Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the evaluation of the new active isopyrazam in the Product Seguris Flexi Fungicide

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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, Department of Energy and the Environment (DofEE), 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 application requirements and data guidelines on the APVMA website at: www.apvma.gov.au

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

About this document

This is a Public Release Summary.

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

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

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

Making a submission

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

Submissions must be received by the APVMA by close of business on 27 March 2018 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

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

When making a submission please include:

- contact name
- company or group name (if relevant)
- email or postal address (if available)
- the date you made the submission.

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

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

Case Management and Administration Unit
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

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

Further information

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

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

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

1 INTRODUCTION

1.1 Applicant

Syngenta Australia Pty Ltd

1.2 Purpose of application

Syngenta Australia Pty Ltd has applied to the APVMA for registration of the new product Seguris Flexi Fungicide containing the new active constituent isopyrazam (125 g/L) as an emulsifiable concentrate (EC) formulation.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Seguris Flexi Fungicide, and approval of the new active constituent, isopyrazam.

1.3 Product claims and use pattern

Seguris Flexi Fungicide is intended for the control of black spot (scab) (*Venturia inaequalis*) and powdery mildew (*Podosphaera leucotricha*) in apples and black spot (scab) (*Venturia pirina*) in pears. For both apples and pears, Seguris Flexi Fungicide is to be applied as a protectant spray against development of the target diseases, beginning applications at green tip and making further applications at 7–10 day intervals with a maximum of 3 sprays per season.

The use of Seguris Flexi Fungicide is proposed at a product rate of 80 mL/100 L for black spot (scab) control in both apples and pears, and at the same rate in apples for control powdery mildew from open cluster onwards. The shorter application intervals are used under higher disease pressure and periods of rapid tree growth.

1.4 Mode of action

Isopyrazam is a new carboxamide broad-spectrum foliar fungicide with an inhibitory mode of action on the enzyme succinate dehydrogenase (complex II) within the fungal mitochondrial respiration chain. This active substance belongs to the chemical class of ortho-substituted phenyl amides (OPAs). There is some evidence to suggest that isopyrazam can be translocated in the vascular system of plants, however isopyrazam is not considered highly systemic. It is predominantly protectant in its effect on the pathogen. For resistance management purposes it is a Group 7 succinate dehydrogenase inhibitor designated as such by the Fungicide Resistance Action Committee (FRAC).

Isopyrazam consists of two diastereoisomers, designated syn- and anti-isomers identified as SYN534969 and SYN534968, respectively. Both of the isomers are biologically active and the proposed formulation A15149W will contain the active identified as SYN502453 with an isomer ratio between 70:30 and 100:0 (syn:anti).

1.5 Overseas registrations

Products containing isopyrazam are registered in a number of countries globally. Seguris Flexi Fungicide is registered in New Zealand and Chile for control of black spot and powdery mildew in pome fruit. Isopyrazam is also registered as a co-formulation with difenoconozole in Romania, Serbia and Belarus on pome fruit.

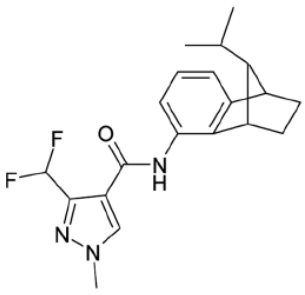
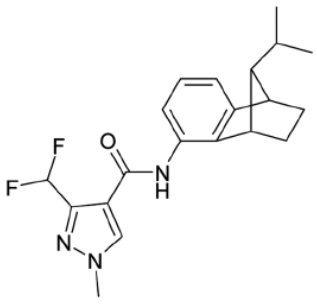
2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

The active constituent isopyrazam is a broad spectrum preventative and curative fungicide with a pyrazole carboxamide structure. It will be manufactured overseas and imported in Australia as fully formulated product. Isopyrazam is not listed in an FAO (Food and Agriculture Organisation of the United Nations) specification.

Isopyrazam is a mixture of syn-isomers and anti-isomers. Technical isopyrazam contains syn (SYN534969) and anti (SYN534968) isomers at ratios ranging from 70:30 to 100:0 syn:anti.

NOMENCLATURE OF THE ACTIVE CONSTITUENT

COMMON NAME (ISO):	Isopyrazam
CHEMICAL NAME:	A mixture of: 70-100% 3-(difluoromethyl)-1-methyl-*N*-[(1*RS*,4*SR*,9*RS*)-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalen-5-yl]pyrazole-4-carboxamide (syn epimer), and 30-0% 3-(difluoromethyl)-1-methyl-*N*-[(1*RS*,4*SR*,9*SR*)-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalen-5-yl]pyrazole-4-carboxamide (anti epimer)
CAS REGISTRY NUMBER:	881685-58-1
MANUFACTURER'S CODES:	SYN 520453 (isopyrazam) SYN 534969 (syn epimer) SYN 534968 (anti epimer)
MOLECULAR FORMULA:	$C_{20}H_{23}F_2N_3O$
MOLECULAR WEIGHT:	359.4
STRUCTURAL FORMULA:	 syn-epimer (SYN 534969)  anti-epimer (SYN 534968)

Isopyrazam is an off-white solid at room temperature, with low volatility, very sparingly soluble in water, highly soluble in polar organic and aromatic solvents, and slightly soluble in non-polar aliphatic solvents. It gives an essentially neutral pH on dispersion in water. Isopyrazam is hydrolytically stable, although it does degrade on exposure to natural light, with a half-life for aqueous photolysis of approximately 60 days under summer sunlight. It is not flammable, corrosive, or oxidising.

PHYSICO-CHEMICAL PROPERTIES OF THE ACTIVE CONSTITUENT

PHYSICAL FORM:	Powder
COLOUR:	Off-white (technical material, 95.5% purity). White (individual pure isomers, 99.5% and 99.6% purity for the syn- and anti-isomers respectively)
ODOUR:	Odourless
PH:	6.1 (1% w/v, at 22 °C)
DISSOCIATION CONSTANT:	No pKa found for either the syn or anti isomers in the pH range 1–12.
MELTING POINT:	Syn-isomer (99.5% purity): 130.2 °C Anti-isomer (99.6% purity): 144.5 °C
BOILING POINT:	Syn-isomer (99.5% purity): >261 °C (decomposes) Anti-isomer (99.6% purity): >274 °C (decomposes)
VAPOUR PRESSURE:	Syn-isomer (99.5% purity): 2.4×10^{-7} Pa at 20 °C, 5.6×10^{-7} Pa at 25 °C Anti-isomer (99.6% purity): 2.2×10^{-7} Pa at 20 °C, 5.7×10^{-7} Pa at 25 °C
HENRY'S LAW CONSTANT (CALCULATED:	Syn-isomer (99.5% purity): 1.9 × 10-4 Pa m3mol-1 Anti-isomer (99.6% purity): 3.7 × 10-5 Pa m3mol-1
RELATIVE DENSITY:	1.332 g/cm3 @ 25 °C
SURFACE TENSION:	63.1 mN/m @ 19.8 °C
WATER SOLUBILITY:	Syn-isomer (99.5% purity): 1.05 mg/L at 25 °C Anti-isomer (99.6% purity): 0.55 mg/L at 25 °C
OCTANOL/WATER PARTITION COEFFICIENT (KOW):	Log Pow is 4.1 and 4.4 at 25 °C for the syn- and anti-isomers respectively, and is not affected by pH
SOLUBILITY IN ORGANIC SOLVENTS (TECHNICAL MATERIAL, 95.5 PURITY, 25 ºC):	Acetone: 314 g/L Dichloromethane: 330 g/L Ethyl acetate: 179 g/L Hexane: 1.17 g/L Methanol: 119 g/L Octanol: 44.1 g/L Toluene: 77.1 g/L
HYDROLYTIC STABILITY (DT_{50}):	Stable at all environmental pH (5, 7 and 9) values after 5 days @ 49.7 °C or 30 days @ 25.3 °C (i.e. no hydrolysis occurred in that time)

PHOTOSTABILITY (DT_{50}):	60–64 days under summer sunlight @ 25 °C, pH 7
FLAMMABILITY:	Not flammable
AUTO-FLAMMABILITY:	No ignition below the melting point
OXIDISING PROPERTIES:	Not an oxidising substance
CORROSION PROPERTIES:	Tin plate: no corrosion Galvanised sheet metal: no corrosion Stainless steel: no corrosion Sheet steel: slight corrosion—but no weight change

The APVMA has evaluated the chemistry aspects of isopyrazam active constituent (identification, physico-chemical properties, stability, manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable.

