Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active Sedaxane in the Product VIBRANCE Fungicide Seed Treatment

APVMA Product Number 64098

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This publication is available from the APVMA website: www.apvma.gov.au.

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PREFACE

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

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

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

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

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

About this document

This is a Public Release Summary.

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

- the toxicology of both the active constituent and product
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop 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 **VIBRANCE Fungicide Seed Treatment** 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 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 **23 October 2012** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing *via* email or by post.

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

When making a submission please include:

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

All personal information, and confidential information judged by the APVMA to be ***confidential commercial information (CCI)***[1] contained in submissions will be treated confidentially.Written submissions on the APVMA's proposal to grant the application for registration that relate to the **grounds for registration** should be addressed in writing to:

Contact Officer
Pesticides Program
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
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Phone: (02) 6210 4748
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Email: pesticides@apvma.gov.au

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

Further information

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

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

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

1 INTRODUCTION

1.1 Purpose of application

Syngenta Crop Protection Pty Limited has applied to the APVMA for approval of the new product VIBRANCE Fungicide Seed Treatment (formerly A16874F Fungicide Seed Treatment) containing the new active constituent sedaxane (13.8 g/L) and the registered active constituents difenoconazole (66.2 g/L) and metalaxyl-M (16.5 g/L), as a flowable concentrate for seed treatment. The application was jointly reviewed with regulatory authorities in Canada, Europe and the United States.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of VIBRANCE Fungicide Seed Treatment, and approval of the new active constituent sedaxane.

1.2 Function of active constituent

Sedaxane is a carboxamide fungicide belonging to the subclass of the pyrazole-carboxamides. Sedaxane has systemic properties that affects target pests by inhibition of succinate dehydrogenase (SDH), a key enzyme in cellular respiration and energy production. SDH inhibitors are currently classified as bearing medium to high risk of resistance by the Fungicide Resistance Action Committee (FRAC Group 7). As a result, sedaxane is formulated in combination with difenoconazole and metalaxyl-M, which are in different fungicide classes (FRAC Groups 3 and 4) to which no cross resistance is expected.

1.3 Product claims and use pattern

VIBRANCE Fungicide Seed Treatment is intended for use as a seed treatment for the control of various seedling diseases in barley, oats, triticale and wheat. The product is to be used at a rate of 180 mL/100 kg seed for control of smuts, common bunt, net blotch and *Pythium* root rot and 360 mL/100 kg seed for suppression of *Rhizoctonia* bare patch disease.

The product is applied as a water-based slurry using standard slurry treatment equipment with undiluted product (360 mL/100 kg seed) or diluted with water to a total volume of 600mL (product plus water)/100kg seed. Treatment may be in a commercial seed treatment facility or on-farm using equipment equivalent in function to commercial seed treatment facilities. Treated seed is to be stored in clearly marked bags or other containers and kept apart from other grain.

The 180-360mL/100kg seed rates deliver 2.5-5.0g sedaxane, 12-24g difenoconazole and 3.0-5.9g metalaxyl-M per 100 kg seed. The combination of the active constituents difenoconazole and metalaxyl-M is currently approved in the registered product Dividend Formula M Fungicide Seed Treatment (APVMA approval no. 56880) with the same claims for barley and wheat at similar rates of 9.2-24g difenoconazole and 2.3-6.0g metalaxyl-M per 100kg seed. Therefore, the risk associated with the proposed use of difenoconazole and metalaxyl-M in VIBRANCE Fungicide Seed Treatment is not greater than that previously assessed.

1.4 Registrations in other countries

Seed treatment products containing the same combination of active constituents as VIBRANCE Fungicide Seed Treatment were recently granted registration in Canada (VIBRANCE XL Seed Treatment, PMRA registration number 30437) and the United States (VIBRANCE Extreme Fungicide, EPA registration number 100-1282) for use at the same rate ranges on barley, oats, triticale, wheat and rye.

Seed treatment products containing sedaxane alone are also registered in Canada (VIBRANCE 500FS Seed Treatment, PMRA registration number 30438) and the United States (VIBRANCE Fungicide, EPA registration number 100-1374) for protection against smuts caused by *Ustilago* spp. and seed decay, seedling blight and damping off caused by *Rhizoctonia solani* at 2.5-5.0 g ac/100 kg seed on the barley, oats, triticale, wheat, rye, canola and soybeans.

Seed treatment products containing the same active constituents as VIBRANCE Fungicide Seed Treatment plus the insecticide thiamethoxam were also granted registration in Canada and the United States to also allow protection against certain insect pests on barley, oats, triticale, wheat and rye.

2 CHEMISTRY AND MANUFACTURE

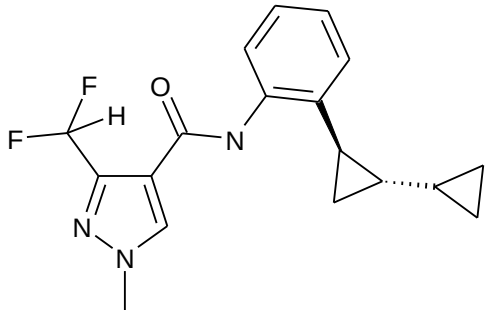
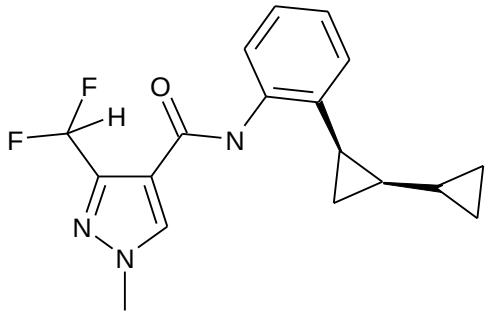
2.1 Active Constituent

Identity

Sedaxane is a carboxamide fungicide belonging to the sub-class of the pyrazole-carboxamides, which is a racemic mixture of two diastereomers (*trans* and *cis* isomers) with the typical *trans:cis* ratio is 85:15, the *trans* isomer is an active isomer while the *cis* isomer is a non-active isomer.

The toxophore of sedaxane is not fully elucidated but the activity of the compound depends on the amide (O=C-NH) heterocycle configuration. Sedaxane is a highly potent succinate dehydrogenase inhibitor of fungal pathogens.

COMMON NAME:	Sedaxane
IUPAC NAME:	Mixture of 2 *trans*-isomers: 2′-[(1*RS*,2*SR*)-1,1′-bicycloprop-2-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxanilide; and 2 *cis*-isomers: 2′-[(1*RS*,2*RS*)-1,1′-bicycloprop-2-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxanilide The typical *trans:cis* ratio is 85:15
CAS NAME:	1*H*-pyrazole-4-carboxamide, N-[2-[1,1'-bicyclopropyl]-2-ylphenyl]-3 (difluoromethyl)-1-methyl-
CAS REGISTRY NUMBER:	874967-67-6 (sedaxane) 599197-38-3 (*trans* isomer) 599194-51-1 (*cis* isomer)
MANUFACTURER'S CODES:	SYN524464 (sedaxane) SYN508210 (*trans* isomer) SYN508211 (*cis* isomer)
MINIMUM PURITY	976 g/kg
MOLECULAR FORMULA:	$C_{18}H_{19}F_2N_3O$
MOLECULAR WEIGHT:	331.4

STRUCTURAL FORMULA:	 *Trans* isomer (SYN508210), active  *Cis* isomer (SYN508211), non-active

Manufacturing site

The active constituent sedaxane is manufactured by Syngenta Crop Protection Monthey SA, Route de l'Ile au Bois, CH-1870 Monthey, Switzerland.

APVMA active constituent standard for sedaxane

CONSTITUENT	SPECIFICATION
Sedaxane	Sedaxane (total): not less than 950 g/kg -*Trans* isomers: not less than 810 g/kg

Physical and chemical properties of the active constituent

COLOUR:	White to grey-beige
PHYSICAL STATE:	Solid powder (crystalline)
ODOUR:	Weak, aromatic
MELTING POINT:	121.4°C

VAPOUR PRESSURE AT 20°C:	6.5×10^{-8} Pa
DENSITY AT 20°C:	1.23 g/ml
WATER SOLUBILITY AT 25°C:	14 mg/l, no pH dependence
SOLUBILITY IN ORGANIC SOLVENTS:	Dichloromethane: 500 g/L Acetone: 410 g/L Ethyl acetate: 200 g/L Methanol: 110 g/L Toluene: 70 g/L Octanol: 20 g/L Hexane: 0.41 g/L
PARTITION COEFFICIENT (N-OCTANOL/WATER):	log P_{ow} = 3.3, no pH dependence
UV/VIS ABSORPTION MAXIMA:	Solution / wavelength [nm] / molar extinction coefficient [l/mol x cm] Neutral: 225 / 17233; 265 / 5996; 295 / 874 Acidic: 225 / 17423; 265 / 5683; 295 / 851 Basic: 225 / 17393; 265 / 5833; 295 / 955 No absorption maximum 340-700 nm was observed
DISSOCIATION CONSTANT	Does not dissociate

2.2 Product

Identity

The product VIBRANCE Fungicide Seed Treatment is formulated in Australia and overseas.

DISTINGUISHING NAME:	VIBRANCE Fungicide Seed Treatment
FORMULATION TYPE:	Flowable concentrate for seed treatment (FS)
ACTIVE CONSTITUENTS:	13.8 g/L sedaxane 66.2 g/L difenoconazole 16.5 g/L metalaxyl-M
MANUFACTURER'S CODE:	A16874F
PACK SIZES:	10L, 20L, 100L and 1000L
PACKAGING MATERIAL:	High density polyethylene (HDPE)

Physical and chemical properties of the product

APPEARANCE:	Red opaque liquid
ODOUR:	Faint paint
PH:	6.9 (1% aqueous dilution); 6.7 (100%)
DENSITY:	1.124 g/cm^3 at 20°C
VISCOSITY:	557 mPa(s) at 20°C
FLAMMABILITY:	Not flammable
EXPLOSIVE PROPERTIES:	Not explosive
OXIDISING PROPERTIES:	No oxidising properties
CORROSIVE HAZARD:	Not corrosive to the HDPE container
DIELECTRIC BREAKDOWN VOLTAGE:	Not applicable, product is not to be used around electrical equipment
PRODUCT STABILITY	The product should remain within specifications for at least 2 years under normal conditions in HDPE packaging

2.3 Conclusion

The APVMA is satisfied that the chemistry and manufacture data requirements necessary for the approval of VIBRANCE Fungicide Seed Treatment, containing the active constituents sedaxane, difenoconazole and metalaxyl-M, have been met.

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

Australian independent toxicology assessments have used the terms of no observed effect level (NOEL) and lowest observed effect level (LOEL). However, since this report relies significantly on the global joint review, Australia adopted the no observed adverse effect level (NOAEL) and low observed adverse effect level (LOAEL) approach using scientific justification for their adoption, which are included within this international assessment.

In rats, following oral administration, sedaxane is rapidly and extensively absorbed, and widely distributed to organs and tissues, with the highest level detected in the liver followed by the kidneys. It is extensively metabolised in rats and rapidly eliminated from the body, and predominantly *via* the biliary route with minor elimination by the urinary pathway. There was no evidence of bioaccumulation following repeated dosing.

The estimated human *in vivo* absorption of sedaxane was determined to be low.

Based on the submitted data, sedaxane is of low acute oral, dermal and inhalational toxicity in rats, is not a skin irritant in rabbits but a slight eye irritant in the same species, and was not a skin sensitiser in mice.

Sedaxane was of low toxicity in a short-term dermal toxicity study in rats, with no treatment-related effects observed at the limit dose of 1000 mg/kg bw/day. In dietary toxicity studies in rodents, common toxicity findings were decreased body weight/body weight gain and food efficiency. In rats, changes in clinical chemistry and liver and heart histopathology were observed at the LOAEL, while in mice, changes in liver and testes weights and bilirubin were identified. These treatment-related effects were observed at moderately high doses. Similarly, in an oral toxicity study in dogs, treatment-related effects (body weight/body weight gain decreases) were observed at moderately high doses. Overall, sedaxane was of relatively low toxicity in short-term/sub-chronic studies.

In the chronic toxicity study in dogs, decreased body weights, body weight gains and food consumption, decreased spleen weights in both sexes, plus decreased cholesterol levels and decreased testes weight in males were identified at the top dose level.

In chronic dietary toxicity studies in rodents (rats and mice), toxicity findings included increased liver weight and corresponding histopathology findings in the liver (such as centrilobular hepatocyte hypertrophy and hepatocyte pigmentation) and accompanied by clinical chemistry changes that were consistent with an adaptive change in the liver, and decreased body weight and body weight gain. Alterations in thyroid histopathology were also noted in rats. Sedaxane was not considered to be carcinogenic in rodents as observed increase in the incidence of tumours in the liver, thyroid and uterus were only seen at a dose level that exceeded the maximum tolerated dose and/or were at a similar incidence to that seen in the historical control range.

Sedaxane was not a reproductive or developmental toxicant in rats and/or rabbits, and tested negative *in vitro* and *in vivo* in a battery of mutagenicity and/or genotoxicity studies. Additionally, the available data indicated that sedaxane did not demonstrate neurotoxic or immunotoxic potential in rats, and little relative difference in toxicity was observed between the *cis* and *trans* forms of sedaxane. Additionally, the sedaxane

metabolite CSCD465008 was of low toxicity in an acute oral toxicity study and a short-term dietary study in rats, and was not mutagenic or genotoxic *in vitro* with and without metabolic activation.

Based on the findings of the toxicological studies evaluated, the product VIBRANCE Fungicide Seed Treatment has low acute oral, dermal and inhalational toxicity in rats. It is not a skin irritant in rabbits but a slight eye irritant in the same species, and was not a skin sensitiser in guinea pigs.

3.2 Evaluation of Toxicology

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

Since the assessment report relies significantly on the global joint review, Australia has adopted the no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) approach with scientific justification for the adoption of these NOAEL/LOAEL positions.

Toxicokinetics and Metabolism

In rats, absorption was similar in both sexes and at both dose levels (1 or 80 mg/kg bw) and with both radiolabelled forms of sedaxane ([pyrazole-5-^{14}C]-sedaxane or [phenyl-U-^{14}C]-sedaxane). Absorption at the low dose level was estimated to be 87.4 and 87.9% using the ^{14}C-pyrazole radiolabel and 89.1 and 87.5% using the ^{14}C-phenyl radiolabel in males and female rats respectively. At the high dose level, absorption was estimated to be 89.5 and 92.5% using the ^{14}C-pyrazole radiolabel and 93.9 and 87.1% using the ^{14}C-phenyl radiolabel in males and female rats respectively.

