of cattle, goats, horses, hogs and sheep	0.01
		Meat byproducts of cattle, goats, horses, hogs and sheep	0.01
		Fat of cattle, goats, horses, hogs and sheep	0.01

5.3 Potential risk to trade

The risk to trade is considered to be low, as none of the proposed use patterns in crops involve major export commodities, and finite residues of oxathiapiprolin are not expected to be found in mammalian or poultry meat or offal, eggs, or milk.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

The purpose of this assessment is for registration of DUPONT ZORVEC ENICADE FUNGICIDE, containing 100 g/L oxathiapiprolin as an oil-based suspension concentrate (OD) formulation, for the control of downy mildew in a range of crops including bulb vegetables, brassicas vegetables, cucurbit vegetables, leafy vegetables and poppies.

6.1 Health hazards

Oxathiapiprolin (CAS 1003318-67-9) is currently not listed on the Safe Work Australia Hazardous Substances Information System (HSIS) database (SWA, 2015).

Based on the available toxicology information, oxathiapiprolin (CAS: 1003318-67-9) is not classified as a hazardous substance in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

Acute toxicity studies on the product have been provided and therefore the toxicological data will override the NOHSC cut-off concentrations for acute toxicity listed on the Safe Work Australia (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2015). Based on the results of the acute oral, acute dermal, acute inhalation as well as the skin and eye irritation studies and the skin sensitisation study with the product, DUPONT ZORVEC ENICADE FUNGICIDE, the minimum requirements for classification of the product with risk phrases according to the NOHSC Approved Criteria for Classifying hazardous Substances (NOHSC 2004) are met.

Based on the product toxicology information of the product, DUPONT ZORVEC ENICADE FUNGICIDE is classified as a hazardous substance in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004) with the following risk phrase:

	RISK PHRASE
R43	May cause sensitisation by skin contact

6.2 Formulation, packaging, transport, storage and retailing

DUPONT ZORVEC ENICADE FUNGICIDE will be manufactured and formulated overseas and imported into Australia in 1 and 5 PE/EVOH rectangular bottles.

6.3 Use pattern of the product

The proposed use rates of DUPONT ZORVEC ENICADE FUNGICIDE are 350 mL product/ha (35 g oxathiapiprolin/ha) and applied by ground boom equipment (but not aerial application methods), with no more than 2 or 3 times per season for each crop.

6.4 Exposure during use

Based on the proposed use patterns the likely pattern of exposure for the professional user is expected to be short-term however, based on the range of crops on the draft label, long term exposure is also possible. The main routes of exposure are likely to be dermal and inhalational with possible accidental ocular exposure.

In the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (US EPA 1998) was used to estimate exposure. The toxicity endpoint of concern and the most appropriate identified NOAEL (205.5 mg/kg bw/d based on a NOAEL of 411 mg/kg bw/d from a two generation reproduction dietary study in rats and a bioavailability correction factor of 0.5) for risk assessment is derived from a repeat dose study in animals, and in this instance a margin of exposure (MOE) of 100 or above is considered acceptable. The MOE takes into account both potential inter-species extrapolation and intra-species variability. Based on the risk assessment for workers conducting mixing/loading and application of DUPONT ZORVEC ENICADE FUNGICIDE by ground boom application, the margins of exposure are all considered to be acceptable (i.e. MOE >100) without the use of specific PPE in this instance.

However, based on the acute hazard of this product, specific precautionary/hazard statements have been recommended for slight skin irritation and skin sensitisation and were incorporated into the development of product safety directions.

6.5 Exposure during re-entry

As the product is intended to be used on growing crops, post-application exposure is considered likely since workers may re-enter treated crops to scout for disease control, weeding, irrigation and harvesting.

The MOE estimate for workers re-entering treated areas to conduct high exposure activities is considered acceptable on day zero after treatment (i.e. MOE > 100) for brassica, cucurbit, bulb and leafy vegetables when using the dermal risk assessment NOAEL of 1000 mg/kg bw/d. The MOE estimate for high exposure activities in all crops was >23,000. Therefore, it is expected that the risk associated with re-entry into areas where the product has been used according to the label instructions will be low, and no post-application re-entry interval is required.

6.6 Recommendations for safe use

Users should follow the First Aid Instructions, Safety Directions and Re-entry statements on the product label.

6.7 Conclusion

The approval of the active constituent oxathiapiprolin and registration of the product DUPONT ZORVEC ENICADE FUNGICIDE for the control of downy mildew in bulb, brassica, cucurbit and leafy vegetables and poppies is supported.

DUPONT ZORVEC ENICADE 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 Safety Data Sheet.

7 ENVIRONMENTAL ASSESSMENT

The purpose of this assessment is for registration of DUPONT ZORVEC ENICADE FUNGICIDE, containing 100 g/L oxathiapiprolin as an oil-based suspension concentrate (OD) formulation, for the control of downy mildew in a range of crops including bulb vegetables, brassicas vegetables, cucurbit vegetables, leafy vegetables and poppies.

7.1 Use pattern of the product

The product is proposed to be applied at the application rate of 350 mL product/ha by ground application corresponding to 35 g ac/ha with a maximum number of 6 applications per year; a maximum of 2 consecutive sprays with a minimum retreatment interval of 7 days followed by a fungicide of another chemical group. No more than 3 sprays of the proposed product per crop per year are permitted or 6 applications per growing area.