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

CONSTITUENT	PARAMETER	SPECIFICATION
Isopyrazam	Total isopyrazam	920 g/kg minimum
	Isopyrazam syn isomers	780 g/kg minimum
	Isopyrazam anti isomers	150 g/kg maximum

Based on a review of the data provided by the applicant, the APVMA is satisfied that the chemistry and manufacturing details of isopyrazam are acceptable.

2.2 Product

Seguris Flexi Fungicide will be formulated overseas, with some re-packaging and re-labelling taking place in Australia. It is an emulsifiable concentrate formulation containing isopyrazam as the only active constituent. Seguris Flexi Fungicide will be packaged in high density polyethylene (HDPE) or polyethylene terephthalate (PET) containers ranging in size from 1 to 10 L. Suitable details of the product formulation, specifications for the ingredients, formulation and quality control processes, product specifications, stability data for the product when stored in the proposed packaging, analytical methods for the active constituent in the product, and details of the proposed containers, were provided and evaluated.

The stability data indicates that the product will remain stable for up to two years when stored under normal conditions.

SEGURIS FLEXI FUNGICIDE®

DISTINGUISHING NAME:	SEGURIS FLEXI FUNGICIDE
FORMULATION TYPE:	Emulsifiable Concentrate (EC)
ACTIVE CONSTITUENT CONCENTRATION:	isopyrazam (125 g/L)

PHYSICAL AND CHEMICAL PROPERTIES OF SEGURIS FLEXI FUNGICIDE®

PHYSICAL FORM:	Brown-orange liquid with no characteristic odour
SPECIFIC GRAVITY:	0.954
PH (1% DILUTION):	5.1
VISCOSITY:	10.7 mPa.s at 10 s^{-1} 12.0 mPa.s at 200 s^{-1} @20 °C 4.9 mPa.s at 10 s^{-1}; 6.1 mPa.s at 200 s^{-1} @40 °C
SURFACE TENSION:	31.1 mN/m (undiluted, @ 20°C) 30.5 mN/m (0.1% aqueous solution, @ 20°C) 28.3 mN/m (3% aqueous solution, @ 20°C)
FLASH POINT:	91 ± 5 °C
AUTO-IGNITION TEMPERATURE:	225 ± 5 °C
EXPLOSIVE PROPERTIES:	Non-explosive
OXIDISING PROPERTIES:	Non-oxidising
CORROSIVE HAZARD:	Not corrosive to tinplate, galvanised sheet metal, sheet steel, stainless steel, HDPE, FHDPE or HDPE/PA
DANGEROUS GOODS CLASSIFICATION:	Class 9 UN-Number 3082; Environmentally hazardous substance, liquid, N.O.S. PG III
PACK SIZES:	1–10 L
PACKAGING MATERIAL:	HDPE or PET

Registration of Seguris Flexi Fungicide is supported from a chemistry perspective.

3 TOXCOLOGICAL ASSESSMENT

The toxicological data submitted for isopyrazam consisted of a standard suite of toxicology studies, including long-term oral studies in the mouse and rat, a 12–month study in beagle dogs, as well as a range of studies on metabolites. The majority of the studies submitted complied with GLP, and were undertaken according to standard test guidelines.

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, which produce effects in animal studies.

3.1 Chemical class

Isopyrazam (SYN520453) is a new carboxamide broad-spectrum foliar fungicide which inhibits the enzyme succinate dehydrogenase (complex II) within the fungal mitochondrial respiration chain. This active constituent belongs to the chemical class of ortho-substituted phenyl amides (OPAs).

3.2 Toxicokinetics and metabolism

In rats, isopyrazam (92.8:7.2 syn:anti ratio) was rapidly but moderately (63.1–72.9%) absorbed by the oral route. In tissue distribution examinations, isopyrazam (92.2: 7.8 syn:anti ratio) was rapidly and widely distributed throughout the body; by 24–48 hours the majority of the dose had been excreted, with significant levels only detectable in the gastrointestinal tract, liver and kidney. Isopyrazam was extensively metabolised, giving rise to up to 25 metabolites (including conjugates). The bio-transformation of isopyrazam was postulated to proceed by hydroxylation in the bicyclo-isopropyl region, followed by further oxidation to form carboxylic acid and/or to give rise to multiple hydroxyl moieties with subsequent formation of glucuronic acid or sulphate conjugates. The bio-transformation of isopyrazam appeared to be independent of sex, dose regimen and isomeric form. The major elimination pathway for both isomers was via bile (47.6%–57.9% administered radiolabel), followed by faeces (21.2%–35.7% administered radiolabel) and urine (7.3%–15.9% administered radiolabel).

Percutaneous absorption

Based on the *in vitro* dermal absorption data in rat and human epidermis, and the *in vivo* dermal absorption data in the rat, the estimated *in vivo* human dermal absorption of SYN520453 (applying the “triple pack” calculation where *in vivo* data in rats was corrected for the ratio of absorption between rats and humans *in vitro*) is 0.7%, 1.3% and 1.34% of applied dose for the EC formulation concentrate, the 1/83 dilution and the 1/1250 dilution respectively.

Acute toxicity

Isopyrazam was of low acute oral toxicity in rats (LD50 > 2000 mg/kg bw for 100% syn-isomer or 92.8:7.2 syn:anti ratio; 550 < LD50 < 2000 mg/kg bw for 69.7:30.3 syn:anti ratio; LD50 = 310 mg/kg bw for 100% anti-isomer or 50:50 syn:anti ratio).

Isopyrazam was of low acute dermal toxicity in rats (LD50 > 5000 mg/kg bw for 92.8:7.2 syn: anti ratio) and low acute inhalational toxicity (LC50 > 5280 mg/m3 for 92.8: 7.2 syn:anti ratio). Isopyrazam (92.8:7.2 syn:anti ratio) was not a skin irritant but was a slight eye irritant in rabbits, and was a skin sensitiser in a local lymph node assay in mice.

The formulated product, Seguris Flexi Fungicide was of low acute oral toxicity (LD50 = 1750 mg/kg bw in female rats), low acute dermal toxicity (LD50 > 5000 mg/kg bw in rats) and low acute inhalational toxicity (LC50 > 2710 mg/kg bw in rats). The product was a moderate skin irritant and a severe eye irritant in rabbits, but was not a skin sensitiser in guinea pigs (Buehler test).

Systemic toxicity

The systemic toxicity of isopyrazam observed in repeat-dose oral toxicity studies consisted primarily of reductions in body weight and body weight gain, and evidence of liver toxicity (such as increased liver weight and hepatocellular hypertrophy with associated clinical chemistry changes). Effects were generally seen at intermediate and higher dose levels. These systemic effects were observed in short-term, sub-chronic and chronic toxicity studies in rats, mice and dogs. The available data indicate that the rat was the most sensitive species. Liver histopathological changes (hepatocellular hypertrophy, pigment in centrilobular hepatocytes, eosinophilic foci of altered hepatocytes, vacuolation of centrilobular hepatocytes and hyperplasia and fibrosis of the bile ducts) were observed at all dose levels in rats in the 104 week combined chronic and carcinogenicity oral toxicity study.

Genotoxicity and Carcinogenicity

There was no evidence of a mutagenic/genotoxic potential in vitro (Ames test, cytogenetic assay, chromosomal aberration test and mouse lymphoma mutation assay) with and without metabolic activation, and no evidence of a genotoxic potential in vivo (Unscheduled DNA Synthesis (UDS) assay and micronucleus test).