Whole body autoradiography conducted in a preliminary rat study showed that the administered radioactivity was distributed widely throughout the internal organs after 5 hours. At 24 h post dose, levels of total radioactivity had decreased markedly in all tissues.

The excretion and tissue distribution studies in rats, at both dose levels, showed that residues of radioactivity were very low in blood and tissues seven days after dosing and were only reliably measured in both sexes in the liver and kidney. Tissue distribution was generally similar in both sexes and at both dose levels, with the only difference being slightly higher residues in thyroid, spleen, lung and the gastrointestinal tract in male

rats at the high dose level. In total, radioactive residues in tissues accounted for <0.1% of the dose at both dose levels. Radioactivity in the residual carcass accounted for <0.2% of the dose at both dose levels.

The routes and rates of excretion were similar in male and female rats and at both dose levels. By seven days after dosing, males and females excreted 97.2% and 96.3% respectively of a 1 mg/kg bw dose and 102.1% and 104.9% of an 80 mg/kg bw dose. The major route of excretion was *via* the faeces accounting for 88.4 and 79.4% of a low dose level in males and females respectively. With corresponding values of 83.1 and 74.9% for the high dose level. Urinary excretion accounted for 11.8 and 19.6% of a low dose level in male and female rats respectively, with corresponding values of 11.9 and 17.6 % for the high dose level. In a preliminary rat study, no radioactivity was measured in expired air.

Biliary elimination was significant at both dose levels in both male and female rats, accounting for between 78.6 and 81.1% of the dose in males and females at the low dose level and between 81.0 and 85.3% of the dose in males and females at the high dose level over 48 hours after dosing in the studies conducted with ^{14}C-pyrazole and ^{14}C-phenyl–labelled sedaxane.

Following repeated daily oral administration of 1 mg [^{14}C]-sedaxane/kg bw to male rats, tissue concentrations of radioactivity were highest in the liver followed by the kidney. Following the cessation of dosing, all tissue concentrations declined, with no evidence of any persistence. With the exceptions of liver, kidney and spleen, tissue concentrations had declined to values close to or below the limit of reliable measurement by day 28 after the cessation of dosing.

Sedaxane was extensively metabolized in the rat *via* demethylation, hydroxylation, oxidation and conjugation affording an array of hydroxylated metabolites and metabolites formed by cleavage of the terminal cyclopropyl moiety. An equivalent range of metabolites of desmethyl sedaxane were also formed. There were no major sex or dose related differences apparent in the qualitative metabolite profile for sedaxane. Little evidence of any cleavage of the sedaxane molecule between the phenyl and pyrazole moieties was seen with samples obtained from rats receiving ^{14}C-pyrazole or ^{14}C-phenyl sedaxane affording similar metabolic profiles. A small amount (<1%) of a pyrazole amide metabolite was detected in bile samples. The phenolic and hydroxy metabolites of sedaxane and desmethyl sedaxane were subject to glucuronic acid, sulphate and glutathione conjugation.

The dermal absorption of sedaxane determined using the ‘triple-pack’ approach was low, with an estimated human *in vivo* absorption of 0.01–0.21 % for concentrations between 2.5–500 g/L sedaxane.

Acute Studies

Sedaxane is of low acute toxicity by the oral (LD_{50} > 5000 mg/kg bw), dermal (LD_{50} > 5000 mg/kg bw) and inhalation (4-hr LC_{50} > 5240 mg/m^3) routes of exposure in rats. It is not a skin irritant in rabbits, but is slightly irritating to rabbit eyes. Sedaxane was not a skin sensitiser based on the results of a mouse local lymph node assay.

VIBRANCE Fungicide Seed Treatment (containing 13.8 g/L sedexane, 66.2 g/L difenoconazole and 16.5 g/L metalaxyl-M) is of low oral (LD_{50} > 5000 mg/kg bw), dermal (LD_{50} > 5050 mg/kg bw) and inhalation (4-hr LC_{50} > 2630 mg/m^3) toxicity in rats. It is not a skin irritant in rabbits, but is slightly irritating to rabbit eyes. Sedaxane was not a skin sensitiser based on the results of a Buehler assay in guinea pigs.

Systemic Effects

In repeat dose (dietary) toxicity studies in rats and mice, and repeat oral (capsule) studies in dogs, common toxicity findings were decreased body weight, body weight gain and/or food efficiency. Rats were slightly more sensitive by the oral route to the general systemic effects of sedaxane treatment than mice and dogs. Mice were less sensitive than other tested species, where effects were observed only at the highest tested dose.

In rats, changes in clinical chemistry and liver and heart histopathology were observed at the LOAEL, while in mice, changes in liver and testes weights and bilirubin were identified. These treatment-related effects were observed at moderate doses (> 70 mg/kg bw/day). Similarly, in an oral toxicity study in dogs, treatment-related effects (body weight/body weight gain decreases) were observed at moderate doses (> 50 mg/kg bw/day). Overall, sedaxane was of relatively low repeat dose oral toxicity in short-term/sub-chronic studies in experimental animals.

Similar systemic (non-neoplastic) findings were seen in long-term oral toxicity studies in rats, mice and dogs. In a 1-year oral (capsule) toxicity study in dogs, no treatment-related effects were observed at ≤ 50 mg/kg bw/day. At the LOAEL of 200 mg/kg bw/day, decreased body weights, body weight gains and food consumption, decreased spleen weights in both sexes, plus decreased cholesterol levels and decreased testes weight in males were identified. In a 80-week dietary study in mice, decreased body weight, body weight gain and food efficiency were seen at the LOAEL of 900 and 1001 mg/kg bw/d in males and females respectively. In a 2-year dietary study in rats, increased liver weight, increased incidences of hepatocyte hypertrophy and eosinophilic foci, and thyroid follicular cell hypertrophy, basophilic colloid and epithelial desquamation in males, and decreased body weight and body weight gain, decreased AST and ALT, increased liver weight and the same thyroid histopathology changes as observed in males, were sent at the LOAEL of 67 and 86 mg/kg bw/d in males and females respectively.

Sedaxane was of low toxicity in a short-term repeat dermal toxicity study in rats, with no treatment-related effects observed up to and including the limit dose of 1000 mg/kg bw/day.

Carcinogenicity

In the combined dietary chronic/carcinogenicity study in rats, there was no robust evidence that sedaxane was carcinogenic to male and female rats after treatment for up to 104 weeks. Since, while compared to controls an increase in the incidence of follicular cell carcinomas and adenomas was seen in males at 67 mg/kg bw/d (4 and 8% respectively), it was within the laboratory's historical control range (0-6% and 2-11% respectively). Furthermore, a slight increase in follicular cell adenomas (15%) and follicular cell adenomas and carcinomas combined (17%) in males that exceeded the laboratory's historical control range at 218 mg/kg bw/d (2-15% for thyroid tumours combined) was at a dose level that substantially exceeded the maximum tolerated dose (MTD), as demonstrated by the observance of a 50% decrease in body weight gain. Consequently, these thyroid findings in one sex do not provide robust evidence of a carcinogenic potential. Similarly, an increase in liver tumours, hepatocellular adenomas only (10%), above the historical control range (0 -3%) was only seen in male rats at 218 mg/kg bw/d which substantially exceeded the MTD. Consequently, these thyroid findings in one sex do not provide robust evidence of a carcinogenic potential.

In female rats, an increased incidence of uterine adenocarcinoma was seen at the top dose of 261 mg/kg

bw/d (17.3%). However, this incidence was within the historical control range of the laboratory (0 –19%) and was seen at a dose level that exceeded that MTD as demonstrated by the observance of a 24% decrease in body weight gain. Consequently, these uterine findings are considered likely incidental and not treatment related.

In a dietary carcinogenicity study in mice, there was no robust evidence that sedaxane was carcinogenic to male and female mice after treatment for up to 80 weeks. Although compared to controls an increase in the incidence of hepatocellular adenomas (30%) and carcinomas (20%) was seen in males at 900 mg/kg bw/d that exceeded the laboratory's historical control range (10-28% and 6-10%), this finding in one sex was not considered to be treatment related for the following reasons. The tumour findings were seen in the absence of treatment-related (non-neoplastic) changes and at a dose level that was considered the MTD based on a decrease in body weight gain of 10%, the increase in adenomas was only slightly above the laboratory's historical control range, the laboratory's historical control database is based on 3 studies and may not convey the true 'incidence' of finding and it is noted that for this strain of mouse the Registry of Industrial Toxicology Animal-data indicates a spontaneous rate of 4 – 22% for hepatocellular carcinomas. Additionally, there is no evidence of a mutagenic and/or genotoxic potential for sedaxane *in vitro* and *in vivo*. Consequently, these liver findings in one sex at the MTD which is close to the limit dose are considered likely incidental and not treatment related.

Genotoxicity

Sedaxane was not mutagenic in bacterial strains or mammalian cells *in vitro* with and without metabolic activation. It was also not genotoxic in an *in vitro* chromosome aberration study in mammalian cells with and without metabolic activation, or in an *in vivo* micronucleus test in mice. Additionally, sedaxane did not induce unscheduled DNA synthesis in rat liver hepatocytes *in vivo*.

Reproductive Toxicity

In a dietary two-generation reproductive toxicity study in rats, there were no indications of any significant differences in sensitivity to sedaxane between the different generations or between parental animals and offspring. With regard to fertility, while reproductive performance was unaffected by treatment at up to the top dose of 120 - 134 and 141 - 143 mg/kg bw/d in males and females, a decrease in absolute and relative ovary weights was noted to be associated with decreases in ovarian follicular counts identified in female animals at 120 – 134 mg/kg bw/d (decreased primordial follicles in P_0 and decreased antral/growing follicles in F_1). The decreased ovarian follicle counts at the high dose level were associated with an increased incidence in the number of females in lactational diestrous (i.e. not cycling due to a prolonged lactation period). It is considered that this ovarian follicle finding, in the absence of other reproduction and fertility effects across both generations at 1500 ppm, is not robust evidence of reproductive toxicity, and there is a reasonable expectation that based on the available information, similar effects are unlikely to occur at the next lowest dose of 46 – 47 mg/kg bw/d in females. However, while sedaxane was not considered to be a reproductive toxicant in rats in this study, a conservative evaluation of the data was taken and a reproductive NOAEL of 46 mg/kg bw established in females, while the NOAEL in males was 120 mg/kg bw/d the top dose tested.

For maternal toxicity, a NOAEL was established at 41 and 46 mg/kg bw/d in males and female respectively. This was based on decreased body weights (females throughout two generation), body weight gain (females during P_0 premating), food consumption (P_0 males premating, females throughout two generations) and

decreased ovarian weights (P_1 females). Similarly in offspring, a NOAEL was established at 41 and 46 mg/kg bw/d in males and female respectively. This was based on decreased pup body weights, delayed vaginal patency (equivocal), increased anogenital distance (females only, equivocal), increased liver weight and decreased spleen weight.

Thus, there were no adverse effects at the intermediate dose level of 41-46 mg/kg bw/d in adults or pups indicating that this was the NOAEL for parental, fertility and offspring toxicity.

Developmental Toxicity

Data from both the rat and rabbit oral developmental toxicity studies with sedaxane showed no potential for teratogenic effects, with the developmental toxicity NOAEL values equal to or higher than the maternal NOAEL values, indicating a lack of sensitivity of developing offspring to the effects of sedaxane.

In the rat dietary study, the maternal toxicity NOAEL was established at 100 mg/kg bw/d based on decreased body weight, body weight gain and food consumption, while the developmental toxicity NOAEL was 200 mg/kg bw/d the highest dose tested based on the absence of treatment related effects. In rabbits, the maternal toxicity NOAEL was established at 200 mg/kg bw/d based on two abortions that were associated with decreased body weight, body weight gain and food consumption, with decreased defecation also observed in does, while the developmental toxicity NOAEL was 200 mg/kg bw/d based on decreased foetal weight which was considered a secondary non-specific consequence to the observed maternal toxicity.

Neurotoxicity

Clear evidence of systemic toxicity was noted at 250 mg/kg bw and greater in the acute oral (gavage) neurotoxicity study in rats. Findings included observations of reduced activity, decreased rearing, initial inactivity, piloerection, ruffled fur and recumbency, decreased body weight, body weight gains and food consumption (in males); plus weakened condition, swaying gait, decreased activity, reduced muscle tone and decreased locomotor activity and rearing (in females). Similarly, clear evidence of systemic toxicity was noted at the top dose of 260 and 302.9 mg/kg bw/day in males and female rats respectively, in the dietary subchronic neurotoxicity study. Findings included decreased body weight, body weight gains, food consumption, food efficiency, as well as reduced locomotor activity.

The decreased motor activity was seen at week 2 and 5 but not 9 or 13 at 260 mg/kg bw/day in females only, and there were no treatment-related effects on other FOB parameters, grip strength, landing foot splay or neuropathological changes at necropsy. Therefore, as for the acute neurotoxicity study, this subchronic neurotoxicity study did not provide reliable evidence of neurotoxicity.

Immunotoxicity

Sedaxane was not immunotoxic in male mice at 1080.1 mg/kg bw/d, a dose slightly exceeding the limit dose, in a 28-day dietary study.

Toxicological Studies on Metabolites

The sedaxane metabolite CSCD465008 was of low toxicity in an acute oral toxicity study in rats (LD_{50} >2000 mg/kg bw). It was also of low toxicity in a 28 day oral dietary study in rats with no treatment related effects seen up to and including the top dose level of 1018 and 1107mg/kg bw/d in males and females. Additionally, the sedaxane metabolite CSCD465008 was not mutagenic in bacterial strains and mammalian cells *in vitro*, or genotoxic in mammalian cells *in vitro*, with and without metabolic activation.

Special Studies

In a 28-day dietary comparative toxicity study, *cis/trans* forms of sedaxane were examined for toxicity in Wistar rats. Overall, the test materials caused similar qualitative effects and there was little difference in the incidence and severity of treatment-related findings between the *cis* form, the *trans* form and a 1:1 combination of the *cis* and *trans* forms of sedaxane.

3.3 Public Health Standards

Poisons Scheduling

On the 30th May 2012, the delegate to the Secretary to the Department of Health and Ageing made a delegate only decision on sedaxane. The Secretary's delegate recommended that sedaxane be included in Schedule 5 of the Standard for the Uniform Scheduling of Medicines and Poisons with no cut-off, along with an implementation date of 1st September 2012.