7.2 Environmental fate

Hydrolysis

The hydrolysis of oxathiapiprolin in sterile buffer solutions was slow. In pH 4, 7 and 9 buffer solutions, <10% degradation occurred at 50ºC, indicating that oxathiapiprolin is stable to hydrolysis.

Photolysis

Aqueous photolysis

Oxathiapiprolin was degraded in irradiated sterile pH 7 buffer solutions and in natural water at 25ºC under simulated sunlight (xenon arc light, continuous irradiation). The photolysis half-life of oxathiapiprolin in sterile pH 7 buffer was 15.4 days under continuous irradiation. In pH 7 buffer, one major degradation product was formed (IN P3X26) reaching a mean maximum concentration of 12.34% of the application rate (AR) at Day 15. IN-P3X26 degraded slowly to minor metabolite IN-RSA90 which then degraded to the minor metabolite IN-RLD51. In sterile natural water, the photolytic half-life of oxathiapiprolin was 20.2 days under continuous irradiation.

Soil photolysis

Three metabolites IN-E8S72, IN-RDT31 and IN-RAB06 were formed at 5–10% AR in soil treated with either [pyrazole-5-^{14}C] oxathiapiprolin or [isoxazoline-5-^{14}C] oxathiapiprolin irradiated for 15 days. All are known aerobic soil metabolites. Numerous minor metabolites were observed, though none exceeded 10% AR at any sample interval by the end of the study.

Oxathiapiprolin data showed DT_{50} values of 28.2 days and 36.3 days in irradiated moist soils and in irradiated dry soils, respectively.

Degradation of oxathiapiprolin by photolysis in soil proceeded along the same multiple pathways as the aerobic soil. It is believed that photolysis does not contribute significantly to the degradation of oxathiapiprolin under field conditions.

Biodegradation

Aerobic soil metabolism

The rate of aerobic degradation of oxathiapiprolin in the laboratory was measured in five different soils. Under laboratory conditions, the DT_{50} values ranged from 16 to 162 days at 20ºC. No correlation was observed between the rate of degradation of oxathiapiprolin and soil pH. In addition, laboratory studies showed that the degradation of oxathiapiprolin in soil results in the formation of several metabolites, including CO_2 and non-extractable residue. The major degradation products of oxathiapiprolin identified in the study were IN-RDT31, IN-RAB06, IN-QPS10 and IN-E8S72. Ultimately oxathiapiprolin and its degradation products degraded to CO_2 and bound residues.

Degradation of oxathiapiprolin in dark aerobic soil proceeded along multiple pathways which included the cleavage of the pyrazole ring to form IN-QPS10 and IN-E8S72. Hydroxylation of the methyl group on the pyrazole ring followed by oxidation results in the formation of IN-RAB06. Hydroxylation at the 4–position of the piperidine ring results in the formation of IN-RDT31. IN-RDT31 undergoes cleavage of the piperidine to form IN-WR791 which then degrades to IN-E8S72.

Laboratory degradation studies were performed on IN-RDT31, IN-RAB06, IN-QPS10, and IN-E8S72. The rate of aerobic degradation of IN-E8S72 was measured in five different soils and DT_{50} values ranged from 271 to 685 days at 20ºC. No correlation was observed between the rate of degradation of IN-E8S72 and soil pH.

The rate of aerobic degradation of IN-QPS10 was measured in four different soils and DT_{50} values ranged from 3.5 to 364 days at 20ºC. A correlation was observed between the rate of degradation of IN-QPS10 and soil pH.

The rate of aerobic degradation of IN-RAB06 was measured in six different soils conducted with IN-RAB06 as parent. Under laboratory conditions, the DT_{50} values ranged from 3 to 201 days at 20ºC. A slight correlation was observed between the rate of degradation of IN-RAB06 and soil pH under laboratory conditions. However additional information on the degradation of IN-RAB06 provided from the field studies showed no correlation.

The rate of aerobic degradation of IN-RDT31 was measured in five different soils and DT_{50} values ranged from 50 to 773 days at 20ºC. No correlation was observed between the rate of degradation of IN-RDT31 and soil pH. In addition, laboratory studies showed that the degradation of the metabolites studied in soil ultimately resulted in the formation of CO_2 and non-extractable residue.

Anaerobic soil metabolism

No major metabolites were formed in soil treated with either [pyrazole-5-^{14}C] oxathiapiprolin or [isoxazoline 5-^{14}C] oxathiapiprolin. Numerous minor metabolites were observed, though none exceeded 10% AR at any

sample interval or 5% AR at any two consecutive sample intervals. Metabolites identified were IN-QPS10, IN-E8S72, IN-RDT31, and IN-RAB06.

Oxathiapiprolin degrades slowly under anaerobic conditions in the sandy loam soil tested with DT_{50} and DT_{90} values of 1505 and 4998 days, respectively.