The carcinogenic potential of isopyrazam was evaluated in a combined chronic toxicity and carcinogenicity study in the rat and in a carcinogenicity study in the mouse. No increased incidence was seen in any tumour type in male or female mice in the 80–week dietary study. In contrast, isopyrazam was carcinogenic in both male (thyroid tumours) and female (liver and uterine tumours) rats in the combined chronic toxicity and carcinogenicity study. Submitted mechanistic studies indicated a likely Mode of Action (MOA) for isopyrazam-induced liver tumours in rodents similar to that elicited by phenobarbital, while other tumours identified in the long-term studies occurred at doses above the maximum tolerated dose. Based on the weight of evidence evaluation, isopyrazam was considered not to be carcinogenic to humans.

Reproductive and Developmental Toxicity

In a dietary two generation study in rats, no isopyrazam treatment related effects on the reproductive system were observed during the study. Treatment related effects in parental animals and pups were similar and observed at middle and high doses. The effects observed in pups were considered to be related to general toxicity.

In an oral gavage developmental toxicity study in rats with a 92.8:7.2 syn:anti isomer mixture of isopyrazam, incomplete ossification was observed in a small number of foetal ossification centres at an intermediate dose (75 mg/kg bw/d) without any marked maternal toxicity; however, in a similar oral gavage developmental toxicity study in rats with a 69.7:30.3 syn:anti isomer mixture of isopyrazam, maternal toxicity was observed at the same dose level as foetal incomplete/delayed ossification (i.e. the intermediate dose level of 75 mg/kg bw/d). No significant evidence of a developmental toxicity potential was seen in oral (gavage) developmental toxicity studies in rabbits up to the dose levels that produced marked maternal toxicity, though microphthalmia was noted at doses where maternal toxicity was observed. Overall, isopyrazam is not classified as a developmental toxicant.

Neurotoxicity

No macroscopic or microscopic neuro-histopathological findings were seen in acute and 90 day oral neurotoxicity studies in rats with isopyrazam (92.8:7.2 syn:anti ratio). Isopyrazam was not neurotoxic in rats.

Immunotoxicity

Isopyrazam was not immunotoxic in female mice.

Toxicity of Metabolites

Metabolites of isopyrazam were neither genotoxic nor developmental toxicants, and were of low acute oral toxicity in rats. A metabolite, CSCD459488, elicited some repeat dose toxicity in a 28-day oral rat toxicity study, primarily as liver effects (increased liver weights, centrilobular hypertrophy and abnormal liver chemistry).

3.3 Public Health Standards

Poisons Standard

On 23 June 2016, the Delegate of the Secretary of the Department of Health published a final scheduling decision to create a new Schedule 6 entry for isopyrazam in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP), with an implementation date of 1 October 2016.

ADI

The acceptable daily intake (ADI) for humans is the level of intake of an agricultural or veterinary chemical which can be ingested daily over an entire lifetime without appreciable risk to health. It is calculated by dividing the overall NOEL (No Observed Effect Limit) for the most sensitive toxicological endpoint from a suitable study (typically an animal study) by an appropriate safety factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans, intra-species variation, and the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

The ADI for isopyrazam is established at 0.06 mg/kg bw/d using the NOAEL (No Observed Adverse Effect Level) of 5.5 mg/kg bw/d from a 104 week dietary chronic/carcinogenicity study in male rats on the basis of decreased body weight gain in females and foci of eosinophilic hepatocytes and clinical chemistry changes (triglycerides, bilirubin) of equivocal toxicological significance in both sexes at 27.6 mg/kg bw/d.

ARfD

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

An ARfD of 0.3 mg/kg bw derived from the NOEL of 30 mg/kg bw in the rat acute neurotoxicity study, on the basis of nonspecific clinical signs of toxicity (weak appearance and decreased activity) at 250 mg/kg bw was established.

4 RESIDUES ASSESSMENT

The residues assessment for isopyrazam considered plant and animal metabolism studies, supervised residue trials, processing studies and trade aspects associated with the proposed uses in apples and pears.

4.1 Metabolism and Residue Definition

Metabolism studies in wheat, grapes, lettuce, confined rotational crops (turnips, lettuce and wheat), rats, lactating goats and laying hens were provided.

The major metabolic pathways in plants after direct application of isopyrazam are, in order of importance:

- Hydroxylation at several positions, including the primary and tertiary carbons of the isopropyl substituent, the 2–position in the naphthalenyl moiety, and the bridgehead carbon (9-position in the naphthalenyl moiety). This is in some cases followed by conjugation of the newly formed hydroxyl groups;
- *N*-Demethylation at the 1–position in the pyrazole ring;
- Cleavage of the amide linkage between the pyrazolyl and naphthalenyl moieties of the molecule to yield pyrazolyl carboxylic acid metabolites.

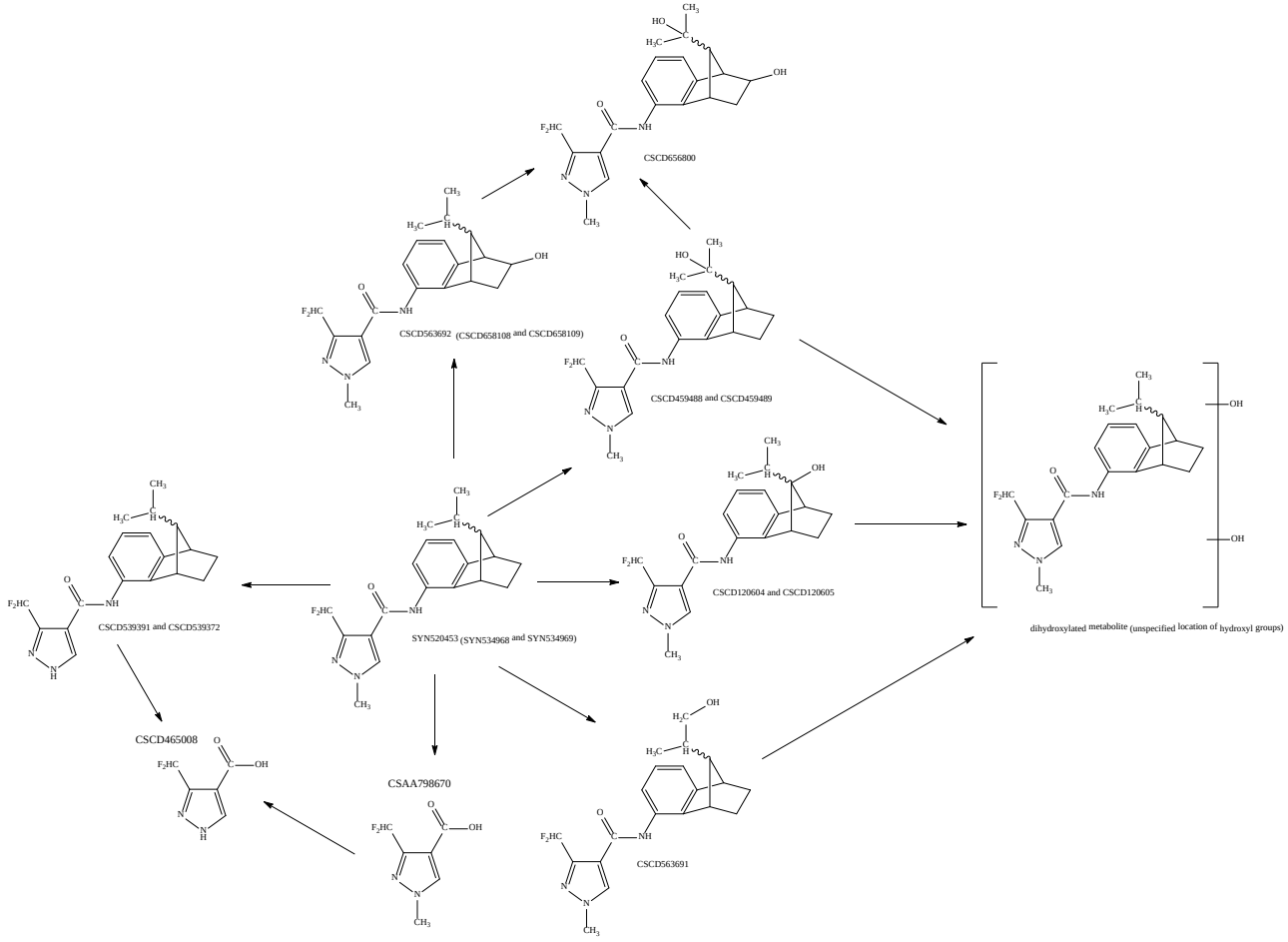
Parent compound was the largest component of the residue in both food and feed matrices, comprising 53.3–65.6% of the TRR (Total Radioactive Residues) in wheat grain, 89.4–90.3% of TRR in grapes, 34.8–45.3% of TRR in mature lettuce, 78.8–91.3% of TRR in wheat forage, and 60.7–68.7% of TRR in wheat straw. The next most significant component were the tertiary alcohol metabolites CSCD459488/CSCD459489 (syn/anti isomers respectively, IUPAC name 3-(difluoromethyl)-1-methyl- N-[1,2,3,4-tetrahydro-9-(1-hydroxy-1-methylethyl)-1,4-methanonaphthalen-5-yl]-1H-pyrazole-4-carboxamide), particularly in lettuce, where they comprised 14.1–17.1% of the TRR (mostly as conjugates), with much smaller proportions being found in wheat grain (1.2–1.4% of TRR), grapes (0.8–1.4% of TRR), wheat forage (0.4–2.4% of TRR), and wheat straw (7.3–9.7% of TRR). With the exception of mature lettuce, in which CSCD459488 comprised 0.031-0.053 mg eq./kg, and combined residues of another two monohydroxylated compounds CSCD563692 and CSCD610195 comprised 0.011-0.018 mg eq./kg, no identified component of the residues other than parent exceeded 0.01 mg eq./kg in any of the food matrices.