NOAEL/ADI

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

The ADI for sedaxane is established at 0.11 mg/kg bw/day, based on a NOAEL of 11 mg/kg bw/day (males) in a two-year combined chronic/carcinogenicity study, and applying a default 100-fold safety factor for potential inter- and intra-species differences. Observation of treatment-related effects observed at the LOAEL (non-neoplastic changes in the liver, decreased body weight gain and minor changes in clinical chemistry) and the lack of serious toxicological effects in other repeat-dose toxicity studies indicated that additional safety factors were not required.

ARfD

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

An acute reference dose (ARfD) was not established since sedaxane was considered unlikely to present an acute hazard to humans after single dose administration. Since, an acute study indicated sedaxane is of low acute toxicity, and did not demonstrate evidence of a neurotoxic, reproductive or developmental toxicity potential.

3.4 Conclusion

The APVMA is satisfied that the proposed use of VIBRANCE Fungicide Seed Treatment**,** containing the active constituents sedaxane, difenoconazole and metalaxyl-M, is not likely to be harmful to human beings if used according to the product label directions.

4 RESIDUES ASSESSMENT

4.1 Introduction

As part of the residues assessment for sedaxane, plant and animal metabolism studies, supervised residue trials and trade aspects were considered, along with residues data for difenoconazole and metalaxyl.

4.2 Metabolism

Plants

In primary crops, the metabolism and distribution of sedaxane has been investigated in three different crops (wheat, soybean and Swiss chard) representative of the cereals, pulses and oilseeds and leafy crops groups.

Spring wheat

Spring wheat seed was treated with [phenyl-U-^{14}C] or [pyrazole-5-^{14}C] labelled sedaxane at approximately 40 g ai/100 kg seed. The treated seeds were sown into containers containing sandy loam soil in a glasshouse. Samples of forage were taken at BBCH 22, hay at BBCH 41-57, and grain and straw at BBCH 89. For the [phenyl-U-^{14}C] sedaxane treated spring wheat, the total radioactive residue (TRR) found in forage was 0.435 mg equiv./kg, 0.762 mg equiv./kg in hay and 1.005 mg equiv./kg in straw. The TRR in wheat grain was 0.005 mg equiv./kg. For the [pyrazole-5-^{14}C] sedaxane treated spring wheat, the TRR found in forage was 0.610 mg equiv./kg increasing to 1.042 mg equiv./kg in hay and 0.805 mg equiv./kg in straw. The TRR in wheat grain was 0.007 mg equiv./kg. Grain samples were not analysed further due to the low TRR. Samples of forage, hay and straw were extracted and analysed by thin layer chromatography (TLC) and HPLC. Sedaxane was observed in wheat hay treated with [pyrazole-^{14}C] sedaxane at levels up to 0.163 mg/kg, 15.7% TRR. The *trans* para phenol metabolite CSCD658906 was the most significant metabolite in all commodities with maximum residue levels observed in wheat hay of 0.178 mg equiv./kg, ≤ 17.1% TRR.

Soybean

Soybean seed was treated with [phenyl-U-^{14}C] or [pyrazole-5-^{14}C] labelled sedaxane at approximately 100 g ai/100 kg seed. The treated seeds were sown into containers containing sandy loam soil in a glasshouse. Samples of forage were taken at BBCH 16, hay at BBCH 61 and seeds at maturity. For the [phenyl-U-^{14}C] sedaxane treated soybean the TRR found in forage was 0.132 mg equiv./kg increasing to 0.419 mg equiv./kg in hay. The level in the seeds was 0.009 mg equiv./kg. For the [pyrazole-5-^{14}C] sedaxane treated soybean a similar profile was seen where the TRR found in forage was 0.123 mg equiv./kg increasing to 0.427 mg equiv./kg in hay and decreasing to 0.054 mg equiv./kg in seeds. In the soybean forage, parent sedaxane represented 12.0 and 16.5% TRR (0.016 and 0.020 mg/kg) for the phenyl and pyrazole treatments, respectively. CSCD667555 and CSCD667556 represented 24 - 28% and 13 - 17% TRR (0.029 - 0.039 and 0.018 – 0.020 mg equiv./kg), respectively, for the two labels. In the soybean hay, parent sedaxane represented 23.2% and 16.6% TRR (0.082 and 0.073 mg/kg) for the phenyl and pyrazole treatments, respectively. CSCD667555 and CSCD667556 represented 22 - 27% and 13 - 22% TRR (0.095 – 0.098 and

0.044 – 0.097 mg equiv./kg), respectively for the two labels. In the soybean, no parent sedaxane was detected. The N-demethylated acid CSCD465008 and its aspartic acid and sugar conjugates were the major metabolites representing 9.3%, 9.7% and 12.4% TRR (0.005, 0.005 and 0.007 mg equiv./kg), respectively.

Swiss chard

Swiss chard seed was treated with [phenyl-U-^{14}C] or [pyrazole-5-^{14}C] labelled sedaxane at approximately 40 g ai/100 kg seed. The treated seeds were sown into containers containing sandy loam soil in a glasshouse. The crop was harvested at BBCH 14-15 (4 to 5 fully open leaves) generating a single raw agricultural commodity for each radiolabel. Total radioactive residues in the crop at harvest were equivalent to 0.0452 mg equiv./kg for the phenyl label experiment and 0.0556 mg equiv./kg for the pyrazole-labelled experiment. Parent sedaxane was the major identified residue in Swiss chard from both radiolabelled experiments representing maximum residue levels of 52.3% TRR, 0.024 mg/kg. In the pyrazole labelled Swiss chard, N-desmethyl pyrazole acid, CSCD465008, represented 11.5% TRR, 0.006 mg equiv./kg, and the pyrazole amide, CSCC210616, 12.9% TRR, 0.007 mg equiv./kg.

A metabolic pathway for sedaxane in crops has been proposed (Figure 2). The main pathways involved oxidation of the phenyl and cyclopropane rings, N-demethylation of the pyrazole ring and cleavage between the pyrazole and phenyl rings.

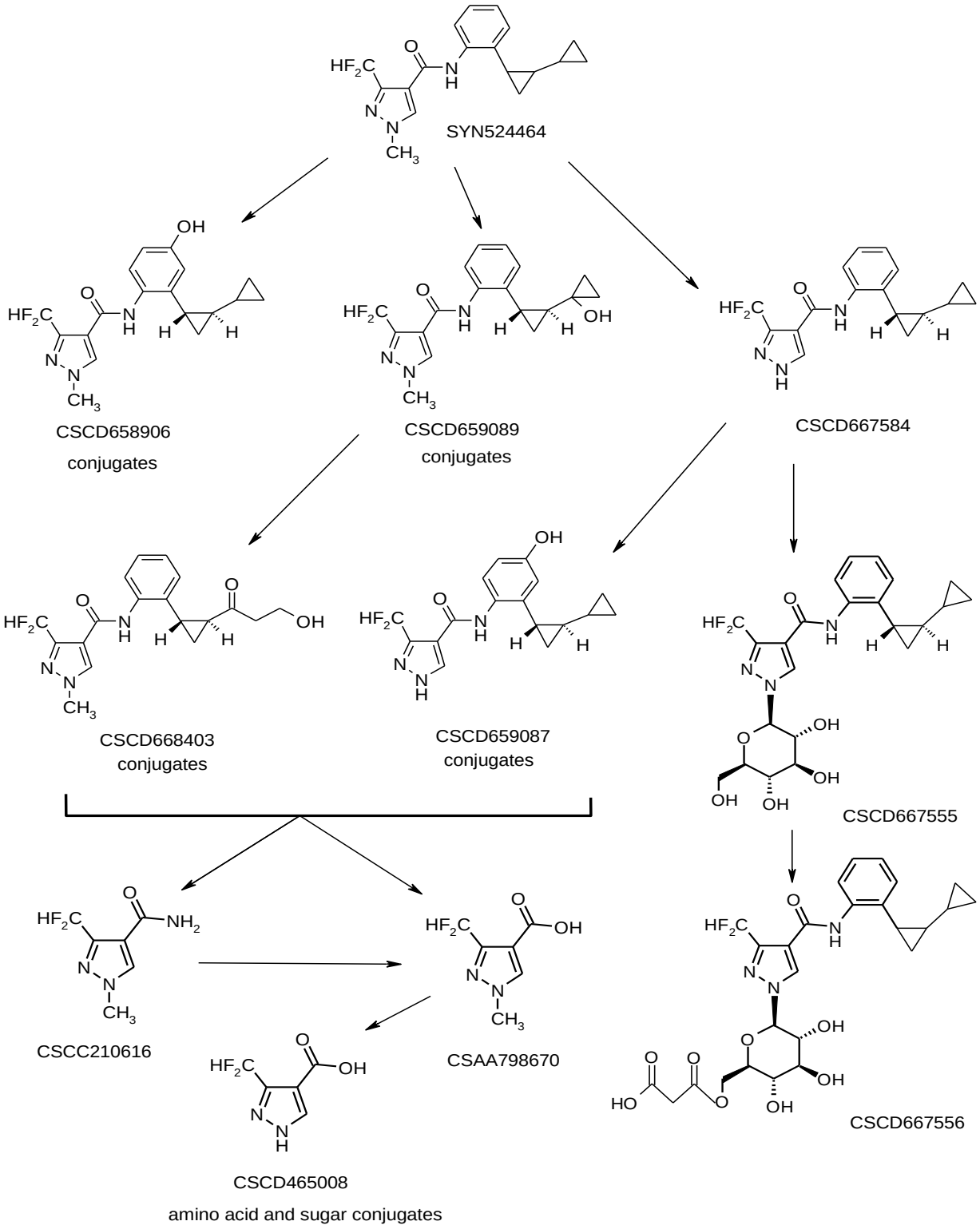


Figure 2: Proposed metabolic pathway for sedaxane in primary crops.

Confined rotational crops

Two confined rotational crop studies are available. In the first sedaxane is applied by a seed treatment, in the second study sedaxane is applied to bare soil.

Application as a seed treatment

[Pyrazole-5-^{14}C] and [phenyl-U-^{14}C] labelled sedaxane was applied to soybeans as a seed treatment. The seeding rate was targeted to an application rate of 100 g ai/ha (~20×).

The following seeds were planted following re-tilling of soybean plants into the soil : wheat (30, 120 and 365 day PBI), radish (30, 120 and 365 days PBI) and lettuce (30, 151 and 365 day PBI). Raw agricultural commodities (RACs) were harvested at appropriate intervals.

Initial extracts released from all commodities 66.4 - 94.9% of the TRR for the pyrazole label and 67.2 - 90.2% of the TRR for the phenyl label.

The major ^{14}C-residues included : parent, three hydroxylated intact metabolites, both free and sugar-conjugated forms (CSCD668403, CSCD659087 and CSCD659089), pyrazole amide (CSCD210616) and two pyrazole acids, both free and conjugated forms (CCAA798670 and CSCD465008). These major residues, especially conjugated forms, were particularly high in the 120 day PBI wheat straw extracted samples allowing for extensive characterization and identification.

Parent was often a minor residue in 30 and 120/151 day PBI RACs or even non-detectable in some 365 day PBI RACs. The highest TRR of parent was found in 30 day PBI phenyl radish root (0.015 mg/kg, 57.7% TRR).

Application to bare soil

[Pyrazole-5-^{14}C] and [phenyl-U-^{14}C] labelled sedaxane, formulated as a flowable concentrate A14635, were applied to bare soil at a nominal rate of 100 g ai/ha (~20×). Succeeding crops of wheat, turnip and lettuce were sown 29, 90 and 300 days after the application of the test substance. Raw agricultural commodities (RACs) were harvested at appropriate intervals.

Uptake of radioactive residues in food commodities i.e. leafy vegetables, grain and root tubers were low representing ≤0.03 mg/kg. In feed commodities, residues were highest in wheat straw representing a maximum of 1.095 mg equiv./kg at 29 DAT (pyrazole label). Extractability of the residue into acetonitrile and acetonitrile : water mixtures was >85% TRR for all commodities except wheat grain where extractability ranged from 22 to 60% TRR.

Parent sedaxane (maximum 62.5% TRR, 0.003 mg/kg in 29 DAT phenyl label mature lettuce and 57.3% TRR, 0.175 mg/kg in 29 DAT phenyl label wheat hay), N-demethylated parent CSCD667584 (maximum 13.7% TRR, 0.001 mg equiv./kg in 90 DAT phenyl label turnip roots 5.4% TRR, 0.059 mg equiv./kg in 29 DAT phenyl label wheat straw) and the two pyrazole acids, CSCC465008 and CSAA798670 (maximum 51.0% TRR, 0.025 mg equiv./kg in 90 DAT turnip leaves and 29.8% TRR, 0.129 mg equiv./kg in 90 DAT wheat straw when combined) were present in all commodities.

A metabolic pathway for sedaxane in rotational crops has been proposed (figure 3). As for primary crops the main pathways involved oxidation of the phenyl and cyclopropane rings, N-demethylation of the pyrazole ring and cleavage between the pyrazole and phenyl rings.