Aerobic aqueous metabolism

The fate of oxathiapiprolin was studied in two disparate water/sediment systems incubated in the dark at 25ºC under aerobic conditions: loamy sand sediment (Swiss Lake; water: pH 5.8 and sediment: pH 6.3) and silt loam sediment (Calwich Abbey; water: pH 6.7 and sediment: pH 7.3). In both test systems, oxathiapiprolin partitioned from the water into the sediment phase and underwent further degradation in the sediment phase. In both the loamy sand and silt loam sediment systems, there were no major metabolites formed in the water phase, but numerous minor degradation products were identified (<5% AR): IN-RYJ52 (two isomers), IN-RSE01, IN-RAB06, IN-S2K66, and IN Q7D41. In the sediment phase of the test systems, multiple major components were observed: IN-RYJ52 (two isomers), IN RSE01, IN-S2K66, and IN-Q7D41 were observed near 10% AR or at 5% at two consecutive sampling intervals. The only other identified metabolite was minor (<10% AR): IN-RAB06. No other unidentified component exceeded 5% AR. Un- extractable residues in the loamy sand and silt loam sediment reached a maximum of 8.95 and 16.60% AR, respectively. Evolved $^{14}CO_2$ was less than 1% AR in the loamy sand system but reached maximum levels of 7.19% AR in the silty loam system.

The DT_{50} values for oxathiapiprolin in the water phase of the aerobic sediment systems ranged from 5.5 to 13.6 days in the two water/sediment systems. The DT_{50} value for oxathiapiprolin in the sediment extracts ranged from 112.7 to 249.2 days in the two water/sediment systems. For the total system, the DT_{50} values for oxathiapiprolin ranged from 24.4 to 44.7 days in the two water/sediment systems.

Anaerobic aqueous metabolism

The fate of oxathiapiprolin was studied in two disparate water/sediment systems incubated in the dark at 25ºC under anaerobic conditions: sand sediment (water: pH 6.5-7.0 and sediment: pH 5.8-5.9) and silt loam sediment (water: pH 7.5-7.8 and sediment: pH 7.3-7.5). In both test systems, oxathiapiprolin partitioned from the water into the sediment phase and underwent further degradation in the sediment phase. In the water phase of the test systems, multiple major components were observed: IN-S2K66, IN-S2K67, IN-RYJ52 (two isomeric forms), IN-QFD61, IN-RSE01, and 2,6-difluorobenzoic acid were observed near or above 10% AR or at 5% AR at two consecutive sampling intervals. Other identified metabolites were minor (<5% AR): e.g. IN Q7D41. No unidentified component exceeded 5% AR. In the sediment phase of the test systems, multiple major components were observed: IN-S2K66 and IN-Q7D41 were observed near or above 10% AR or at 5% AR at two consecutive sampling intervals. Other identified metabolites were minor (<5% AR): 2,6-difluorobenzoic acid, IN-S2K67, IN QFD61, IN-RYJ52 (two isomeric forms), and IN RSE01. No unidentified component exceeded 5% AR. Un-extractable residues in the sand and silt loam sediment reached a maximum of 5.12 and 5.48% AR, respectively. Evolved $^{14}CO_2$ was less than 1% AR in the sand and silt loam systems.

The DT_{50} values for oxathiapiprolin in the water phase of the anaerobic sediment systems ranged from 14.6 to 33.0 days in the two water/sediment systems. The DT_{50} values for oxathiapiprolin in the sediments ranged from 110 to 240 days in the two water/sediment systems. For the total system, the DT_{50} values for oxathiapiprolin ranged from 44.8 to 56.4 days in the two water/sediment systems.

Field dissipation

Field dissipation studies for oxathiapiprolin were conducted in Europe (France, Germany, Spain, and UK), USA (California, Texas, New York, and Florida) and Canada (Manitoba and British Columbia) and used to determine the rate of degradation of oxathiapiprolin and its metabolites IN-RDT31, IN-RAB06, IN-QPS10, and IN-E8S72. Oxathiapiprolin was applied at the application rates of 200–560 g ac/ha and the field studies ran from 202–741 days following application where soil samples were taken to a depth of 90 cm. Oxathiapiprolin and its metabolites were found generally confined to the upper soil segment (0–15 cm) with the highest concentration found in the 0–5 cm segment. The metabolites of oxathiapiprolin were slightly more mobile through the soil depths however none of these generally moved below the 15 cm depth in any significant amounts. There were very little residues detection in the 15–30 and 30–50 cm soil depths and none in depths below 50 cm.

Kinetic analysis included parent-only kinetics following FOCUS (2006) guideline. Oxathiapiprolin residues were observed to degrade in the field dissipation trials with DT_{50} values of 3.9 to 205.3 days, indicating that oxathiapiprolin degrades readily to being persistent in soil.

Mobility

Data from the batch equilibrium adsorption/desorption studies showed that oxathiapiprolin was strongly sorbed to soils with Koc ranging from 4,541–19,214 mL/mg in sandy loams, clay loam, loam and silty clay with organic carbon contents of 1.2 to 2.97% and pH ranged from 5.7–7.7. The Kf values for oxathiapiprolin showed no correlation with pH, clay content or cation exchange capacity (CEC). The Kf value did correlate with percent organic carbon. This lack of mobility was confirmed in the field dissipation studies where oxathiapiprolin was confined to upper soil segment (0–15 cm).