In rotational crops, parent compound was generally only a minor component of the residue, at up to 0.032 mg eq./kg (in wheat straw) and up to 34.3% of the TRR (in turnip roots, although that only corresponded to 0.005 mg eq./kg). In most rotational crop matrices, the most significant component was the hydroxylated metabolite CSCD459488, at up to 0.17 mg eq./kg (in wheat straw), and at up to 25.3% of TRR (in wheat hay). Residues of CSCD459488 did not exceed 0.01 mg eq./kg or 10% of the TRR in any of the food matrices. The pyrazole label specific fragments, CSAA798670 (3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylic acid) and CSCD465008 (3-(difluoromethyl)-1*H*-pyrazole-4-carboxylic acid), resulting from cleavage of the amide linkage, were present in all matrices, most notably in lettuce and turnips. CSCD798670 reached levels up to 0.005 mg eq./kg and 13.5% of TRR in food matrices, and up to 0.039 mg eq./kg and 12.3% of TRR in feed matrices. CSCD465008 reached levels of up to 0.025 mg eq./kg and 47.7% of TRR in food matrices and up to 0.038 mg eq./kg and 21.6% of TRR in feed matrices. Significant proportions of the CSCD459488, CSAA798670, and CSCD465008 residues were present as conjugates.

No significant degradation of radiolabelled isopyrazam was observed under hydrolytic conditions simulating pasteurisation, boiling/baking/brewing or sterilisation. Isopyrazam is therefore stable to hydrolytic processes such as pasteurisation, boiling/baking/brewing or sterilisation.

In the field residue studies in apples and pears, finite residues of isopyrazam were found in most samples harvested from 0 to 42 days after the last application. Residues of CSCD459488 and CSCD459489 were mostly <LOQ, (Limit of Quantification) although some finite residues, particularly of the syn isomers CSCD459488, were found, particularly at longer harvest intervals. A subacute toxicity study (28–day repeat dose oral study in rats) showed CSCD459488 to be of comparable toxicological significance to parent compound over the same timescale.

Metabolism of isopyrazam in plants after direct application



Given that parent compound was the most significant residue in both the plant metabolism studies and the pome fruit residue studies, it is the best analyte for monitoring compliance with MRLs (Maximum Residues Limits). The proposed residue definition for enforcement in plant commodities is therefore *isopyrazam*.

Since the metabolite CSCD459488 was significant in some of the plant metabolism studies, was occasionally found in the pome fruit residue studies and is of comparable toxicological significance to parent, it is proposed to include CSCD459488, and the corresponding anti isomers CSCD459489 in the plant residue definition for dietary risk assessment. Although the metabolites CSAA798670 and CSCD465008 were found in rotational crop metabolism and field rotational residue studies, they are of lesser toxicological significance than parent compound. Further, no uses in rotational crops are currently proposed for isopyrazam, and both CSAA798670 and CSCD465008 are metabolites common to other pesticides such as fluxapyroxad and sedaxane. It is not therefore proposed to include CSAA798670 or CSCD465008 in the risk assessment residue definition.

The proposed definition for dietary risk assessment in plant commodities is therefore *sum of isopyrazam and 3-(difluoromethyl)-1-methyl- N-[1,2,3,4-tetrahydro-9-(1-hydroxy-1-methylethyl)-1,4-methanonaphthalen-5-yl]-1H-pyrazole-4-carboxamide and its conjugates, expressed as isopyrazam*.

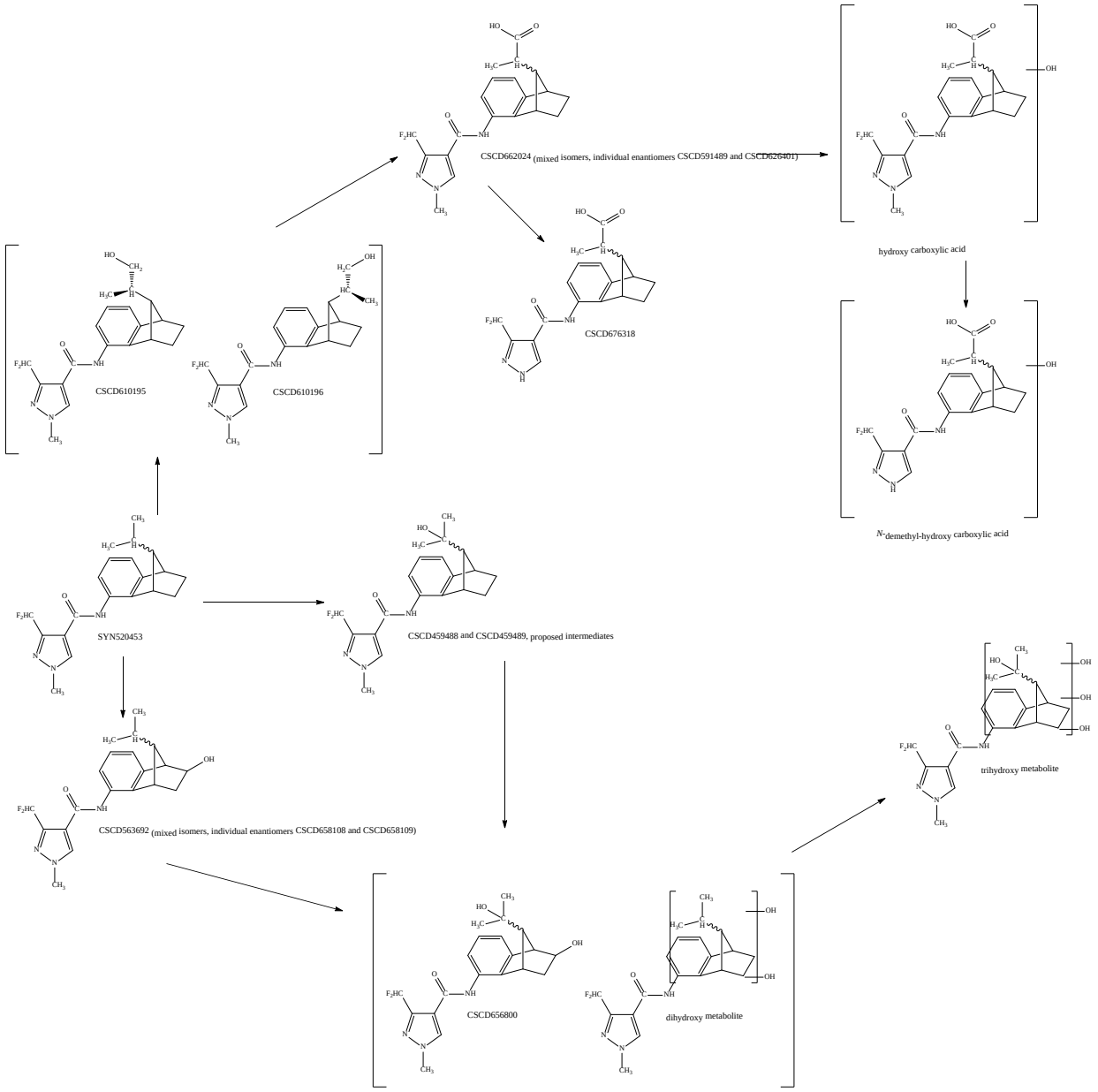
The major metabolic pathways for isopyrazam in animals were:

- *N*-Demethylation of the pyrazolyl moiety (more extensive in rats than in goats or hens);
- Hydroxylation of the primary and tertiary carbons of the isopropyl group, the bridgehead carbon, and the naphthalenyl moiety 2-position, sometimes multiply, leading to di- and tri-hydroxylated metabolites;
- Subsequent oxidation of primary carbon hydroxy groups on the isopropyl to carboxylic acids; and
- Sulphate or glucoronate conjugation of the resultant hydroxy or carboxylic acid groups and to a lesser extent at the 1-position of the pyrazolyl moiety (confirmed for rats).

Parent compound was found in milk and all tissues in the isopyrazam goat metabolism study. It was the only identified residue component in fat (0.0047–0.010 mg eq./kg, or 39.6–51.0% of TRR), and was a minor component in all other matrices (for example, a maximum of 0.0063 mg eq./kg or 1.9% of TRR in liver and a maximum of 0.0019 mg eq./kg or 8.6% of TRR in muscle). The dihydroxylated metabolite CSCD656800 was significant in matrices other than fat, at 0.0081–0.0192 mg eq./kg (14.7–31.7% of TRR) in milk, 0.021–0.104 mg eq./kg (6.2–17.0% of TRR) in liver, 0.023–0.038 mg eq./kg (13.2–24.7% of TRR) in kidney, and 0.0066–0.013 mg eq./kg (29.2–43.8% of TRR) in muscle. In liver, naphthalenyl –OH compounds CSCD658108/CSCD658109 and the carboxylic acids CSCD591489/CSCD626401 were significant, at 0.026–0.127 mg eq./kg (7.8–21.0% of TRR) and 0.015-0.042 mg eq./kg (2.5–8.1% of TRR) respectively for the isomer pairs.

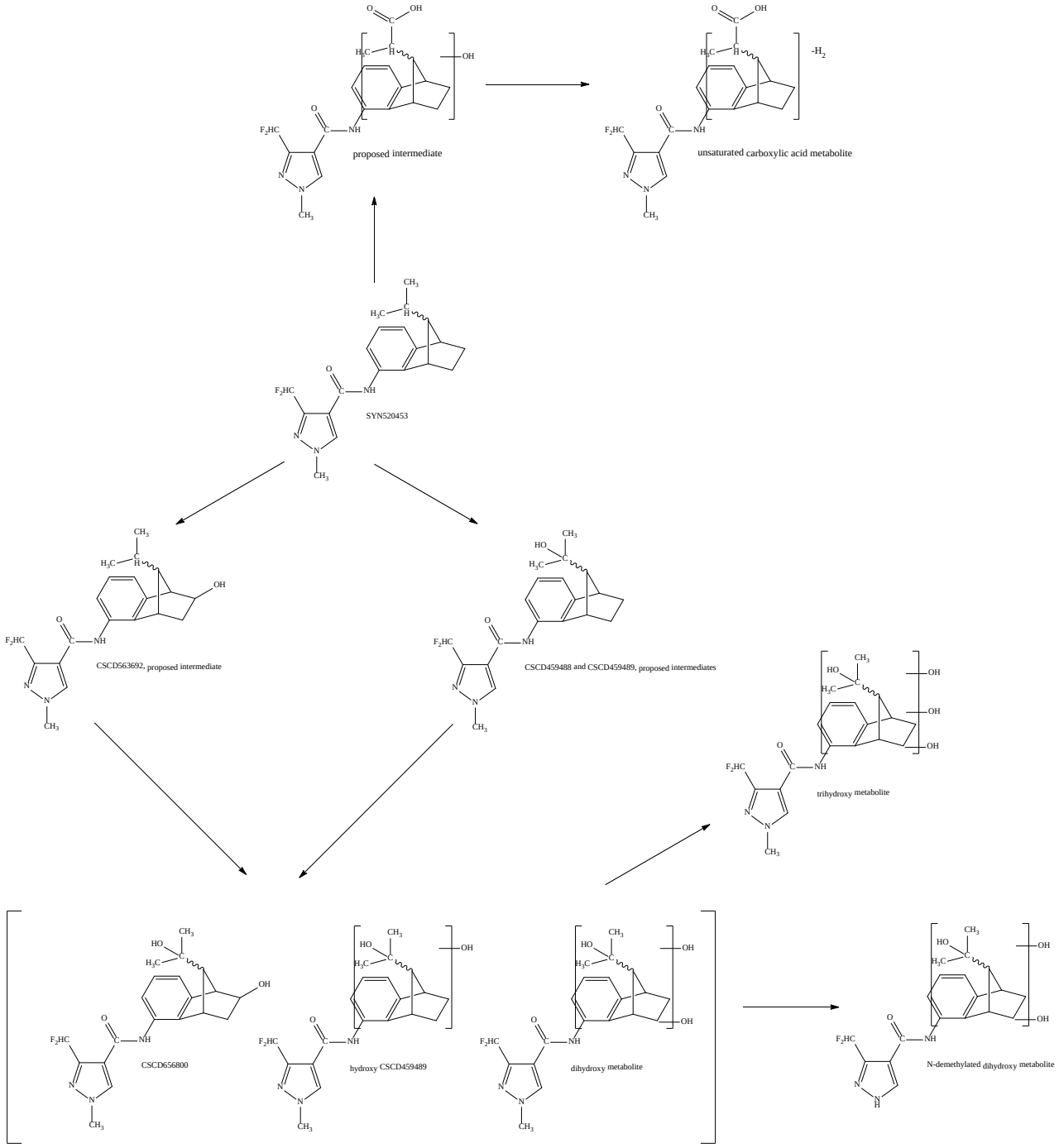
Metabolism in goats and rats was generally comparable, indicating that a metabolism study for a food-producing monogastric animal (eg pigs) is not required.

In the goat metabolism study for the monohydroxylated plant metabolite CSCD459488, the dihydroxylated compound CSCD656800 was the most significant component of the residue (as for the parent compound metabolism study), at >33%TRR in all samples and at 0.159 and 0.090 mg eq./kg in liver and kidney respectively.