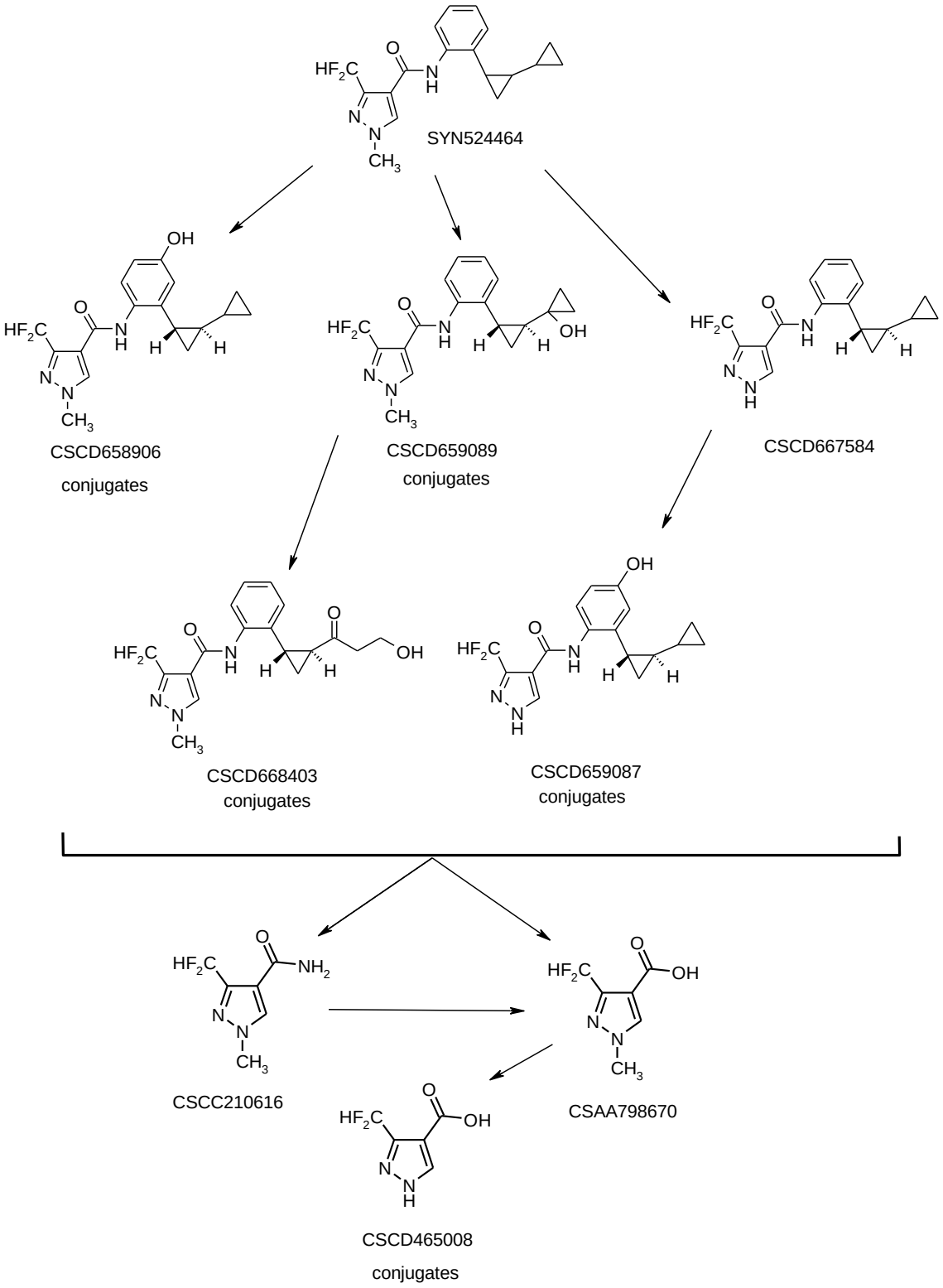


Figure 3: Proposed metabolic pathway for sedaxane in rotational crops.

Livestock

The metabolism of sedaxane was investigated in laying hens and lactating goats.

Laying hen

Five laying hens each were dosed orally by gelatin capsule with either [pyrazole-5-^{14}C]-sedaxane or with [phenyl-U-^{14}C]-sedaxane for 14 days. The mean daily dose administered from Day 1-13 ranged from 18.7 to 21.6 ppm for birds dosed with [phenyl-U-^{14}C]-sedaxane and from 18.12 to 23.47 ppm for birds dosed with [pyrazole-5-^{14}C]-sedaxane. Eggs were collected twice daily throughout the study (yolk and white were separated); excreta and cage wash were collected once daily. The birds were sacrificed approximately 12 hours after the final dose and liver, peritoneal fat, subcutaneous fat with skin, and muscle tissues were taken for quantification and analysis.

For eggs TRRs were highest in yolks (up to 0.078 mg equiv./kg), with a plateau reached after approximately 9 days. For tissues, TRRs were highest in liver (up to 0.264 mg equiv./kg). Lower residues were found in the other tissues (muscle 0.005 mg equiv./kg, skin and fat up to 0.024 mg/kg).

The majority of the radioactivity was solvent extracted with ACN, ACN/water mixtures, water, and/or DCM for all matrices: ~78% to 79% TRR in egg yolk, ~94-97% TRR in egg white, ~64-65% TRR in liver, ~73-83% TRR in muscle, ~92-94% TRR in abdominal fat, and ~70-78% TRR in skin and fat.

Low residues in muscle precluded identification of metabolites.

In egg yolk, sedaxane was present at low levels accounting for 1.5-2.1% TRR (0.001-0.002 mg/kg). CSCD667584 was also present at a low level and accounted for 1.6-1.9% TRR (0.001 mg/kg). The major residue was identified as the *trans*-para phenol metabolite CSCD658906 and the corresponding *cis* isomer CSCD659090 which together accounted for 14.2-17.0% TRR (0.010-0.014 mg equiv./kg). These were present both in non-conjugated and conjugated form.

Sedaxane and CSCD667584 were present in egg white at low levels and accounted for 4.7%-13.7% TRR (0.001 mg equiv./kg).

Sedaxane was not detected in liver from either the phenyl or pyrazole label experiments. The major residue in liver was identified as the *trans* para phenol metabolite CSCD658906 and the corresponding *cis* isomer CSCD659090 which together accounted for 14.6%-17.1% TRR (0.033-0.039 mg equiv./kg), the majority of which (13.6%-15.6% TRR, 0.030-0.036 mg equiv./kg) was present as conjugates.

The most significant radiolabelled residues detected in fat were assigned as sedaxane and CSCD667584. Sedaxane accounted for 46.0%-53.1% TRR (0.004-0.007 mg/kg) and 24.6%-26.9% TRR (0.003-0.006 mg/kg) for abdominal fat and skin and fat, respectively. CSCD667584 accounted for 7.5%-9.3% TRR (0.001 mg equiv./kg) and 6.0%-7.9% TRR (0.001 mg equiv./kg) for abdominal fat and skin and fat, respectively.

The proposed metabolic pathway is shown in Figure 4. The primary mechanisms for the proposed biotransformation pathway of sedaxane in the laying hen were : N-demethylation, hydroxylation of sedaxane to give para phenols CSCD658906 and CSCD659090 and the cyclopropyl alcohol CSCD659089, O-

Glucuronidation of the hydroxylated metabolites of sedaxane and N-desmethyl sedaxane. There was no indication of significant cleavage between the phenyl and pyrazole moieties.

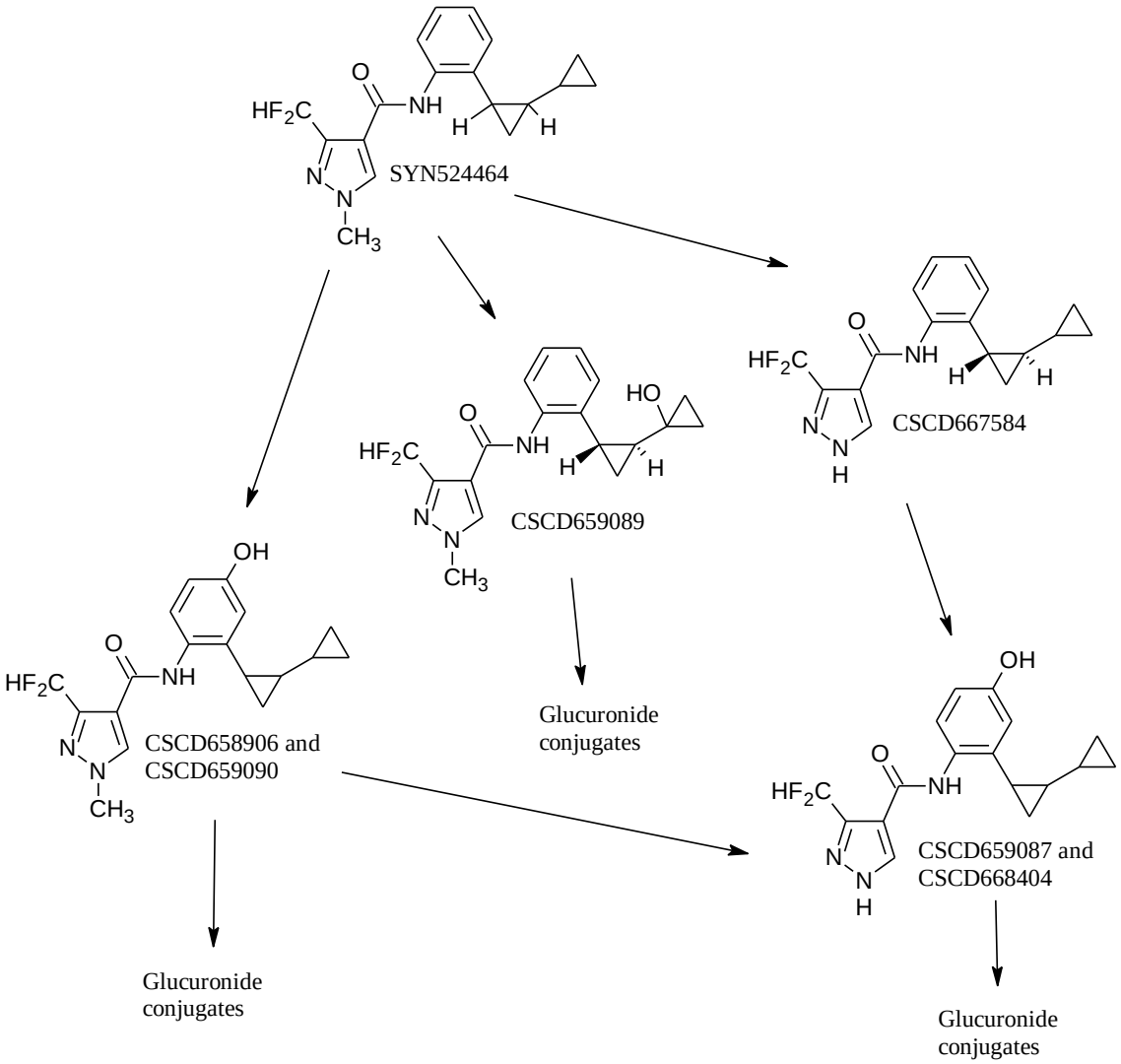


Figure 4: Proposed metabolic pathway for sedaxane in the laying hen.

Lactating goat

Two lactating goats were dosed orally with either [phenyl-U-^{14}C]-sedaxane or [pyrazole-5-^{14}C]-sedaxane for 7 consecutive days at a nominal rate of 20 ppm, based on dietary dry matter intake. The actual mean daily dose administered was 24.045 and 22.793 ppm (dry weight) for the goats dosed with [phenyl-U-^{14}C] and [pyrazole-5-^{14}C]-sedaxane, respectively.

Milk was collected twice daily throughout the acclimatisation and dosing periods. Tissues, including muscle (composite of forequarter, hindquarter, and tenderloin), fat (composite of perirenal, omental, and subcutaneous), liver, and kidneys, were collected at sacrifice, ~12 hours after the final dose.

TRRs in milk indicated that a plateau was reached after approximately 2 days. TRRs were highest in liver (up to 0.614 mg equiv./kg) with lower levels in other tissues (kidney up to 0.190 mg equiv./kg, muscle up to 0.006 mg equiv./kg and fat up to 0.015 mg equiv./kg).

The majority of the radioactivity was solvent extracted with acetone and acetone/water for milk (both labels; ~97% TRR), with acetonitrile (ACN), ACN/water, and water for tissues (both labels; ~89-92% TRR for kidney and ~85-88% TRR for muscle), and with dichloromethane (DCM), ACN, and ACN/water for fat (both labels; ~96%). Solvent extraction released lower amounts of radioactivity from liver (both labels; ~57-69% TRR).

Low residues in muscle precluded identification of metabolites.

Sedaxane was not present at detectable levels in milk. The major components were identified as the para phenol metabolites CSCD658906 and CSCD659090, which accounted for 2.8-6.3% TRR (0.001-0.002 mg equiv./kg) and the desmethyl para phenol metabolites CSCD659087 and CSCD668404, which accounted for 8.5-9.7% TRR (0.003-0.004 mg equiv./kg). These were present both in non-conjugated and conjugated form.

In liver from the phenyl label experiment, unchanged sedaxane was detected only at low levels and accounted for 5.5% TRR (0.034 mg/kg). The major residue was identified as the *trans* para phenol metabolite CSCD658906 and the corresponding *cis* isomer CSCD659090, which together accounted for 20.5% TRR (0.126 mg/kg), the majority of which (19.1% TRR; 0.117 mg/kg) was present as conjugates.

In liver from the pyrazole label experiment, unchanged sedaxane was detected only at low levels and accounted for a maximum of 2.0% TRR (0.009 mg/kg). The major residue was identified as the *trans* para phenol metabolite CSCD658906 and the corresponding *cis* isomer CSCD659090, which together accounted for 15.6% TRR (0.073 mg equiv./kg), the majority of which (13.4% TRR; 0.063 mg equiv./kg) was present as conjugates.

In kidney, no unchanged sedaxane was detected in either experiment. The major residue was again identified as the *trans* para phenol metabolite CSCD658906 and the corresponding *cis* isomer CSCD659090, which together accounted for 23.6% TRR (0.044 mg/kg) and 16.6% TRR (0.013 mg/kg) for the phenyl and pyrazole label experiments, respectively, the majority of which was present as conjugates. Metabolite CSCD659088 was also detected at 12.6% TRR (0.024 mg/kg) for the phenyl label.

The most significant radiolabelled residues detected in fat were identified as sedaxane and CSCD667584, which accounted for 28.4% TRR (0.004 mg/kg) and 17.6% TRR (0.003 mg equiv./kg), respectively for the phenyl label experiment and 43.7% TRR (0.005 mg/kg) and 16.1% TRR (0.002 mg equiv./kg), respectively for the pyrazole label experiment.

The proposed metabolic pathway for sedaxane in lactating goats is shown in Figure 5. The primary mechanisms for the proposed biotransformation pathway of sedaxane in the lactating goat were : N-Demethylation, hydroxylation of sedaxane to give the para phenols CSCD658906 and CSCD659090 and the cyclopropyl alcohol CSCD659089, hydroxylation of desmethyl sedaxane to give the para phenols CSCD659087 and CSCD668404 and the desmethyl cyclopropyl alcohol CSCD659088, opening of the

terminal cyclopropyl moiety of sedaxane followed by oxidation of the side chain to give a β-hydroxycarbonyl sedaxane metabolite (the trans isomer CSCD668403 was identified), conjugation of hydroxylated metabolites and desmethyl sedaxane.