The batch equilibrium adsorption studies suggest that the major soil metabolites IN-QPS10, IN-RAB06, and IN RDT31 are moderately to strongly sorbed to soil. IN-QPS10 has a Koc of 2584–18017 mL/mg, IN-RAB06: 431–1361 mL/mg and IN-RDT31: 1048–3969 mL/mg. The Kf values for IN-QPS10, IN-RAB06, and IN RDT31 did not correlate with pH or percent organic carbon. IN-E8S72 was weakly sorbed to soil with a Koc of 4.6–12 mL/mg. The Kf values for IN-E8S72 did not correlate with pH or percent organic carbon.

Bioconcentration

Oxathiapiprolin has a log Pow of 3.67 (pH 7) suggesting that it has a potential for fat solubility. However, the bluegill bioconcentration study showed BCF value of 87 for whole fish. Steady State BCF = (mean tissue concentration/mean water concentration); edible (11), non-edible (98) and whole fish (62) suggesting that oxathiapiprolin is not bioaccumulative in fish (BCF <100).

The mean measured concentration of ^{14}C-labelled oxathiapiprolin in edible, non-edible and whole fish by Day 35 of depuration for the low level and high level were ≤10% of the mean tissue concentration, at Day 35 of uptake. No metabolites were detected in the edible or non-edible tissues sampled from the control or two treatment groups on Day 35 of the depuration phase.

Degradation in air

No calculated half-life based on reaction with hydroxyl radicals was provided. However, on the basis of the volatility data provided, it is unlikely that oxathiapiprolin will volatilise in air.

7.3 Environmental effects

Birds

Oxathiapiprolin is practically non-toxic to bobwhite quail and slightly toxic to zebra finch via the acute oral exposure route. Five day dietary toxicity studies in which bobwhite quail and juvenile mallard were exposed to oxathiapiprolin via their diet identified no oxathiapiprolin treatment related deaths. Oxathiapiprolin and the formulation are at worst, moderately toxic (LC_{50} >561 mg ac/kg feed) to birds on a sub-acute dietary basis. A 20 week feeding/reproduction study with bobwhite quail and juvenile mallard identified no dose responsive adverse effects on either adults or reproductive success. The two chronic studies with mallard ducks were downgraded in reliability due to one being a pilot study of short duration and the other exhibiting uncertainty as to whether the NOEC could be lower. The 20 week NOEC was determined to be 1,200 and 900 mg ac/kg feed for bobwhite quails and juvenile mallards, respectively.

Mammals

Oxathiapiprolin has negligible acute effects in mammals. The oral acute toxicity was >5,000 mg/kg body weight (100,000 mg/kg diet) for rats tested with oxathiapiprolin.

Aquatic organisms

Effects on fish

In three acute fish toxicity studies using rainbow trout, bluegill sunfish and sheepshead minnow exposed to oxathiapiprolin for 96 hours under static conditions, the toxicity (i.e. LC_{50}) exceeded the solubility limit of oxathiapiprolin in water (0.184 mg ac/L) on all occasions. Freshwater and marine fish species show a similar sensitivity to oxathiapiprolin where the acute measured LD_{50} values of >0.65 to 0.72 mg ac/L represents the

highest mean measured concentration tested, and also the apparent limit of solubility in those test systems. A similar result was obtained with the formulation.

The toxicity of eleven oxathiapiprolin degradation products (IN-E8S72, IN-P3X26, IN-Q7D41, IN-QFD61, IN-QPS10, IN-RAB06, IN-RDT31, IN-RSE01, IN-RYJ52, IN-S2K66, and IN-S2K67) to rainbow trout was investigated in static exposure studies. The 96 h LC_{50}s ranged from >0.18 to >100 mg ac/L with the LC_{50} values exceeding the highest test concentration in all cases, indicating the toxicity of the metabolites ranged from at worst, highly toxic to practically non-toxic to fish. *Oncorhynchus mykiss* were less sensitive to metabolites of oxathiapiprolin than to parent oxathiapiprolin in acute toxicity tests. The most sensitive chronic NOEC for freshwater fish (rainbow trout) is 0.46 mg/L and for marine fish (sheepshead minnow) is 0.34 mg/L, rating the chemical as slightly toxic to fish chronically.

Effects on aquatic invertebrates

The most sensitive acute freshwater and marine species EC_{50} values are 0.63 mg/L (*Daphnia magna*) and >0.33 mg/L (*Crassostrea virginica*), indicating that oxathiapiprolin is highly toxic to daphnia up to its limit of water solubility. The latter value represents the highest mean measured concentration tested and the apparent limit of solubility in that test system. The most sensitive chronic values are 32 days NOEC = 0.058 mg/L for mysid shrimp (*Americamysis bahia*) and a 28 day NOEC = 0.11 mg/L in aqueous phase and 2.8 mg ac/kg sediment for sediment dwelling organisms (*Chironomus riparius*). *Daphnia magna* were less sensitive to metabolites of oxathiapiprolin than to parent oxathiapiprolin in acute toxicity tests.

Effects on algae and aquatic plants

The most sensitive ErC_{50} values for freshwater algae (*Pseudokirchneriella subcapitata*) and aquatic plants (*Lemna gibba*) were >0.142 and >0.79 mg/L, respectively; the highest concentration tested and also the apparent limit of solubility in that test system. The most sensitive chronic endpoint for algae was determined to be 0.142 mg ac/L, indicating that oxathiapiprolin is at worst slightly toxic to green algae on a chronic basis. Metabolites of oxathiapiprolin have no toxic effects to algae and aquatic plants in acute toxicity tests.