Metabolism of isopyrazam in goats

In the isopyrazam hen metabolism study, parent was found in egg yolk, skin with fat and peritoneal fat (in the last two, it was the only identified component). Levels of parent were 0.001–0.004 mg eq./kg (3.4–4.9% of the TRR) in egg yolk, <0.001 mg eq./kg (0.2% of TRR in liver), 0.001–0.002 mg eq./kg (7.6–13.9% of TRR) in skin and fat, and <0.001–0.004 mg eq./kg (2.5–21.4% of TRR) in peritoneal fat. The only other conclusively identified compound was CSCD656800, at 0.001–0.005 mg eq./kg (6.8–29.0% of TRR) in egg white, 0.005–0.006 mg eq./kg (6.6–11.5% of TRR) in egg yolk, and 0.001–0.002 mg eq./kg (1.0–1.6% of TRR) in liver.



Metabolism of isopyrazam in laying hens

In the cattle feeding study, at the lowest feeding level (15 ppm), no residues of parent were found above LOQ in whole or skim milk, kidney, subcutaneous fat, or muscle, while low levels were found in other matrices (up to 0.010 mg/kg in cream, up to 0.0099 mg/kg in liver, and up to 0.0079 mg/kg in mesenteric and perirenal fat). In contrast with the goat metabolism study, which showed significantly higher levels of metabolites (notably CSCD656800) than parent, no residues of CSCD677927/CSCD678302 (syn and anti-isomers of CSCD656800), or CSCD658108/CSCD658109 (syn and anti-isomers of 2-naphthalenyl-OH isopyrazam) were observed above LOQ in milk or tissues of cattle dosed at 15 ppm. Levels of the metabolites may have been adversely affected by storage prior to analysis (no stability data available).

Similar results were noted in the poultry feeding study. At the lowest feeding level (3 ppm), residues of isopyrazam in eggs were mostly <LOQ, with a single result just above the LOQ (0.0052 mg/kg), with low finite levels also being observed in most tissues (up to 0.0051 mg/kg in liver, 0.0096 mg/kg in fat and 0.0071 mg/kg in skin with fat). Residues of CSCD677927/CSCD678302 and CSCD658108/CSCD658109 (both free and conjugated) were <LOQ in all eggs and tissues of hens at the 3 ppm feeding level.

It is noted that residues hydrolysable to the common moiety CSAA798670 were determined in both the cattle and hen feeding studies. However, the use of a residue definition involving CSCD798670 (3-difluoromethyl-1-methyl-1*H*-pyrazole-4-carboxylic acid) as a common moiety would be problematic due to other active constituents (eg fluxapyroxad and sedaxane) containing the same moiety.

As parent was found in most matrices in the goat metabolism study and was found at finite levels in some matrices for the lowest dose in the cattle feeding study, parent is a suitable marker residue for enforcement in animal commodities. The proposed definition for enforcement in animal commodities is therefore: *isopyrazam*.

No toxicological information was presented regarding significant animal metabolites such as CSCD656800 (CSCD677927/CSCD678302), CSCD658108/CSCD658109, or CSCD591489/CSCD626401. These metabolites were observed in the rat metabolism study. Given that the metabolite CSCD459488 (monohydroxylated in the tertiary position on the isopropyl group) was observed to have comparable repeat dose toxicity to parent, it is possible that CSCD656800 (dihydroxylated, in the tertiary position on the isopropyl group and at the 2 position on the naphthalenyl moiety) may likewise have comparable toxicity to parent.

For assessment of dietary risk in animal commodities, it is proposed to include the metabolites CSCD656800 (CSCD677927/CSCD678302) and CSCD563692 (CSCD658108/CSCD658109) in the residue definition. A validated method is available for determination of these components, including their conjugates.

The proposed residue definition for dietary risk assessment in animal commodities is therefore: *sum of isopyrazam, 3-(difluoromethyl)-1-methyl- N-[1,2,3,4-tetrahydro-2-hydroxy-9-(1-hydroxy-1-methylethyl)-1,4-methanonaphthalen-5-yl]-1H-pyrazole-4-carboxamide, and 3-(difluoromethyl)-1-methyl- N-[1,2,3,4-tetrahydro-2-hydroxy-9-isopropyl-1,4-methanonaphthalen-5-yl]-1H-pyrazole-4-carboxamide and their conjugates, expressed as isopyrazam.*

4.2 Residue analytical methods

Determination of isopyrazam residues in plant commodities

A method was developed and validated in a range of plant matrices for determination of residues according to the proposed enforcement definition (parent only). This involved extraction of samples with acetonitrile/water, followed by analysis using LC-MS/MS (Liquid Chromotography/Mass Spectrometry). The LOQ is 0.005 mg/kg for the syn and anti-isomers of isopyrazam.

A similar method was developed for determination of residues of the two metabolites proposed for inclusion in the plant commodity risk assessment definition (CSCD459488 and CSCD459489). After a similar extraction with acetonitrile/water, the extracts were treated by heating with dilute hydrochloric acid to hydrolyse conjugates, then analysed by LC-MS/MS. The validated LOQ was again 0.005 mg/kg for each isomer.

Determination of isopyrazam residues in animal commodities

For determination of isopyrazam parent compound (the proposed enforcement definition) in animal matrices, sampled were extracted with acetonitrile/water, then analysed by LC-MS/MS. The validated LOQ was 0.0025 mg/kg for each of the isomers.

A method incorporating a hydrolysis step was developed to enable determination of the metabolites included in the proposed risk assessment definition for animals. After extraction of samples with acetonitrile/water, the extracts were treated enzymatically to hydrolyse conjugates, then analysed by LC-MS/MS. The validated LOQ was 0.01 mg/kg for each compound.

Stability of residues

Stability studies were conducted for residues of parent compound and the metabolites CSCD459488 and CSCD459489 fortified into a range of plant matrices and stored frozen. Residues of parent and metabolites were shown to be stable for the full storage period (6 months for parent in spinach, 24 months for parent in tomato, rapeseed, lentil, potato, barley grain and straw, and ryegrass forage, and 28 months for metabolites in orange, wheat grain and straw, rapeseed, apple, lentil, spinach and carrot). Stability studies were conducted for parent compound (over 14 months) and common moiety residues (fortification of parent compound and representative structurally related metabolites) determined as CSAA798670 (over 12 months) in milk, egg, liver, kidney, muscle and fat. Residues were stable in animal matrices over these periods of frozen storage.

The stability studies were sufficient to verify that samples from the field residue trials, field rotational crop studies, and cattle and hen feeding studies were unlikely to have been adversely affected by storage.

4.3 Residue trials

Pome fruit

In apple and pears, the proposed GAP is 3 × 10 g ai/100 L dilute foliar spray applications at 7 day intervals, with a 21–day harvest withholding period. A maximum of two consecutive isopyrazam applications is specified, with an application of a chemical from a different mode of action group required before a further application of isopyrazam is made.

Residue data in apples and pears from trials conducted in Australia and northern and southern Europe was used to propose an MRL.

The combined Australian and European pome fruit isopyrazam parent compound data set involving 3 × 8.3 – 15 g ai/100L and a 21 day PHI is: 0.050, 0.061, 0.083, 0.085, 0.086 (2), 0.11, 0.12, 0.13, 0.14 (2), 0.15, 0.16 (3), 0.19 (2), 0.21, 0.22, 0.24, 0.25, 0.26, 0.27, 0.29, 0.31, 0.32, 0.33 (2), 0.38, and 0.42 mg/kg.

The combined pome fruit total residues data set is: 0.060, 0.071, 0.093, 0.095, 0.096, 0.11, 0.13, 0.14, 0.15 (2), 0.16, 0.17 (3), 0.18, 0.20, 0.21, 0.22, 0.23, 0.25, 0.26, 0.27, 0.28, 0.32, 0.33, 0.34 (2), 0.36, 0.39, and 0.43 mg/kg.

Based on the above parent compound residue data set and noting the OECD MRL calculator estimate of 0.6 mg/kg, an MRL of 0.7 mg/kg is proposed for isopyrazam in pome fruit, in conjunction with a 21–day harvest withholding period. Based on the total residue data set, an STMR (Supervised Trials Median Residues) and an HR (Highest Residue) of 0.175 and 0.43 mg/kg are estimated for dietary intake calculations.