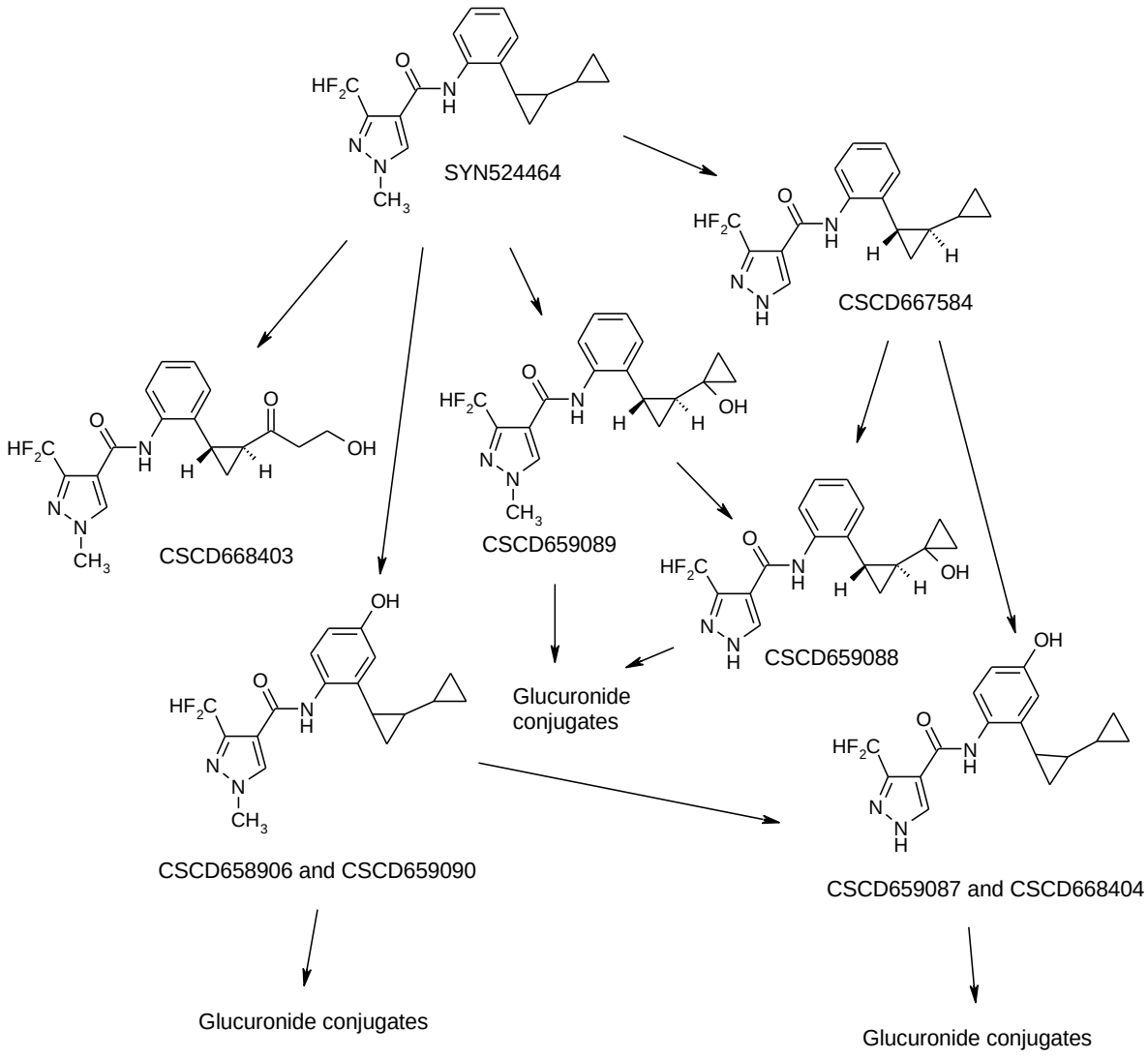


Figure 5: Proposed metabolic pathway of sedaxane in lactating ruminents.

4.3 Analytical methods

Sedaxane – plant commodities

For the sedaxane field trials in Australia, wheat, barley and oats samples were analyzed for residues of SYN 508210 (*trans* isomer), SYN 508211 (*cis* isomer) and the metabolites CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555 and CSCD465008 using a method of analysis (GRM023.03A)

based on liquid chromatography with tandem mass spectrometry detection (LC-MS-MS). Samples were extracted with acetonitrile/ water (80:20 v/v) and the extracts centrifuged. Separate aliquots were taken for the analysis of different analytes. For analysis of SYN508210 and SYN508211 aliquots were diluted with ultra-pure water and cleaned up by solid phase extraction (SPE) prior to instrumental analysis. For analysis of CSCD667584, CSCD658906, CSCD659089 and CSCD668403 aliquots were evaporated to remove acetonitrile, buffered, then hydrolysed overnight at 37°C. This was followed by SPE clean-up prior to instrumental analysis. For analysis of CSCD667555 aliquots were hydrolysed with 0.1M sodium hydroxide at 60°C, then cooled and diluted with ultra-pure water, prior to instrumental analysis. For analysis of CSCD465008 aliquots were evaporated and partitioned with hexane, acidified and cleaned-up by SPE prior to instrumental analysis.

The method was adequately validated prior to and in conjunction with the analysis of the field trial samples, using untreated samples fortified separately with sedaxane at 0.005 - 0.10 mg/kg and metabolites at 0.01-0.1 mg/kg. The validated limit of quantitation (LOQ) was 0.005 mg/kg for isomers of sedaxane and 0.01 mg/kg for metabolites CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555 and CSCD465008.

Sedaxane - animal commodities

Details of an analytical method to determine residues of sedaxane and metabolites in animal commodities has been provided. The method was tested on hens eggs and on bovine muscle, fat, kidney, liver, milk and blood. Animal matrices are extracted by homogenization with 80/20 (v/v) acetonitrile/water. For analysis of sedaxane (as the *trans* and *cis* isomers SYN508210 and SYN508211) an aliquot of the extract is diluted with water. The sample is further diluted with an appropriate amount of 60/40 (v/v) water/methanol for quantification using high performance liquid chromatography with triple quadrupole mass spectrometric detection (HPLC-MS/MS).

For analysis of metabolites CSCD658906 and CSCD659087, an aliquot of the extract is diluted with water. The sample is evaporated to ~1 mL. The sample is mixed with buffer solution (0.4M sodium acetate) followed by approximately 10 mg of β-glucoronidase, for hydrolysis for 6 hours (or overnight - 16-20 hrs in validation) at 37°C. Samples are diluted with 50/50 v/v acetonitrile/water, filtered then diluted further with 70/30 v/v water/acetonitrile for quantification using high performance liquid chromatography with triple quadrupole mass spectrometric detection (HPLC-MS/MS).

The limit of quantification for SYN508210 and SYN508211 residues in animal commodities using method GRM023.10A was established at 0.005 mg/kg. The limit of quantification for CSCD568906 and CSCD569087 residues in animal commodities using method GRM023.10A was established at 0.01 mg/kg. Recoveries from fortified samples of hens eggs and bovine muscle, fat, kidney, liver, milk and blood were within acceptable limits.

Difenoconazole and metalaxyl-M – plant commodities

In Australian oat trials provided with the application, difenoconazole and metalaxyl-M were extracted from samples by homogenisation with methanol/water (90:10 v/v). The extracts were centrifuged and an aliquot diluted with water and saturated sodium chloride solution. The residue was purified by partitioning into dichloromethane. An aliquot of the organic phase was evaporated and re-dissolved in acetone prior to

analysis by GC/MS. The LOQ was 0.01 mg/kg for each of difenoconazole and metalaxyl-M in oat forage, grain and straw. Recoveries of difenoconazole and metalaxyl-M from fortified control samples of oat forage, grain and straw were within acceptable limits.

Stability of pesticide residues in stored analytical samples

Three studies were conducted to investigate the stability of residues of sedaxane (as SYN508210 (*trans*) and SYN528211 (*cis*)) and its major metabolites (CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555, CSCD465008, CSCC210616 and CSAA798670) in various raw agricultural commodities (RACs); and one study was done to investigate the stability of Sedaxane and metabolites in processed commodities.

The first study investigated the stability of sedaxane (as its cis and trans isomers SYN508210 and SYN508211) in wheat grain, wheat straw, spinach, potato, orange, lentils, and soybeans. Untreated samples of each of these commodities were homogenized and fortified with either SYN508210 or SYN508211 at a level of 0.20 mg/kg. Residues of SYN508210 and SYN508211 showed no significant decrease (>30% as compared to the zero time value) in any of the crop matrices studies after frozen storage for at least 24 months.

The second study investigated the stability of the metabolites CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555, and CSCC210616 in wheat grain, wheat straw, spinach leaves, potato tuber, orange, dried broad bean, and soybean seeds and CSCD465008 in orange, broad bean, and soybean. Untreated samples of each of these commodities were homogenized and fortified with the metabolites at a level of 0.20 mg/kg. The residues of CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555, CSCC210616 and CSCD465008 showed no significant decrease (>30% as compared to the zero time value) in any of the crop matrices studies after frozen storage for at least 24 months.

The third study investigated stability of sedaxane (SYN508210 and SYN508211), and CSCD465008 in processed commodities from wheat (flour, germ, and bran), soybean (meal, hulls, and oil) and orange (dried pulp, juice, and oil). The residues of SYN508210, SYN508211, and CSCD465008 (soybean only) showed no significant decrease (>30% as compared to the zero time value) in any of the crop matrices studies after storage deep frozen for at least 12 months.

Difenoconazole and metalaxyl-M

Storage stability of difenoconazole and metalaxyl-M has been demonstrated to be satisfactory in previous evaluations. In the Australian residue trials submitted, all samples were maintained under freezer conditions, (i.e.–18 °C) prior to analysis and tested within 7 months of collection. This is acceptable for the purposes of the current application.

4.4 Residue Definition

Unchanged sedaxane accounted for a significant proportion of the residue in all three primary crop metabolism studies: 18% TRR (0.082 mg/kg) in wheat forage, 15.7% TRR (0.163 mg/kg) in wheat hay, 13.4% TRR (0.151 mg/kg) in wheat straw, 23% TRR (0.082 mg/kg) in soybean hay to 52% TRR (0.024

mg/kg) in Swiss chard. Parent sedaxane was also significant in the confined rotational crop studies, occurring at levels of 62.5% TRR (0.003 mg/kg) in mature lettuce, 60.7% TRR (0.002 mg/kg) in turnip roots and 57.3% TRR (0.175 mg/kg) in wheat hay.

The recommended residue definition for sedaxane for commodities of plant origin is parent sedaxane, sum of isomers.

In livestock the metabolism of sedaxane has been investigated in laying hens and lactating goats. Compounds exceeding 10% TRR in the animal metabolism studies were parent sedaxane (SYN524464), the *trans*-para phenol (CSCD658906) and N-desmethyl *trans*-para phenol (CSCD659087). Only the *trans*-para phenol (CSCD658906) was detected in an animal transfer study at the highest dose level. Since CSCD658906 and CSCD659087 were not observed in the feeding study at dose levels relevant to the likely livestock dietary burden for the proposed use they will not be included in the residue definition for animal commodities.

The recommended residue definition is:
Commodities of animal origin: Sedaxane, sum of isomers.

4.5 Residue Trials

Australian residue data for sedaxane on wheat, barley and oats have been provided in support of the application. The Australian data is supported by overseas trials on wheat and barley conducted in North America and Europe.

Cereal grain

In 16 Australian trials on wheat (8), barley (4) and oats (4), residues of sedaxane (*cis* and *trans* isomers) in grain grown from seed treated at 5 g ai/100 kg (1×) were <0.01 mg/kg (n = 16). Residues of sedaxane in grain were also <0.01 mg/kg (n = 16) after treatment of seed at 10 g ai/100 kg (2×). In 36 North American trials on wheat, residues of sedaxane in grain grown from seed treated at 5 g ai/100 kg (1×) were <0.01 mg/kg (n = 36). In 23 European trials on spring and winter wheat residues of sedaxane in grain grown from seed treated at 10 g ai/100 kg (2×) were <0.01 mg/kg (n = 23). In 24 North American trials on barley, residues of sedaxane in grain grown from seed treated at 5 g ai/100 kg (1×) were <0.01 mg/kg (n = 24).

An MRL of *0.01 mg/kg is recommended for sedaxane on GC 0080 Cereal grain.

Cereal straw

In 16 Australian trials on wheat (8), barley (4) and oats (4), residues of sedaxane (cis and trans isomers) in straw grown from seed treated at 5 g ai/100 kg (1×) were <0.01 mg/kg (n = 16). In 36 North American trials on wheat, residues of sedaxane in straw grown from seed treated at 5 g ai/100 kg (1×) were <0.01 mg/kg (n = 36). In 24 North American trials on barley, residues of sedaxane in straw grown from seed treated at 5 g ai/100 kg (1×) were <0.01 mg/kg (n = 24).

An MRL of *0.01 mg/kg is recommended for sedaxane on AS 0081 Straw and fodder (dry) of cereal grains.

Cereal forage

In 16 Australian trials on wheat (8), barley (4) and oats (4), residues of sedaxane in forage harvested 40-42 days after sowing seed treated at 5 g ai/100 kg were <0.01 (n = 5, fresh weight), 0.07 (n = 7, dry weight) and 0.08 (n = 4, DW) mg/kg. In 20 US trials on wheat, residues of sedaxane in forage at 45 days after planting seed treated at 5 g ai/100 kg ranged from <0.01 – 0.015 mg/kg. In 16 Canadian trials on wheat residues in forage at 13 - 50 days after planting were all <0.01 mg/kg. Assuming a dry matter content of 25% for wheat forage the HR from the North American wheat trials is 0.06 mg/kg.

An MRL of 0.2 mg/kg is recommended for sedaxane on Cereal forage (green), with a grazing withholding period of 6 weeks.

Difenoconazole and metalaxyl-M

To support the additional uses of difenoconazole and metalaxyl-M on oats and triticale the applicant has supplied details of 4 new Australian GLP trials on oats.

No quantifiable residues (<0.01 mg/kg) of difenoconazole or metalaxyl-M were detected in oat foliage at 40 – 44 days after sowing seed which had been treated at up to 24 + 6 g ai/100 kg (n = 4). There were also no quantifiable residues (<0.01 mg/kg) of difenoconazole or metalaxyl-M in oat grain or straw at harvest after treatment of seed at the maximum proposed rate (n = 4).

It is recommended that the difenoconazole and metalaxyl MRLs each at *0.01 mg/kg for GC 0640 Barley and GC 0654 Wheat are replaced with MRLs also at *0.01 mg/kg for GC 0080 Cereal grains.

The MRLs for difenoconazole and metalaxyl both at *0.1 mg/kg for Barley forage (green) and Wheat forage (green) should be replaced with MRLs also at *0.1 mg/kg for Cereal forage (green), with a grazing withholding period of 6 weeks.

The MRLs for difenoconazole and metalaxyl both at *0.05 mg/kg for AS 0640 Barley straw and fodder, dry and AS 0654 Wheat straw and fodder, dry should be replaced with MRLs also at *0.05 mg/kg for AS 0081 Straw and fodder (dry) of cereal grains. The MRL of T*0.05 mg/kg for difenoconazole on Cereal grain fodder and forage should be deleted.