On the basis of the results provided, the most sensitive acute and chronic endpoints were determined to be 48 h EC_{50} = 0.63 mg ac/L for *Daphnia magna* and 32 days NOEC = 0.058 mg ac/L for mysid shrimp in the fresh water and marine environment, respectively. In sediment the chronic endpoint was determined to be 28 day NOEC = 0.11 mg ac/L in the aquatic phase and NOEC = 2.8 mg ac/kg sediment in sediment for *Chironomus riparius*.

Terrestrial organisms

Effects on bees

The laboratory honey bee acute oral and contact LD_{50} values for oxathiapiprolin were >40.26 µg ac/bee (tested up to the highest possible dose for oral toxicity, which was limited by solubility) and >100 µg ac/bee, respectively. Tests on formulated product indicates that both contact and oral LD_{50} >100 µg ac/bee. The laboratory acute oral LD_{50} values for the two major plant metabolites IN-WR791 and IN E8S72 were >56.2 µg/bee (tested up to the highest possible dose for oral toxicity, which was limited by solubility) and >109 µg/bee, respectively. The laboratory acute contact LD_{50} values for the major plant metabolites IN-WR791 and IN E8S72 were >100 µg/bee and >100 µg/bee, respectively. These results indicate that

oxathiapiprolin and its metabolites IN-WR791 and IN E8S72 are very slightly toxic on a contact basis, and at worst, slightly toxic on an acute oral basis.

No treatment related effect on honey bee mortality, flight intensity, behaviour, brood development or colony strength was observed for the oxathiapiprolin treatments up to the final assessment in a semi field study at up to 3 × 180 g ac/ha.

Effects on non-target terrestrial arthropods

Testing for effects on arthropod species other than bees was carried out using the formulated product Oxathiapiprolin 100 g/L OD. In laboratory toxicity tests, the LR_{50} value for the parasitic wasp, *Aphidius rhopalosiphi* was 116.1 g ac/ha and for the mite, *Typhlodromus pyri* was >200 g ac/ha, the highest rate tested. There were no significant effects on reproduction.

Extended laboratory studies using natural substrates on the parasitic wasp (*Aphidius rhopalosiphi*) and green lacewing (*Chrysoperla carnea*) were conducted with Oxathiapiprolin 100 g/L OD. No significant effects were observed on mortality and reproduction. The 48–hour LR_{50} (mortality) and ER_{50} (reproduction) for both species were >200 g ac/ha, the highest rate tested.

Predatory mite field studies using Oxathiapiprolin 100 g/L OD indicated that three applications of 60 g ac/ha did not lead to a statistically significant reduction in predatory mite populations as compared to the control.

Effects on earthworms and other soil macro-organisms

Mortality and reproduction studies conducted with Collembola (*Folsomia candida*) indicated significant effects on mortality or reproduction effects, following 28–day exposure to soil, treated with oxathiapiprolin, Oxathiapiprolin 100 g/L OD and soil metabolites, IN RDT31, IN RAB06, IN QPS10 and IN E8S72. The NOEC value for oxathiapiprolin was 25 mg ac/kg soil. The NOEC value for its metabolites was 100 mg/kg soil.

Oxathiapiprolin had no significant effect on reproduction in soil mites (*Hypoaspis aculeifer*), with a 14–day NOEC of 1000 mg/kg soil. The respective NOEC values for metabolites were 25 mg/kg soil (IN-RAB06), 50 mg/kg soil (IN-QPS10) and 100 mg/kg soil (IN-E8S72 and IN-RDT31).

Effects on soil micro-organisms

Laboratory testing was conducted to evaluate the effects of oxathiapiprolin and its major soil metabolites IN RDT31, IN RAB06, IN QPS10 and IN E8S72 on non-target soil micro-organisms. The results demonstrated that no effects >25% compared to the control were observed in nitrogen transformation and carbon mineralisation rates in soil treated at rates in excess of the proposed maximum application rate.

Effects on terrestrial plants

Non-target plant testing with Oxathiapiprolin 100 g/L OD to evaluate potential effects following pre-emergent (soil) exposure resulted in ER_{50} values for all test species greater than the applied rate of 600 g ac/ha and the NOER = 600 g ac/ha. Likewise, non-target plant testing with Oxathiapiprolin 100 g/L OD to evaluate potential effects following post-emergent (foliar) exposure resulted in ER_{50} values for all test species to be greater than 600 g ac/ha and the NOER = 600 g ac/ha.

7.4 Risk Assessment

Du Pont (Australia) Pty Ltd has applied for the registration of a new product DUPONT ZORVEC ENICADE FUNGICIDE containing a new active constituent, oxathiapiprolin, for the control of various fungal diseases in vegetables and poppies. Chemical fate and ecotoxicity data were provided in support of their application for the environmental assessment. The submitted data has been considered with particular attention given to potential risk to organisms in aquatic and terrestrial environment for the proposed use.

The potential for direct overspray on water bodies is limited by the method of application. The risk from spray drift is considered acceptable without the requirement for a downwind buffer zone for the protection of the aquatic environment and terrestrial plants. Likewise the risk to the aquatic environment, including sediment systems, from run-off was acceptable.