A processing study in apples was conducted using fruit grown in southern France. Apples at two trial sites were treated with 3 × 300 g ai/ha applications at 7–day intervals. Raw fruit was processed using simulated commercial processes into apple juice (including pomace as a by-product), dried apple, canned apple and apple sauce.

Residues of isopyrazam did not concentrate in apple sauce, juice, or canned apple, while they did concentrate in apple peel, apple pomace and dried apples. Based on a processing factor of 5.8 (for parent compound residues) and using the parent compound residue STMR and HR of 0.19 and 0.42 mg/kg respectively for apples, an STMR-P (Supervised Trials Median Residues-Processing) and an HR-P (Highest Residue-Processing) of 1.1 and 2.4 mg/kg respectively were calculated. An MRL of 4 mg/kg is therefore recommended for isopyrazam in apple pomace, dry. Using the processing factor of 5.8 for total residues in dry apple pomace, and the total residue STMR and HR values in apples of 0.20 and 0.43 mg/kg respectively, STMR-P and HR-P values of 1.2 and 2.5 mg/kg respectively were calculated for apple pomace (dry) for dietary burden calculations.

4.4 Rotational cropping

Confined rotational crop metabolism data, and limited field rotational cropping studies were provided. Currently, isopyrazam is only proposed for use in pome fruit, which are not a rotational crop. It may be necessary to consider MRLs for rotational crop residues in the future, if use of isopyrazam in non-permanent crops, or in situations where animal feeds may be produced, is proposed.

4.5 Animal commodities

The only livestock feed of significance for the proposed use pattern is apple pomace. Apple pomace can be fed to beef and dairy cattle at up to 20% and 10% of the diet respectively. As apple pomace is a bulked and blended commodity, with fruit from many different orchards typically being combined for juice manufacture, the STMR-P is the appropriate residue value to use in calculating the livestock dietary burden. The dietary burdens will be 0.22 and 0.11 mg/kg (parent compound only, for MRL estimation) for beef and dairy cattle respectively, and 0.24 and 0.12 mg/kg (total residues, for dietary risk assessment) for beef and dairy cattle respectively.

A feeding study in cattle was provided with the application. After dosing with isopyrazam for 28 days at 15 ppm in feed (the lowest dose level and the closest to the calculated dietary burdens), residues of parent compound in whole and skim milk, kidney, muscle and subcutaneous fat did not exceed the LOQ (0.005 mg/kg for the sum of both isomers). Residues of isopyrazam parent compound in cream, liver, perineal fat, and mesenteric fat reached maximum levels of 0.011, 0.0099, 0.0079, and 0.0069 mg/kg respectively.

Given that the estimated residues of isopyrazam parent compound are <LOQ in mammalian milk, muscle, fat, liver and kidney after feeding at the estimated dietary burden, MRLs at the LOQ (0.005 mg/kg, the validated LOQ) are proposed for mammalian meat (in the fat), milks and edible offal (mammalian).

Given that the goat metabolism study showed significantly higher levels of the metabolites included in the risk assessment definition compared with parent, in contrast to the cattle feeding study, and in view of the lack of metabolite stability data for the feeding study, the residues in mammalian meat, offal and milk for risk assessment purposes were estimated using the goat metabolism study as a conservative measure. The calculated total residues of isopyrazam in animal commodities according to the proposed risk assessment residue definition are all well below the LOQ for parent compound (0.005 mg/kg for the sum of both isomers).

The dietary burdens for isopyrazam in poultry are nil, given that apple pomace is not commonly fed to poultry in Australia. Given the nil dietary burden for isopyrazam in poultry, it is proposed that MRLs for poultry meat (in the fat), offal and eggs be established at the LOQ (0.005 mg/kg). Likewise, the residue estimates for dietary risk assessment in poultry commodities will be set at the LOQ.

No forage or fodder data has been provided for isopyrazam. Therefore, it is proposed to include a restriction on grazing of treated orchards on the label.

4.6 Spray drift

Calculations showed that livestock grazing downwind of a pome fruit orchard treated at the maximum proposed rate are not likely to ingest a dose of isopyrazam sufficient to result in residues above the LOQ in milk, offal or meat. Therefore, a buffer zone is not required in order to protect international trade.

4.7 Bioaccumulation potential

The octanol-water partition coefficient ($log_{10}K_{OW}$ value) for the syn-epimer of isopyrazam is 4.1, while the value for the anti-epimer is 4.4 (at 25 °C and using unbuffered milli-Q water in both cases). It is noted that residues of isopyrazam parent compound were higher in cream than in skim milk in the cattle feeding study, and higher in fatty tissues than in muscle in both the cattle and poultry feeding studies. Residues of isopyrazam are therefore considered to be fat soluble and the meat MRLs will be established 'in the fat'.

4.8 Risk assessment conclusions

Estimated dietary intake

The chronic dietary exposure to isopyrazam 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 primarily 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 isopyrazam is equivalent to <2% of the ADI. A similar result was achieved using the HARVEST calculation. It is concluded that the chronic dietary exposure to isopyrazam is 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[5] with 97.5th percentile food consumption data derived primarily from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food. The highest acute dietary intake for isopyrazam was estimated at <15% of the ARfD. It is concluded that the acute dietary exposure is acceptable.

2 WHO (2008). Consultations and workshops: Dietary Exposure Assessment of Chemicals in Food: Report of a joint FAO/WHO Consultation, Annapolis, Maryland, USA, 2-6 May 2005.

Recommendations

The following amendments to the MRL Standard are recommended in relation to the proposed use of SEGURIS FLEXI FUNGICIDE:

TABLE 1

COMPOUND		FOOD	MRL (mg/kg)
ADD:			
	Isopyrazam		
MO	0105	Edible offal (Mammalian)	*0.005
PE	0112	Eggs	*0.005
MM	0095	Meat [mammalian] [in the fat]	*0.005
ML	0106	Milks	*0.005
FP	0009	Pome fruit	0.7
PO	0111	Poultry, Edible offal of	*0.005
PM	0110	Poultry meat [in the fat]	*0.005

TABLE 3

COMPOUND	RESIDUE
ADD:	
Isopyrazam	*For enforcement in plant and animal commodities*: isopyrazam
	For assessment of dietary risk in plant commodities: sum of isopyrazam and 3-(difluoromethyl)-1-methyl- *N*-[1,2,3,4-tetrahydro-9-(1-hydroxy-1-methylethyl)-1,4-methanonaphthalen-5-yl]-1*H*-pyrazole-4-carboxamide isomers (CSCD459488 and CSCD459489) and their conjugates, expressed as isopyrazam
	For assessment of dietary risk in animal commodities: sum of isopyrazam, 3-(difluoromethyl)-1-methyl- *N*-[1,2,3,4-tetrahydro-2-hydroxy-9-(1-hydroxy-1-methylethyl)-1,4-methanonaphthalen-5-yl]-1*H*-pyrazole-4-carboxamide (CSCD656800) and 3-(difluoromethyl)-1-methyl- *N*-[1,2,3,4-tetrahydro-2-hydroxy-9-isopropyl-1,4-methanonaphthalen-5-yl]-1*H*-pyrazole-4-carboxamide (CSCD563692) and their conjugates, expressed as isopyrazam

TABLE 4

COMPOUND		ANIMAL FEED COMMODITY	MRL (mg/kg)
ADD:			
Isopyrazam			
AB	0226	Apple pomace, dry	4

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

HARVEST WITHHOLDING PERIOD:

APPLES: DO NOT HARVEST FOR 21 DAYS AFTER APPLICATION

GRAZING WITHHOLDING PERIOD:

DO NOT ALLOW LIVESTOCK TO GRAZE TREATED ORCHARDS OR CUT FOR STOCK FOOD.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

5.1 Commodities exported and main destinations

Apples and pears are considered to be major export commodities[3], as are commodities of animal origin, such as meat, offal and dairy products, which may be derived from livestock fed feeds produced from treated apples.