4.6 Processing studies

Barley

Two barley processing studies were submitted. One was performed in a manner typical of European processing and the other in a manner typical of North American processing.

In the European study, pot barley, barley flour and bran were produced using typical industrial practices from barley grown from seed that had been treated at an exaggerated rate (36 g ai/100 kg seed). Residues of sedaxane and its metabolites (CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555, CSCC210616, and CSCD465008) were not found in the RAC barley grain nor were they found in the barley processed commodities.

In the North American study, pearl barley, bran, and flour were produced from barley grown at 2 sites from seed that had been treated at 15 g ai/100 kg. Residues of sedaxane, trans and cis isomers, and all metabolites (CSCD667584, CSCD658906, CSCD465008, CSCD659089, CSCD668403, and CSCD667555) were less than the LOQ in all samples.

Wheat

In a North American study wheat bran, flour, middlings, shorts, and germ were produced roughly according to typical industrial practices from wheat grain from 2 sites grown from seed that had been treated at an exaggerated rate (15 g ai/100kg). Residues of sedaxane and its metabolites (CSCD667584, CSCD658906, CSCD465008, CSCD659089, CSCD668403, and CSCD667555) were not found in the RAC wheat grain or in the wheat grain processed commodities.

As detectable residues of sedaxane are not expected to occur in cereal grains as a result of the proposed use and the available processing studies showed no indication of significant concentration of residues following treatment at exaggerated GAP, it is not necessary to establish separate MRLs for sedaxane on any processed commodities derived from cereal grains.

4.7 Animal commodity MRLs

Sedaxane - Cattle

A dairy cow feeding study for sedaxane has been provided in support of the application. In this study three groups of lactating dairy cows (with 3 cows/group) were dosed orally with capsules containing sedaxane at three target doses equivalent to 0.1, 0.5 and 2 ppm in the diet (on a dry-weight basis) for 28 consecutive days.

The cows were milked twice daily, and milk samples were composited daily for each cow. Samples of milk from study days -1, 1, 2, 3, 5, 7, 10, 14, 21, 24, and 28 from all dose groups were taken for analysis. In addition, milk collected from one high-dose animal on days 1, 3, 7, 14, 21, and 28 was also separated into cream and skimmed milk samples. Animals were sacrificed ~22-24 hours after the final dose on Study Day 28. Samples of liver, kidney, fat (mesenterial, perirenal, and subcutaneous) and muscle (round and loin) were collected from each cow.

Milk and tissue samples were analyzed for residues of Sedaxane (as the *trans* and *cis* isomers, SYN508210 and SYN508211) and the para-phenol metabolite (CSCD658906) and the para-phenol-desmethyl metabolite (CSCD659087).

Residues of SYN508210, SYN508211, CSCD658906 and CSCD659087 were below the LOQ (<0.005 mg/kg for the isomers and <0.01 mg/kg for the metabolites) in all milk samples from all dose groups. Skimmed milk and cream samples were only generated for one animal of the high-dose group; residues of SYN508210, SYN508211, CSCD658906 and CSCD659087 were below the LOQ (<0.005 mg/kg for the isomers and <0.01 mg/kg for the metabolites) in all skimmed milk and cream samples.

In tissues, residues of SYN508210, SYN508211, and CSCD659087 were below the LOQ (<0.005 mg/kg for the isomers and <0.01 mg/kg for the metabolite) in all samples of liver and kidney from all dose groups.

Residues of CSCD658906 were also below the LOQ (<0.01 mg/kg) in liver and kidney samples from the low- and mid-dose groups, but were above the LOQ in two of three liver samples (0.0101-0.0273 mg/kg) and two of three kidney samples (0.0121-0.0175 mg/kg) from the high-dose group. Only muscle and fat samples from the high-dose group were analyzed; residues of SYN508210, SYN508211, CSCD658906 and CSCD659087 were below the LOQ (<0.005 mg/kg for the isomers and <0.01 mg/kg for the metabolites) in all samples.

Livestock dietary burden for cattle

The maximum dietary exposure to sedaxane residues as a result of this proposal will be from consumption of cereal forage from treated crops at 100% of the diet as calculated below.

Table 1: Cattle- 500 kg bw, 20 kg DM/day

					LIVESTOCK DIETARY EXPOSURE		
COMMODITY	% IN DIET	FEED	RESIDUE, mg/kg	% DM	mg/ANIMAL	ppm	mg/kg bw
Cereal forage	100	20	0.08 (HR)	100	1.6	0.05	0.0032

Based on the results of the animal transfer study a feeding level of 0.08 ppm would not be expected to result in quantifiable residues in tissues or milk. The following mammalian commodity MRLs are recommended for sedaxane:

Table 2: MRL for cattle commodities

COMPOUND	FOOD	MRL (mg/kg)
MO 0105	Edible offal	*0.01
MM 0095	Meat [mammalian]	*0.01
ML 0106	Milks	*0.01

Sedaxane - Poultry

A poultry animal transfer study for sedaxane has not been provided. However, the available data suggest there is little likelihood of detectable residues occurring in cereal grain and therefore in poultry commodities. The following poultry commodity MRLs are therefore recommended for sedaxane:

Table 3: MRL for poultry commodities

COMPOUND	FOOD	MRL (mg/kg)
PE 0112	Eggs	*0.01
PO 0111	Poultry, Edible offal of	*0.01
PM 0110	Poultry meat	*0.01

Difenoconazole and metalaxyl-M

The livestock dietary exposure to difenoconazole and metalaxyl residues will not change as a result of this application. No changes are required to the animal commodity MRLs for difenoconazole and metalaxyl which remain acceptable for the proposed use.

4.8 Estimated dietary intake

The chronic dietary exposure to sedaxane is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines[2] and is a conservative estimate of dietary exposure to chemical residues in food.

The NEDI for sedaxane is equivalent to <1% of the ADI.

The NEDI for difenoconazole is equivalent to 16% of the ADI.

The NEDI for metalaxyl is equivalent to 8% of the ADI.

It is concluded that the chronic dietary exposures of sedaxane, difenoconazole and metalaxyl are acceptable.

The acute dietary exposure is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food.

The OCS considered that an acute reference dose is not required for sedaxane. A NESTI calculation is therefore not needed for sedaxane.

The acute exposure to difenoconazole residues in cereal grains is acceptable being less than 1% of the acute reference dose for both children and the general population.

An acute reference dose is not established for metalaxyl and was considered unnecessary by the 2002 JMPR. A NESTI calculation is therefore not needed for metalaxyl.

2 Guidelines for predicting dietary intake of pesticide residues, WHO, 1997.

4.9 Bioaccumulation potential

The log P_{ow} of sedaxane is 3.3 at 25°C indicating moderate fat solubility. As detectable residues of sedaxane are not expected to occur in animal commodities as a result of the proposed use, the potential for bioaccumulation is low.

4.10 Spray drift

The product will be used as a seed treatment only. It is not necessary to consider the risk to trade associated with spray drift.

4.11 Recommendations

The following changes are recommended to the MRL Standard:

Table 4: MRL Standard – Table 1 Amendments

COMPOUND		FOOD	MRL (mg/kg)
SEDAXANE			
ADD:			
GC	0080	Cereal grains	*0.01
MO	0105	Edible offal (mammalian)	*0.01
PE	0112	Eggs	*0.01
MM	0095	Meat [mammalian]	*0.01
ML	0106	Milks	*0.01
PO	0111	Poultry, Edible offal of	*0.01
PM	0110	Poultry meat	*0.01
DIFENOCONAZOLE			
DELETE:			
GC	0640	Barley	*0.01
GC	0654	Wheat	*0.01
ADD:			
GC	0080	Cereal grains	*0.01
METALAXYL			
DELETE:			
GC	0640	Barley	*0.01

COMPOUND		FOOD	MRL (mg/kg)
GC	0654	Wheat	*0.01
ADD:			
GC	0080	Cereal grains	*0.01

Table 5: MRL Standard – Table 3 Amendments

COMPOUND	RESIDUE
ADD:	
Sedaxane	Sedaxane, sum of isomers

Table 6: MRL Standard – Table 4 Amendments

COMPOUND		ANIMAL FEED COMMODITY	MRL (mg/kg)
SEDAXANE			
ADD:			
		Cereal forage (green)	0.2
AS	0081	Straw and fodder (dry) of cereal grains	*0.01
DIFENOCONAZOLE			
DELETE:			
		Barley forage (green)	*0.1
AS	0640	Barley straw and fodder, dry	*0.05
		Cereal grain fodder and forage	T*0.05
		Wheat forage (green)	*0.1
AS	0654	Wheat straw and fodder, dry	*0.05
ADD:			
		Cereal forage (green)	*0.1
AS	0081	Straw and fodder (dry) of cereal grains	*0.05
METALAXYL			
DELETE:			
		Barley forage (green)	*0.1
AS	0640	Barley straw and fodder, dry	*0.05
ADD:			

COMPOUND	ANIMAL FEED COMMODITY	MRL (mg/kg)
	Cereal forage (green)	*0.1
AS 0081	Straw and fodder (dry) of cereal grains	*0.05

The following withholding periods are required in relation to the above MRLs:

Barley, Oats, Triticale, Wheat:

Harvest: *NOT REQUIRED WHEN USED AS DIRECTED.*

Grazing: *DO NOT GRAZE OR CUT FOR STOCK FOOD FOR 6 WEEKS AFTER SOWING.*

4.12 Conclusion

The APVMA is satisfied that the proposed use of VIBRANCE Fungicide Seed Treatment will not be an undue hazard to the safety of people using anything containing its residues if used according to the product label directions

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported

Major export commodities affected by the use of VIBRANCE Fungicide Seed Treatment are cereal grains (wheat, barley, oats and triticale) and all livestock commodities derived from animals fed on cereal grain, forage and straw. Oaten hay is also a major export commodity. Residues in these commodities have the potential to unduly prejudice trade.

5.2 Destination and value of exports

Australian exports of wheat totalled 18639 kt and were valued at ~ $5526m in 2010-11[3]. Australian exports of coarse grains totalled 5337 kt and were valued at ~$1493m in 2010-11[2]. Barley was the most significant export (~$1295m) with oats (~$37m). Triticale exports were worth ~$149m in 2010-2011[2].

Major export markets by value are shown below (Australian Commodity Statistics 2011 and other sources).

Table 7: Major export markets

GRAIN	MAJOR DESTINATION
Barley	China, Japan, Middle East, Rep. of Korea
Oats	Statistics not available
Triticale	Statistics not available
Wheat	Asia including Indonesia, Japan, Rep. of Korea, Bangladesh, Malaysia, Thailand, China; Middle East including Iraq, Yemen; Egypt

Approximately 720 kilotonne of hay is exported from Australia, to the value of ~$230-250 million, per annum.[4] Approximately 85% of exports are oaten hay, while 10% is straw and the balance is predominantly lucerne hay and chaff. Approximately 85% of Australian export hay is destined for Japan, while the volume of hay exported to China and the UAE is increasing.

[3] http://adl.brs.gov.au/data/warehouse/agcstd9abcc002/agcstd9abcc0022011/ACS_2011_1.0.3.pdf

[4] Personal communication, AFIA, August 2010

Animal commodities

The significant export markets for Australian beef, sheep and pig meat and offals are listed in Appendix 3 of Part 5B of Ag MORAG. Australia exports significant quantities of dairy products (~$2275m in 2010-11)[2], with the main markets being Japan and other countries in Asia. Less significant are exports of poultry meat and eggs. Exports of poultry meat were valued at ~$38m in 2010-11[2] with the major markets being South Africa, the Philippines, Hong Kong, Singapore and the South Pacific Islands[5]. Exports of eggs were valued at ~$4m in 2005-06 with the major markets being Singapore, the USA and the Philippines[6].

5.3 Comparison of Australian MRLs with Codex and overseas MRLs.

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods. Sedaxane has not been considered by Codex, but is scheduled for evaluation by the JMPR in 2012. The following Codex MRLs have been established for difenoconazole and metalaxyl.

Table 9: Established Codex MRLs

ACTIVE	COMMODITY	CODEX MRL (mg/kg)
Difenoconazole	Edible offal (mammalian)	0.2
	Eggs	0.01
	Meat (from mammals other than marine mammals)	0.05
	Milks	0.005
	Poultry meat	0.01
	Poultry, edible offal	0.01
	Wheat	0.02
	Wheat straw and fodder, dry	3
Metalaxyl	Cereal grains	0.05

[5] www.daff.gov.au/agriculture-food/meat-wool-dairy/ilg/industries/chicken_meat 1 June 2012

[6] www.daff.gov.au/agriculture-food/meat-wool-dairy/ilg/industries/australian_egg_industry 1 June 2012

The following overseas residue MRLs/ tolerances have been established for sedaxane:

Table 10: Overseas residue MRLs/tolerances established for sedaxane

COUNTRY/STATUS	COMMODITY	TOLERANCE, mg/kg
USA	Barley, grain	0.01
	Barley, hay	0.04
	Barley straw	0.01
	Oat, forage	0.015
	Oat, grain	0.01
	Oat, hay	0.06
	Oat, straw	0.015
	Wheat, forage	0.01
	Wheat, hay	0.06
	Wheat, straw	0.01

Compliance with the tolerance levels in the above table is to be determined by measuring only sedaxane, *N*-[2-[1,1'-bicyclopropyl]-2-ylphenyl]-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide, as the sum of its *cis*- and *trans*- isomers.

The applicant has indicated that the following MRLs have been proposed for sedaxane in the EU. The proposed residue definition is parent sedaxane (as sum of its *cis* and *trans* isomers).

Table 11: Overseas residue MRLs/tolerances proposed for sedaxane

COUNTRY	COMMODITY	PROPOSED MRL (mg/kg)
EU	Cereals (wheat, barley, oat, rye and triticale)	0.01
	Soybean	0.01
	Rapeseed	0.01

5.4 Potential risk to trade

Export of treated produce containing finite (measurable) residues of sedaxane, difenoconazole and metalaxyl may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country or (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country.

The risk to trade in wheat, barley, oats and triticale is considered to be low as detectable residues are not expected to occur in the grain as a result of the proposed use as a seed treatment.

Animal feed MRLs for sedaxane have not been established in Japan, the major export market for Australian oaten hay. As this is a negative list there is not considered to be a risk to trade. Also quantifiable residues of difenocononazole and metalaxyl are not expected to occur in animal feeds as a result of the proposed use.