The environmental risk assessment has concluded that the risks from the proposed use of the product will be acceptable to terrestrial organisms including birds, small mammals, honey bees, earthworms, soil microorganisms, beneficial non-target arthropods and non-target plants.

8 EFFICACY AND SAFETY ASSESSMENT

The purpose of this assessment is for registration of DUPONT ZORVEC ENICADE FUNGICIDE, containing 100 g/L oxathiapiprolin as an oil-based suspension concentrate (OD) formulation, for the control of downy mildew in a range of crops including bulb vegetables, brassicas vegetables, cucurbit vegetables, leafy vegetables and poppies.

The results of 33 trials (conducted in Australia and overseas) were presented to demonstrate the efficacy of DUPONT ZORVEC ENICADE FUNGICIDE in controlling downy mildew diseases in brassicas, cucurbits, leafy vegetables, bulb vegetables and poppies. Disease pressure ranged from low to extreme.

The trials on brassicas were on broccoli and cabbage. The trials on cucurbits were on rock melons (cantaloupe) and zucchini. The trials on leafy vegetables were on different cultivars of lettuce and on spinach. The trials on bulb vegetables were all on onions and spring onions.

All trials were randomised complete block with 3–6 replicates and untreated controls. Efficacy of DUPONT ZORVEC ENICADE FUNGICIDE (alone and in combination with other fungicides) was compared with a number of industry standards.

Rates of DUPONT ZORVEC ENICADE FUNGICIDE tested ranged from 2.2 g ac/ha to 280 g ac/ha (22– 2800 mL/ha) with most trials testing 20–70 g ac/ha (200–700 mL/ha).

The trials assessed the incidence and severity of disease, yield and crop safety. The number of applications ranged from 2–8 at intervals of from 4–15 days apart. Several trials tested application at two intervals, 7 and 14 days apart. Water volumes used ranged from 200 L/ha to 750 L/ha with most trials in the range of 250– 500 mL/ha.

Trial results showed that treatment with all rates of DUPONT ZORVEC ENICADE FUNGICIDE, in combination with other registered fungicides, significantly reduced downy mildew disease in brassicas, cucurbits, leafy vegetables, bulb vegetables and poppies. The rate of 20 g ac/ha was less effective than higher rates with 35 g ac/ha (350 mL/ha being the most consistent). Two applications 7–14 days apart (depending on the crop) were the most effective.

DUPONT ZORVEC ENICADE FUNGICIDE, in combination with other registered fungicides, was as effective or more effective, than industry standards and was safe to use on brassicas, cucurbits, leafy vegetables, bulb vegetables and poppies.

It is concluded that DUPONT ZORVEC ENICADE FUNGICIDE containing 100 g/L oxathiapiprolin when applied in two consecutive sprays at spray intervals of 7–14 days apart (depending on the crop), in combination with other registered fungicides, is effective in reducing / controlling downy mildew disease in brassicas, cucurbits, leafy vegetables, bulb vegetables and poppies. The appropriate rate for use is 350 mL/ha.

9 LABELLING REQUIREMENTS

READ SAFETY DIRECTIONS BEFORE OPENING OR USING

DuPont™ Zorvec® Enicade® fungicide

ACTIVE CONSTITUENT: 100 g/L OXATHIAPIPROLIN

GROUP	U15	FUNGICIDE

For the control of certain fungal disease species in oilseed poppies and vegetable crops as per the Directions for Use

DIRECTIONS FOR USE

RESTRAINTS:
DO NOT apply if rainfall is expected within 20 minutes of spray residues drying.
DO NOT use on hydroponic crops.
DO NOT 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.
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.)

FOR USE IN ALL STATES WHERE APPROPRIATE FOR THE CROP AND/OR DISEASE.

CROP	DISEASE	RATE	WHP	CRITICAL COMMENTS	
Bulb vegetables including: Onions	Downy mildew (Peronospora destructor)	350 mL/ha Plus a registered Downy mildew protectant fungicide at registered rates	10 days	Apply up to two consecutive sprays of Zorvec® Enicade®, 10 to 14 days apart. **DO NOT** apply more than 2 sprays of Zorvec® Enicade® to each crop as a precaution against development of disease resistance.	Maintain a regular protectant spray programme. Apply when conditions favour disease development but before the disease is evident. Apply in 250 to 500 L of water per hectare.
Chives Fennel bulb Florence fennel Garlic Leeks Shallots Spring onions				Apply up to two consecutive sprays of Zorvec® Enicade®, 10 days apart and then change to a fungicide from another chemical group. **DO NOT** apply more than 3 sprays of Zorvec® Enicade® to each crop as a precaution against development of disease resistance.	
Brassica vegetables including: Broccoli Brussels sprout Cabbage Cauliflower	Downy mildew (Hyaloperonospora parasitica)	350 mL/ha Plus a registered Downy mildew protectant fungicide at registered rates	Nil	Maintain a regular protectant spray programme. Apply when conditions favour disease development but before the disease is evident. Apply up to two consecutive sprays of Zorvec® Enicade®, 7 to 10 days apart and then change to a fungicide from another chemical group. Use the shorter interval when conditions favouring infection are creating a high risk. Apply in 250 to 500 L of water per hectare. **DO NOT** apply more than 3 sprays of Zorvec® Enicade® to each crop as a precaution against development of disease resistance.	

CROP	DISEASE	RATE	WHP	CRITICAL COMMENTS
Cucurbit vegetables including (field and protected crops): Bitter melon Chokos Cucumber, Gherkin Marrow Melons Pumpkin Rockmelon Squash Zucchini	Downy mildew (Pseudoperonospora cubensis)	350 mL/ha Plus a registered Downy mildew protectant fungicide at registered rates	1 day	Maintain a regular protectant spray programme. Apply when conditions favour disease development but before the disease is evident. Apply up to two consecutive sprays of Zorvec® Enicade® 7 to 10 days apart and then change to a fungicide from another chemical group. Use the shorter interval when conditions favouring infection are creating a high risk. Apply in 250 to 500 L of water per hectare. DO NOT apply more than 3 sprays of Zorvec® Enicade® to each crop as a precaution against development of disease resistance.

CROP	DISEASE	RATE	WHP	CRITICAL COMMENTS
Leafy vegetables including (includes Brassica leafy vegetables): Anaranth leafy Arugula Buk choy Cardoon Chard Celtuce Chevril Chinese broccoli (Gai lum/Gai lan/Kai lan) Chinese cabbage (Pet sai / Wombok / Haksukai) Choy sum, Gai choy / Am soy Corn salad Cress Dandelion leaves Dock Endive Kai choy Kale Leafy mustard including Indian mustard and Mustard spinach (Komatsuma) Lettuce (Head and Leafy) Mibuna New Zealand spinach Orach Pak choy Purslane (Garden and Winter) Radicchio Rocket Spinach Swiss Tat soy	Downy mildew (*Bremia lactucae,* *Peronospora farinose)*	350 mL/ha Plus a registered Downy mildew protectant fungicide at registered rates	3 days	Maintain a regular protectant spray programme. Apply when conditions favour disease development but before the disease is evident. Apply up to two consecutive sprays of Zorvec® Enicade®, 7 to 10 days apart and then change to a fungicide from another chemical group. Use the shorter interval when conditions favouring infection are creating a high risk. Apply in 250 to 500 L of water per hectare. DO NOT apply more than 3 sprays of Zorvec® Enicade® to each crop as a precaution against development of disease resistance.

CROP	DISEASE	RATE	WHP	CRITICAL COMMENTS
Poppies	Downy mildew (Peronspora cristata)	350 mL/ha Plus a registered Downy mildew protectant fungicide at registered rates	6 weeks	Commence spraying early (i.e. before the main disease infection period) with registered non Group U fungicides. Apply Zorvec® Enicade® when conditions favour disease development during the late run-up to hook stage. Apply in 250 to 500 L water per hectare. DO NOT apply later than hook stage. DO NOT apply more than 1 application of Zorvec® Enicade® to each crop, as a precaution against development of disease resistance.

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: NOT REQUIRED WHEN USED AS DIRECTED

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

BRASSICA LEAFY VEGETABLES, LEAFY VEGETABLES: DO NOT HARVEST FOR 3 DAYS AFTER APPLICATION.

CHIVES, FENNEL BULB, GARLIC, LEEKS, ONIONS, SHALLOTS, SPRING ONIONS: DO NOT HARVEST FOR 10 DAYS AFTER APPLICATION.

POPPIES: DO NOT HARVEST FOR 6 WEEKS AFTER APPLICATION.

GRAZING
DO NOT GRAZE OR CUT FOR STOCK FOOD.

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 Zorvec® Enicade®. If you are growing produce for export, please check with DuPont for the latest information on MRLs and export tolerances before using this product.

GENERAL INSTRUCTIONS

DuPont™ Zorvec® Enicade® fungicide is recommended for control of certain foliar plant diseases, and has preventive, and locally systemic activity. Zorvec® Enicade® 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

GROUP U15 FUNGICIDE

For fungicide resistance management DuPont™ Zorvec® Enicade® fungicide is a Group U15 fungicide.

Some naturally occurring fungal biotypes resistant to Zorvec® Enicade® and other Group U15 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungi population if Zorvec® Enicade® and other Group U15 fungicides are used repeatedly. The effectiveness of Zorvec® Enicade® 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 Zorvec® Enicade® to control resistant fungi.

Zorvec® Enicade® may be subject to specific resistance management strategies. To help prevent the development of resistance to Zorvec® Enicade®, use Zorvec® Enicade® fungicide in accordance with the current Fungicide Resistance Management (IRM) strategy for your region. **DO NOT** use Zorvec® Enicade® for more than 33% of the total foliar Downy mildew fungicide program. For a growing area, **DO NOT** apply more than 6 applications per 12 month period.

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 Zorvec® Enicade® required for the area to be sprayed. Add Zorvec® Enicade® 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 250 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

Compatibility

Zorvec® Enicade® is an oil based formulation. Avoid applying Zorvec® Enicade® in tank mixture with other agricultural products that have a history of causing crop injury when applied with oils unless specifically recommended by DuPont.