The overall risk to export trade in animal commodities is considered to be low as detectable residues of sedaxane are not expected to occur in animal commodities as a result of the proposed use. Also no changes are required to the animal commodity MRLs for difenoconazole and metalaxyl which are established at the respective LOQs.

5.5 Conclusion

The APVMA is satisfied that the proposed use of VIBRANCE Fungicide Seed Treatment would not adversely affect trade between Australia and places outside Australia.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Summary

The product VIBRANCE Fungicide Seed Treatment will be used by commercial seed treatment operators and on-farm treaters/planters (i.e. crop growers). Workers may be exposed to the product when opening containers, conducting mixing/treating procedures, bagging or transfer of treated seed, sowing of seed, and cleaning up spills and equipment. The main route of exposure to the product will be *via* the dermal and inhalational routes, although ocular exposure is also possible.

Exposure data was provided for a related fungicide seed treatment product that allowed the daily exposure to each of the three active constituents in VIBRANCE Fungicide Seed Treatment to be determined for both on-farm systems and commercial systems. Exposure to the product during its use was determined to be at an acceptable level, though it is noted that personal protective equipment was worn by mixers/operators in the surrogate exposure data. Consequently, it is recommended that when opening the container and conducting mixing/treating procedures the operator should wear a single layer of clothing (cotton overalls or equivalent clothing) and chemical resistant gloves.

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

6.2 Health hazards

Sedaxane

Sedaxane is currently not listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2012). With the available information, OCS classified sedaxane as a non-hazardous substance according to the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004). No human health risk phrases will be required for this new active constituent.

Difenoconazole

Difenoconazole is currently listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2012) with the following risk phrases:

Xn; R22	Harmful if swallowed
Xi; R36	Irritating to eyes

Metalaxyl-M

Metalaxyl-M is currently listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2012) with the following risk phrases:

R22	Harmful if swallowed
R41	Risk of serious eye damage

VIBRANCE Fungicide Seed Treatment

Based on the product toxicology information and concentrations of sedaxane (1.38%), difenconazole (6.62%), and metalaxyl-M (1.65%) in the product, VIBRANCE Fungicide Seed Treatment is not classified as a hazardous substance in accordance with the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004). Thus, no human health risk phrases have been assigned.

6.3 Use pattern

It is expected that commercial seed treatment operators and on-farm treaters/planters (i.e. crop growers) will be the main users of VIBRANCE Fungicide Seed Treatment.

VIBRANCE Fungicide Seed Treatment may be applied either in a commercial seed treatment facility or on-farm using equipment equivalent in function to commercial seed treatment facilities. Typical activities associated with seed treatment include mixing/loading of product for use (by open or closed systems), treatment of seed and bagging of treated seed.

It is reasonably expected that seed treatment may occur for up to three months a year for commercial operations, based on the crop types described on the product label. This duration of treatment is considered to sufficiently cover the timeframe expected for on-farm seed treatment activities also (typically of limited duration during each crop season).

6.4 Exposure during use

As VIBRANCE Fungicide Seed Treatment is used specifically for seed treatment, domestic use of the product is not expected.

Bystander exposure to VIBRANCE Fungicide Seed Treatment is unlikely, as seed treatment facilities are expected to use closed delivery systems and members of the public are unlikely to be present during mixing/loading activities. While post-application exposure to treated seed is a possibility through contact with treated seed or access to areas where on-farm open mixing/loading systems may be used, the potential exposure is expected to be very low.

The product will be used by commercial seed treatment operators and on-farm treaters/planters (i.e. crop growers). Workers may be exposed to the product when opening containers, conducting mixing/treating procedures, bagging or transfer of treated seed, sowing of seed, and cleaning up spills and equipment. The main route of exposure to the product will be *via* the dermal and inhalational routes, although ocular exposure is also possible.

Exposure data was provided for a related fungicide seed treatment product and were relied on for the human health risk assessment. Utilising the findings from the surrogate study and information on the use pattern for VIBRANCE Fungicide Seed Treatment, the daily exposure to each of the three active constituents in

VIBRANCE Fungicide Seed Treatment could be determined for both on-farm systems and commercial systems.

The toxic endpoint of concern and identified NOAEL is derived from repeat dose study in animals, and in this instance a margin of exposure (MOE) of 100 or above is acceptable. The MOE takes into account both potential interspecies and intraspecies variability, and the seriousness of the critical health effect of concern. Acceptable MOEs (i.e. > 100) for the three active constituents were achieved when using VIBRANCE Fungicide Seed Treatment at the rates proposed. Though it is noted that mixer/operators wore goggles, chemical-resistant gloves and chemical resistant aprons in the surrogate exposure data, however, there is sufficient margin in the MOEs associated with the use of VIBRANCE Fungicide Seed Treatment such that chemical resistant aprons (which are worn over long-sleeved clothing), along with goggles, are not considered necessary in this instance.

Thus, when opening the container and conducting mixing/treating procedures the operator should wear a single layer of clothing (cotton overalls or equivalent clothing) and chemical resistant gloves.

6.5 Exposure during re-handling

The re-handling risks associated with VIBRANCE Fungicide Seed Treatment are considered to be low. However, noting that the surrogate exposure data relied on workers wearing a base level of PPE a general re-handling statement for when handling treated seed is recommended:

> *DO NOT allow re-handling of treated seed until dry, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.*

6.6 Recommendations for safe use

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

6.7 Conclusion

The APVMA is satisfied that the proposed use of VIBRANCE Fungicide Seed Treatment would not be an undue hazard to the safety of people exposed to it during its handling and use.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

Based on a conservatively estimated sowing rate of 150 kg seed/ha to represent a worst case scenario, the maximum seed treatment rate of VIBRANCE Fungicide Seed Treatment at 360 mL/100 kg seed is estimated to be equivalent to 7.5 g/ha for sedaxane, 35.7 g/ha for difenoconazole, and 8.8 g/ha for metalaxyl-M for the maximum rate.

7.2 Environmental fate for sedaxane

Hydrolysis

Sedaxane is stable at pH 4, 5, 7 and 9 with an estimated $t_{½}$ >1 year at 25°C.

Photolysis

Aqueous phtotolysis studies were conducted and the DT_{50} was estimated as 172 days and 48 days Tokyo spring sunlight for direct and indirect photolysis tests, respectively. Both direct and indirect photodegradation of sedaxane were shown to be extensive, with indirect photolysis being approximately 3 times faster than direct photolysis. Four major metabolites were identified as CSAA798670 (which reached a maximum level of 25.7% of applied radioactivity after 28 days), CSCC210616 (which reached a maximum level of 5.4% of applied radioactivity after 28 days), CSCD668095 (which reached a maximum of 15.8% of the applied radioactivity) and CSCD668094 (which reached a maximum of 14.8% of the applied radioactivity).

Soil photolysis studies were conducted and they indicated that sedaxane degraded gradually in moist and dry soils under irradiated conditions but in both cases more rapidly than in the corresponding dark controls. The DT_{50} and DT_{90} values for pyrazole-^{14}C labelled sedaxane were calculated to be 104.7 and 348 days of natural sunlight (30˚N) for air dried soil, 136.9 and 455.2 days natural sunlight (30˚N) for moist soils. The DT_{50} and DT_{90} values for phenyl-^{14}C-labelled sedaxane were calculated to be 230.4 and 765.2 days for dry soil, and 123.6 and 410.6 days for moist soil, with natural sunlight at 30˚N. These values showed that photolysis contributes to a minor extent to the degradation of sedaxane in the environment with the rate of degradation being shown to be faster under photolytic conditions than in non-irradiated control samples. No photodegradation products were detected at significant levels.

Aerobic

The degradation of sedaxane in aerobic soils was conducted under seed application and direct soil application conditions in three studies. The half-life values under seed application conditions were determined to be in the range of 34 – 95 days, indicating sedaxane dissipated slightly in aerobic soils. Under direct soil application, sedaxane dissipated very slightly in aerobic soil with DT_{50} values of 193 days (loam soil) to around 2 years (sandy clay loam) (one year study period). These values should be used with caution since high levels of unextractable residues (up to 58.2%) were detected which was not included in the DT_{50} calculation.

Two main metabolites (CSAA798670 and CSCD465008) were detected when sedaxane was applied under aerobic laboratory soil conditions. CSAA798670 was measured at levels up to 6.1% applied radioactivity, and CSCD465008 was formed *via* cleavage of the carboxamide link and was measured at levels up to 31.9% applied radioactivity. The proposed biotransformation pathway of sedaxane includes amide hydrolysis, demethylation and hydroxylation.

Three field studies were conducted in 5 sites from the USA (Washington, North Dakota and California), North France (Meistratzheim), and Italy (Budrio). Most of the test sites were the proposed market regions for the end-use product and had history for wheat crop. Sedaxane can dissipate slightly under field conditions, with various DT_{50} values between 23 – 118 days for seed application and up to 127 days for in-furrow application. The dissipation rate for direct (in-furrow) soil application is longer than that for seed application. Sedaxane residues were detected in the 10 - 20 cm horizon at levels around the limit of quantification for seed application. The major metabolites were not detected in the 10 -20 cm horizon soil. It is noted that sedaxane residues in the 91G (application rate of 91 g ac/ha) plot reached maximum level of 224 µg/kg at test end of 181 DAT in the 10 - 20 cm horizon soil, indicating possible shifting of sedaxane to deep soil horizon with time.

Anaerobic

In an anaerobic soil study sedaxane is persistent in flooded soil. After water logging, three additional minor degradates appeared, none of which exceeded 0.5% of the applied dose.

In aerobic aquatic conditions (water/sediment systems) sedaxane dissipates by a combination of partitioning to the sediment from the water phase and also degradation in water and sediment. The DT50 values were calculated as 3.3 – 3.6 days for aerobic water and 14.2 – 18.5 days for anaerobic water, and more than one year for the whole aerobic or anaerobic systems. Each of all the observed metabolites were at levels less than 1% of applied radioactivity. Volatile radioactivity in the form of CO_2 was negligible at <2% and the unextracted radioactivity at the end of the study reached a maximum of 12.6% and 7.9% for aerobic and anaerobic scenarios, respectively.

Dissipation from Air

In the event that sedaxane should reach the air, it would be rapidly degraded by hydroxyl radicals as the evaluated half-life in air is 5.1 hours.

Mobility

The K_{OC} values for sedaxane (adsorption step) ranged 461 – 987. The K_{FOC} values for all the tested soils ranged from 262 – 666 for adsorption and 367 – 907 for desorption. The higher K_{FOC} for the desorption process than that for the adsorption process for each of the soils indicates strengthening of binding of sedaxane once adsorbed to soils. Based on the K_{OC} values, sedaxane is considered to have low to medium mobility in soil.

The K_{FOC} values for metabolite CSCD465008 ranged from 0.71 to 3.70 with an overall mean value of 2.12 for the adsorption step for all soils. Based on the K_{FOC} values, the metabolite CSCD465008 is considered to have high mobility in soil.

Volatilisation is not expected to be a major route of dissipation of sedaxane.

Accumulation

A soil accumulation study designed for 5 years, used treated spring wheat/maize seeds. Test data for the first two years application at a rate equivalent to 10 g sedaxane/ha were submitted. After nearly two years, the residues data shows that the potential for accumulation of sedaxane in soil is predicted for long periods of rotation application since annual carryover of sedaxane is evident in soil ≤ 10 cm. No accumulation of sedaxane in soil deeper than 10 cm was detected which corresponds to the adsorption studies indicating sedaxane has low mobility in soil. However, detection of sedaxane residues at 10 - 20 cm horizon in the field application study (91g ac/ha) was reported due to the higher rate and direct soil application for this plot.

Sedaxane is unlikely to bioaccumulate in organisms based on the determined BCF of 97.

7.3 Environmental Effects

Avian

Avian species were not sensitive to sedaxane with LD_{50} values being > 2000 mg/kg bw for acute oral tests and being > 5000 mg/kg feed for dietary tests. No adverse effects on ducks were observed in the 22 weeks reproduction study at levels up to 1050 mg/kg feed.

Mammals

Mammals were not sensitive to sedaxane with an acute oral LD_{50} being > 5000 mg ac/kg bw for female rats.

Fish

Sedaxane is considered to be highly acutely toxic to fish with a 96h LC_{50} of 0.62 mg/L for the most sensitive species carp. The 33d NOEC is 0.165 mg/L for fathead minnow.

The metabolite CSCD465008 is practically non-toxic to fish with an acute 96 h LC_{50} of > 97 mg/L and a NOEC of 97 mg/L.

Aquatic Invertebrates

Aquatic invertebrates were acutely sensitive to sedaxane with a 96h EC_{50} of 1.5 mg ac/L for mysid shrimp as the most sensitive species, and a 48h EC_{50} of 5.96 mg/L for daphnids. The 21d NOEC is 0.75 mg/L for *Daphnia magna*.

The metabolite CSCD465008 is practically non-toxic to *Daphnia magna* with an acute 96 h EC_{50} of > 91.8 mg/L and a NOEC of 91.8 mg/L.

Algae and Aquatic Plants

Algae and aquatic plants were potentially acutely sensitive to sedaxane with a 72 h E_rC_{50} of 2.8 mg/L for algae. The 7d NOEC is 1.2 mg/L for duckweed.

The metabolite CSCD465008 is practically non-toxic to algae with an acute 72 h EC_{50} of > 92.5 mg/L and a NOEC of 92.5 mg/L.

Non-target Arthroprods

The LR_{50} for the ground dwelling species *Aleochara bilineata* is > 225 g test formulation/ha or > 112.5 g ac/ha. The 48 h LR_{50} for the most sensitive arthropod species *Aphidius rhopalosiphi* is 24.6 mL test formulation/ha or 12.3 g sedaxane/ha.

Terrestrial Invertebrates

Bees were not found to be sensitive to sedaxane (contact) to the level tested with an LD_{50} (contact) of > 98.2 µg/bee, and the NOEC is 98.2 µg/bee. The 14 d acute LC_{50} for earthworms was > 1000 mg/kg dry weight soil. A 28 days chronic study with earthworms showed a NOEC of 2 mg/kg dry soil.

Micro-organisms

No long-term influence on the soil nitrogen and carbon transformation was observed at the end of the 28-day incubation period at application rates up to 1 mg/kg dry soil that is equivalent to 750 g/ha.

Terrestrial Plants

No adverse effects at or above 25% as compared to the control for all the plant species were observed after a pre-emergent or a post-emergent application at 100 g ac/ha.