Zorvec® Enicade® is compatible with many commonly used fungicides, liquid fertilisers, herbicides, insecticides, plant growth regulators, 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. Zorvec® Enicade® is compatible with Antracol*, Avatar®, Benevia®, Coragen®, Fontelis®, imidacloprid, mancozeb, Movento*, Octave*, Phosphorous acid, Polyram*, Roval*, Success* Neo, Sumagic*, and Ultimate*.

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.

The mixing sequence recommended is: water soluble bags, dry flowable or water dispersible granules, wettable powders, water based suspension concentrates, water soluble concentrates, oil based suspension concentrates, emulsifiable concentrates, 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 WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

Very toxic to aquatic life with long lasting effect. **DO NOT** contaminate wetlands or watercourses with this product or used containers.

STORAGE AND DISPOSAL

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

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

RE-ENTRY

No re-entry restriction apply to this product.

SAFETY DIRECTIONS

May irritate the skin. Avoid contact with the skin. Repeated exposure may cause allergic disorders.
Sensitive workers should use protective clothing. When opening the container and preparing spray, wear chemical-resistant gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

FIRST AID

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

IN A MEDICAL EMERGENCY CALL
1800 674 415 All Hours

SAFETY DATA SHEET

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

NOTICE TO BUYER

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ABBREVIATIONS

ac	active constituent
ACCS	Advisory Committee on Chemicals Scheduling
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
AR	application rate
ARfD	Acute Reference Dose
BCF	Bioconcentration Factor
bw	bodyweight
CEC	cation exchange capacity
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
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
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
ER_{50}	residue at which 50% of the test population is impacted
EVOH	Ethylene vinyl alcohol
Fo	original parent generation
FRAC	Fungicide Resistance Action Committee
FSANZ	Food Standards Australia and New Zealand
g	gram
GAP	Good Agricultural Practice
h	hour
ha	hectare
HARVEST	HARVEST is a computer dietary modelling program based upon statistical software that is used by FSANZ
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography

id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
IRM	Integrated Resistance Management
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
JMPR	Joint Meeting on Pesticide Residues
kg	kilogram
K_f	Freundlich adsorption constant
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LC-MS/MS	Liquid Chromatography—Mass Spectrometry/Mass Spectrometry
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LR_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection—level at which residues can be detected
LOQ	Limit of Quantitation—level at which residues can be quantified
mg	milligram
mg eq	milligram equivalent
mL	millilitre
mN	millinewton
MOE	Margin of Exposure
mPa	millipascal
MRL	Maximum Residue Limit
SDS	Safety Data Sheet
NEDI	National Estimated Daily Intake

ng	nanogram
NOAEL	No Observable Adverse Effect Level
NOEC	No Observable Effect Concentration
NOER	No Observable Effect Residue
OC	Organic Carbon
OCS	Office of Chemical Safety
OD	Oil-based suspension concentrate
OECD	Organisation for Economic Co-operation and Development
OM	Organic Matter
PE	polyethylene
PHI	Pre-Harvest Interval
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
QuEChERS	Quick Easy Cheap Effective Rugged Safe
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SD	Sprague Dawley
STMR	Supervised Trials Median Residue
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
TRR	Total radioactive residue
µg	microgram
WHO	World Health Organisation

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
Encystment	To enclose or become enclosed in a cyst
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
Mycelial	The vegetative part of a fungus
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Total radioactive residue (TRR)	The total amount of ^{14}C-labelled oxathiapiprolin and its metabolites detected in residue studies
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons
Zoospore	A asexual spore capable of motion

REFERENCES

Australian Pesticides and Veterinary Medicines Authority, *Registration and Permits, Data Guidelines* (2015), apvma.gov.au/registrations-and-permits/data-guidelines.

FOCUS (2006). Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration. Report of the FOCUS Work Group on Degradation Kinetics. EC Document Reference Sanco/10058/2005 version 2.0, 434 pp. June 2006. Available at: http://focus.jrc.ec.europa.eu/dk/

NOHSC (2004). National Occupational Health and Safety Commission (NOHSC), *Approved Criteria for Classifying Hazardous Substances, 3rd Edition [NOHSC:1008(2004)]*, NOHSC, Canberra, 2004. Available at: www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/ns2004criteriaforclassifyinghazardous

OECD (2001). Test Guideline 416. OECD Guideline for Testing of Chemicals. Two-generation reproduction toxicity study. Available at: http://www.oecd-ilibrary.org/environment/test-no-416-two-generation-reproduction-toxicity_9789264070868-en

OECD (2011). Test Guideline 156: Guidance notes on dermal absorption. Paris, Organisation for Economic Co-operation and Development. Available at: http://www.oecd.org/chemicalsafety/testing/seriesontestingandassessmenttestingforhumanhealth.htm

SWA (2015). Safe Work Australia (SWA), *Hazardous Substances Information System (HSIS) Database*, SWA, Canberra, 2015. Available at: hsis.safeworkaustralia.gov.au/

US EPA (1998). United States Environmental Protection Agency (US EPA), *The Pesticide Handlers Exposure Database (PHED), Version 1.1–PHED Surrogate Exposure Guide, Estimates of Worker Exposure*. US EPA, Washington, DC, United States, 1998.

WHO (1997). Joint FAO/WHO Codex Alimentarius Commission. Guidelines for predicting dietary intake of pesticide residues. 1997. Available at: http://www.who.int/foodsafety/publications/pesticides/en/