7.4 Risk Assessment

Given the use pattern of the product is a seed treatment, the risks for the exposure to sedaxane and its metabolite CSCD465008, and difenoconazole were assessed for both terrestrial organisms and aquatic life. The risk to aquatic and benthic organisms is potentially from run-off and the worst case scenario was considered using runoff modelling. No unacceptable risk to the aquatic life and benthic organisms was predicted from the modelling. Leaching of the two active constituents, sedaxane and difenoconazole, to groundwater was conducted using a model and the risk is considered acceptable. Therefore, the proposed application of the product VIBRANCE Fungicide Seed Treatment is not considered to pose an unacceptable risk to the aquatic compartment.

The risk for the exposure of the product to terrestrial organisms, including mammals, birds, bees, micro-organisms, macro-organisms, non-target arthropods and plants was assessed based on the available endpoints and proposed application rate of the product. The assessment shows that the risk from the

proposed use pattern and application rate of the product will be acceptable to terrestrial organisms in spite of the potential of sedaxane and difenoconazole to accumulate in soil.

7.5 Conclusions

The APVMA is satisfied that the proposed use of the new product VIBRANCE fungicide seed treatment**,** containing the active constituents sedaxane, difenoconazole and metalaxyl-M, would not be likely to have an unintended effect that is harmful to animals, plants or things or the environment if used according to the product label directions.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Summary

The submitted efficacy trials demonstrated that VIBRANCE Fungicide Seed Treatment is efficacious and safe to use on barley, oats, triticale and wheat at the recommended label rates of 180 mL to 360mL/100kg of seed. The lower rate is recommended for control of smuts, common bunt, net blotch and *Pythium* root rot and the higher rate is recommended for the suppression of *Rhizoctonia* bare patch disease. There was no evidence of phytotoxicity or negative effects on crop establishment or vigour in any of the submitted trials. The probability of disease resistance arising from the use of the product is considered minimal because the seed treatment is limited to a single pre-planting application, the treatment is preventative by nature, and multiple modes of action are included in the treatment.

8.2 Efficacy

Over twenty field trials on cereals were conducted in several states of Australia, New South Wales, Victoria, South Australia and Western Australia in 2007 to 2010 and greenhouse trials in Tasmania. Data were generated from replicated randomised complete block trials comparing VIBRANCE Fungicide Seed Treatment against other combinations of relevant formulations, including two containing sedaxane alone (A14635A 500 g ac/L; A14635B 100 g ac/L), another with the same active constituents at different levels (A17531A, 15.4 g/L sedaxane, 40 g/L difenoconazole , 9.2 g/L metalaxyl-M), Dividend Formula M Fungicide Seed Treatment (APVMA approval number 56880, 92 g/L difenoconazole, 23 g/L metalaxyl-M) and two other industry standards.

All the claims appearing on the proposed product for barley and wheat are already on the registered Dividend Formula M Fungicide Seed Treatment label, with the addition of control rather than suppression of loose smut on barley. The submitted efficacy data demonstrated that the proposed product and Dividend Formula M Fungicide Seed Treatment at the labelled rates are agronomically equivalent for the claims they have in common. Extrapolation of the same claims to triticale is justified as triticale is closely related to wheat. Extrapolation of the claim for suppression of *Rhizoctonia* root rot (bare patch) to oats was also accepted. Therefore, it was concluded that the claims on the VIBRANCE Fungicide Seed Treatment label for control of smuts, common bunt, net blotch and *Pythium* root rot on barley, wheat and/or triticale at 180 mL/100kg seed and for suppression of *Rhizoctonia* root rot (bare patch) on barley, oats, wheat and/or triticale are supported by the submitted efficacy data.

Replicated greenhouse and field trials with oat seed infected with loose smut spores or *Pythium* demonstrated 99-100% control using a combination of different products at rates equivalent to 5.0g sedaxane, 12g difenoconazole and 3.0g metalaxyl-M per 100 kg seed. Therefore, it was concluded that the claims on the VIBRANCE Fungicide Seed Treatment label for control of loose smut and *Pythium* root rot on oats at 180 mL/100kg seed are supported by the submitted efficacy data.

8.3 Crop safety

There was no evidence of phytotoxicity or negative effects on crop establishment or vigour in any of the submitted trials.

8.4 Resistance management considerations

Sedaxane is classified by FRAC as a group 7 active (succinate dehydrogenase inhibitors). Fungicides from this group pose a medium to high risk of disease resistance development. Difenoconazole is classified as a group 3 active (demethylation inhibitor). The risk for disease resistance development to group 3 fungicides is moderate. Metalaxyl is a group 4 fungicide (phenylamide), which presents a high risk of disease resistance development.

Even though VIBRANCE Fungicide Seed Treatment contains individual active ingredients that present moderate to high risks of disease resistance development, the probability of disease resistance arising from the use of the product is considered minimal because the seed treatment is limited to a single pre-planting application, the treatment is preventative by nature, and multiple modes of action are included in the treatment.

8.5 Conclusions

In relation to its assessment of efficacy under section 14(3)(f), the APVMA is satisfied that data from trials supporting the efficacy of VIBRANCE Fungicide Seed Treatment adequately demonstrate that if used according to the product label directions, the product is effective for its proposed uses.

9 LABELLING REQUIREMENTS

CAUTION

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

syngenta®

ACTIVE CONSTITUENTS: **66.2 g/L DIFENOCONAZOLE**
16.5 g/L METALAXYL-M
13.8 g/L SEDAXANE

GROUP 3 4 7 FUNGICIDE

For the control or suppression of seedling diseases in Barley, Oats, Triticale and Wheat as specified in the Directions for Use

10 / 20 / 100 / 1000 LITRES

Syngenta Crop Protection Pty Limited
Level 1, 2-4 Lyonpark Road, Macquarie Park NSW 2113

In a transport emergency dial 000, Police or Fire Brigade
For specialist advice in an emergency only, call 1800 033 111 (24 hours)

APVMA Approval No.: 64098/49997
Item number

™

DIRECTIONS FOR USE

Crop	*Disease*	Rate mL/100 kg seed	Critical Comments
Barley	Covered Smut (*Ustilago segetum)* Loose Smut (*Ustilago* spp.) Net Blotch (*Pyrenophora teres*) – seed-borne Pythium Root Rot (*Pythium* spp.)	180	Apply diluted with water to clean /healthy seed before sowing. Thorough mixing is required to ensure complete coverage. Coverage of all seeds is essential. Allow seed to dry before bagging. *Rhizoctonia control:* Use the highest rate (360 mL) to suppress this disease in paddocks where paddock history or soil testing indicates a risk of Rhizoctonia root rot and where minimum tillage is used. Note that management of Rhizoctonia bare patch requires a fully integrated disease management strategy.
	Rhizoctonia root rot (bare patch) – suppression	360	
Oats	Loose Smut (*Ustilago avenae*) Pythium Root Rot (*Pythium* spp.)	180	
	Rhizoctonia root rot (bare patch) – suppression	360	
Triticale, Wheat	Common Bunt (*Tilletia* spp.) Flag Smut (*Urocystis agropyri)* – seed and soil-borne Loose Smut (*Ustilago tritici*) Pythium Root Rot (*Pythium* spp.)	180	
	Rhizoctonia root rot (bare patch) – suppression	360	

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

WITHHOLDING PERIODS

Barley, Oats, Triticale, Wheat:

Harvest: NOT REQUIRED WHEN USED AS DIRECTED

Grazing: DO NOT GRAZE OR CUT FOR STOCK FOOD FOR 6 WEEKS AFTER SOWING

GENERAL INSTRUCTIONS

VIBRANCE is a systemic seed dressing that controls or suppresses certain seed-borne and soil-borne diseases of barley, oats, triticale and wheat. It is a mixture of sedaxane, difenoconazole and metalaxyl-M. Metalaxyl-M controls or suppresses infection of roots caused by Pythium. Difenoconazole and sedaxane control or suppress the remaining plant diseases.

More than five loose smut infected heads per hundred heads can produce levels of seed infection that may not be adequately controlled by any seed treatment. Always attempt to use new disease-free seed if possible.

Mixing

Shake well before use to ensure that the suspension is thoroughly mixed. Thoroughly mix the recommended amount of VIBRANCE into the required amount of water or where the highest rate (360mL/100 kg seed) is used apply undiluted. VIBRANCE should be mixed in a minimum volume of 360 mL (product plus water)/100 kg seed and a maximum of 600 mL (product plus water)/100 kg seed before application. Coverage of all seeds is essential. Maintain constant agitation of the slurry during application.

Application
Apply via drill sowing only. Apply VIBRANCE as a water-based slurry using standard slurry treatment equipment that provides uniform seed coverage. Uneven or incomplete seed coverage may not give the desired level of disease control. For best results, VIBRANCE should be used to treat only undamaged seed of high viability.

Fungicide Resistance Warning | Group | 3 | 4 | 7 | Fungicide |
VIBRANCE Fungicide Seed Treatment is a combination of a DMI, a phenylamide and carboxamide fungicide. For fungicide resistance management VIBRANCE is a combination of a Group 3, a Group 4 and a Group 7 fungicide. Some naturally occurring individual fungi resistant to VIBRANCE and other Group 3 and/or Group 4 and/or Group 7 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungi population if these fungicides are used repeatedly. The resistant fungi will not be controlled by VIBRANCE and other Group 3 and/or Group 4 and/or Group 7 fungicides, thus resulting in a reduction in efficacy and possible yield loss. Since the occurrence of resistant fungi is difficult to detect prior to use, Syngenta Crop Protection Pty Ltd accepts no liability for any losses that may result from the failure of VIBRANCE to control resistant fungi.

PRECAUTIONS
DO NOT use treated seed for animal or human consumption.
DO NOT allow seed treated with this product to contaminate seed intended for human or animal consumption.
DO NOT feed treated seed, or otherwise expose, to wild or domestic birds. Any spillages of treated seed, however minor, must be cleaned up immediately, preferably by recovery and re-use. If disposal is required, ensure treated seeds are thoroughly buried and not accessible to birds and other wildlife.
When treated seed is stored it should be kept apart from other grain and the bags or other containers should be clearly marked to indicate the contents have been treated.
Bags which have held treated seed should not be used for any other purpose.
Re-handling treated seed
DO NOT allow re-handling of treated seed until dry, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

PROTECTION OF LIVESTOCK
DO NOT feed treated seeds to animals, including poultry.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT
Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product, used containers or bags which have held treated seeds.

STORAGE AND DISPOSAL
Store in the closed, original container in a cool, well-ventilated area. DO NOT store for prolonged periods in direct sunlight.
[Non-refillable packs]
Triple or preferably pressure rinse containers before disposal. Add rinsings to slurry in auger/mixer**. 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.

[Refillable packs]
Empty contents fully into application equipment. Close all valves and return to point of sale for refill or storage.

SAFETY DIRECTIONS

May irritate the eyes. Avoid contact with eyes.
When opening the container, preparing slurry and using the prepared slurry, wear:

- **cotton overalls buttoned to the neck and wrist (or equivalent clothing)**
- **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 131 126.

MATERIAL SAFETY DATA SHEET

If additional hazard information is required, refer to the Material Safety Data Sheet. For a copy phone 1800 067 108 or visit our website at www.syngenta.com.au

MANUFACTURER'S WARRANTY AND EXCLUSION OF LIABILITY

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

Batch Number	
Date of Manufacture	

ABBREVIATIONS

ac	active constituent
ACN	acetonitrile
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ALT	Alanine aminotransferase (SGPT)
ARfD	Acute Reference Dose
AST	Aspartate aminotransferase (SGOT)
BBCH	Biologisch Bundesanstalt Bundessortenamt und Chemische Industrie scale for phonological development stages of a plant
bw	bodyweight
CXL	Codex Maximum Residue Limit (Codex MRL)
d	day
DAT	Days After Treatment
DCM	dichloromethane
DT_{50}	Time taken for 50% of the concentration to dissipate
DT_{90}	Time taken for 90% of the concentration to dissipate
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
F_1	first generation
g	gram
GAP	Good Agricultural Practice
GLP	Good Laboratory Practice
h	hour
ha	hectare
HDPE	High density polyethylene
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HSIS	Hazardous Substances Information System

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 of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC-MS-MS	Liquid chromatography with tandem mass spectrometry
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOAEL	Lowest observable adverse effect level
LOEL	Lowest observable effect level
LOQ	Limit of Quantitation – level at which residues can be quantified
LR_{50}	rate that kills 50% of the test population of organisms
mg	milligram
mL	millilitre
MOE	Margin of exposure
MRL	Maximum Residue Limit
MS	Mass spectrometry
MTD	maximum tolerated dose
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
NOAEL	Lowest observable adverse effect level
NOEC/NOEL	No Observable Effect Concentration Level
NOHSC	National Occupational Health and Safety Commission
OC	Organic Carbon
P_0	original parent generation
PBI	Plant back interval

PPE	Personal Protective Equipment
ppm	parts per million
RAC	Raw agricultural commodities
SWA	Safe Work Australia
TLC	thin layer chromatography
TRR	Total radioactive residue
µg	Microgram
WHO	World Health Organization

GLOSSARY

Acceptable daily intake	The daily intake of a chemical which, during an entire lifetime, appears to be without appreciable risk to the health of the consumer on the basis of all the known facts at the time. The ADI is expressed in milligrams of the chemical per kilogram of body weight per day (mg/kg/day). It is derived from the no-observed-effect level (NOEL) observed in the most sensitive animal species, utilising an appropriate safety factor.
Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration. The ARfD is expressed as milligrams per kilogram of body weight.
Acute reference dose	The ARfD of a chemical is an estimate of the amount of a substance in food and/or drinking water, normally expressed on a body-weight basis, that can be ingested in a period of 24 hours or less, without appreciable risk to the consumer, on the basis of all known facts at the time of the evaluation.
Carcinogenicity	The ability to cause cancer
CAS registry	A database of the Chemical Abstracts Service (CAS) in which numbers are randomly assigned to compounds and are unique for each compound.
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
Evaluation	A written assessment of study reports or other data examined in the course of an appraisal by the APVMA for the granting or refusing of an application or other consideration
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Maximum residue limit	The maximum concentration of a chemical residue that is legally permitted in or on a food or feed commodity when that chemical is applied according to good agricultural practice (GAP) or good practice in the use of veterinary drugs (GPVD)
Metabolism	The chemical processes that maintain living organisms
New active constituent	An active constituent that has not previously been approved for use in an agricultural /veterinary chemical product in Australia
Photodegradation	Breakdown of chemicals due to the action of light

Photolysis	Breakdown of chemicals due to the action of light
Product	A formulation containing one or more active constituents, and possibly non-active constituent(s), which is intended for application, with or without dilution prior to use, and which is labelled with directions for use
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

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