According to Apple and Pear Australia Ltd, Australian pome fruit is exported to the United Kingdom, Asia, New Zealand and Canada[4]. Apple exports in 2014–15 were worth $5.9 million, while pear exports were worth $12.5 million[5].

The significant export markets for Australian beef, sheep, pig meat and offal are listed in the APVMA Regulatory Guidelines—Data Guidelines: Agricultural—Overseas trade (Part 5B)[3]. Total exports of dairy products in 2014–15 were worth $2.46 billion, with key export destinations including Japan, Singapore, China, Indonesia, Malaysia, Thailand, the Philippines, Korea, and Russia. Total exports of beef and veal were worth $8.86 billion in 2014–15, with the major destinations including Japan, the USA, Korea, China, Taiwan, the EU, the Middle East, and Russia. Total exports of lamb and mutton were worth $2.47 billion in 2014–15, with the key destinations including the USA, China, the Middle East, the European Union, and Japan[5].

5.2 Proposed Australian use pattern

Refer to labelling requirements.

5.3 Overseas registration status

Isopyrazam is registered for use in pome fruit in New Zealand and various countries in Europe.

5.4 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. CXLs are primarily intended to facilitate international trade and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept CXLs when importing foods. Isopyrazam has been considered by Codex, although not for use in pome fruit. Relevant international MRLs for isopyrazam are tabulated below.

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[3] APVMA Regulatory Guidelines—Data Guidelines: Agricultural—Overseas trade (Part 5B)

[4] http://apal.org.au/statistics/#apei

[5] Agricultural Commodity Statistics 2015, Australian Bureau of Agricultural and Resource Economics and Sciences, Department of Agriculture and Water Resources, December 2015 (http://data.daff.gov.au/data/warehouse/agcstd9abcc002/agcstd9abcc0022015/ACS_2015_1.0.0.pdf)

CURRENT AND PROPOSED AUSTRALIAN AND INTERNATIONAL MRLS FOR ISOPYRAZAM

COUNTRY/STATUS	RESIDUE DEFINITION	COMMODITY	MRL, mg/kg
Australia (proposed)	Isopyrazam (for enforcement)	Edible offal (Mammalian)	*0.005
		Eggs	*0.005
		Meat [mammalian] [in the fat]	*0.005
		Milks	*0.005
		Pome fruit	0.7
		Poultry, Edible offal of	*0.005
		Poultry meat [in the fat]	*0.005
EU[6]	Isopyrazam	Edible offal (Mammalian)	*0.01
		Eggs	*0.01
		Mammalian fats	*0.01
		Meat [mammalian]	*0.01
		Milks	*0.01
		Pome fruit	0.7
		Poultry, Edible offal of	*0.01
		Poultry fats	*0.01
		Poultry meat	*0.01
Codex[7]	Isopyrazam	Edible offal (Mammalian)	0.02
		Eggs	*0.01
		Mammalian fats	*0.01
		Meat [mammalian]	*0.01
		Milks	*0.01
		Milk fats	0.02
		Poultry, Edible offal of	*0.01

[6] http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=pesticide.residue.selection&language=EN

[7] http://www.fao.org/fao-who-codexalimentarius/standards/pestres/search/en/

COUNTRY/STATUS	RESIDUE DEFINITION	COMMODITY	MRL, mg/kg
		Poultry fats	*0.01
		Poultry meat	*0.01
Japan[8]		Edible offal (Mammalian)	0.02
		Eggs	0.01
		Mammalian fats	0.01
		Meat [mammalian]	0.01
		Milks	0.01
		Poultry, Edible offal of	0.01
		Poultry fats	0.01
		Poultry meat	0.01
USA[9]	Isopyrazam	Apples	0.7#
New Zealand[10]	Isopyrazam	Pome fruit	0.1

#Import tolerance. *MRL established at the limit of quantitation.

5.5 Potential risk to trade

The Applicant has proposed including the following trade risk mitigation statement on the label, which is considered appropriate and acceptable:

Where this product will be used on apples or pears destined for export markets, seek advice from your industry body or Syngenta Australia Pty Ltd representative to ensure product will meet the requirements of the intended importing country.

For the purpose of compliance with MRLs, the proposed Australian residue definition for isopyrazam is parent compound only, for both plant and animal commodities.

There is a potential for finite residues in pome fruit as a result of the proposed use of *Seguris Flexi Fungicide*. There is a potential risk to trade, as standards for isopyrazam in pome fruit have not been established by Codex, in Canada, or markets in Asia.

[8] http://www.m5.ws001.squarestart.ne.jp/foundation/search.html

[9] http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&sid=1c8c528c83ba8b0f0d1cb05cb5060737&tpl=/ecfrbrowse/Title40/40cfr180_main_02.tpl

[10] http://www.foodsafety.govt.nz/elibrary/industry/register-list-mrl-agricultural-compounds.htm

The risk to Australian trade in animal commodities is considered to be low, as finite residues of isopyrazam are not expected to be found, and MRLs at the LOQ (*0.005 mg/kg) are proposed for milk, eggs, and mammalian and poultry meat [in the fat] and offal.

The APVMA considers that the risk to trade associated with the proposed registration of Seguris Flexi Fungicide, containing the new active constituent isopyrazam, for use on pome fruit is manageable under established industry systems. Comment is sought on this proposed decision.

6 WORK HEALTH AND SAFETY ASSESSMENT

6.1 Formulation, packaging, transport, storage and retailing

The active constituent isopyrazam will be manufactured overseas. The product Seguris Flexi Fungicide will be manufactured overseas, with secondary processing in Australia. Seguris Flexi Fungicide will be available in 1, 5 or 10 L pack sizes in HDPE or PET containers with screw cap closure and with induction heat seal or compression wad and tamper evident rings.

6.2 Use pattern

Seguris Flexi Fungicide is an emulsifiable concentrate (EC) foliar fungicide containing 125 g/L of isopyrazam. Seguris Flexi Fungicide will be used on apples and pears, with up to three applications made over a season and a minimum application interval of seven days. Growers using the product as proposed are likely to apply it on no more than a few days each year, whereas spraying contractors might use the product for longer durations. Professional operators are expected to experience short to medium term (sub-chronic) repeat exposure to the product.

The draft label states that the product will be applied at the maximum application rate of 80 mL per 100 L of water. The applicant has recommended use of 2000 L water per hectare for high volume dilute application. Therefore, the product may be applied at the maximum application rate of 1.6 L/ha using an airblast sprayer.

6.3 Exposure during use

Farmers and their employees, as well as contract sprayers will be the main users of Seguris Flexi Fungicide. Workers may be exposed to the product when opening containers, mixing/loading/application, cleaning up spills, maintaining equipment and entering treated crops. The main route of exposure to the product spray will be dermal and inhalation with minor possibility of ocular exposure.

In the absence of specific exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used to estimate exposure.

The toxic endpoints of concern and the identified NOEL for risk assessment are derived from a repeat dose study in animals; in this instance a margin of exposure (MOE) of 100 or above is considered acceptable. The MOE takes into account both potential inter-species extrapolation and intra-species variability. Based on the risk assessment, the proposed use of the product for apples and pears is acceptable when a worker wears cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow-length chemical-resistant gloves, and goggles when opening the container and preparing the formulation for use.

6.4 Exposure during re-entry

The re-entry risks associated with conducting activities where the product has been applied are expected to be by the dermal route, but the MOEs determined for re-entry activities associated with use of Seguris Flexi Fungicide are acceptable (MOE >> 300) on day zero after application. Therefore, a NIL re-entry statement is appropriate for this product.

6.5 Recommendations for safe use

Based on the risk assessment, the product is appropriate for professional use. Users should follow the First Aid Instructions, Safety Directions and Re-entry statements on the product label.

6.6 Conclusion

The approval of the new active constituent isopyrazam for agricultural use, and the registration of Seguris Flexi Fungicide (containing 125 g/L isopyrazam) for the control of black spot (*Venturia inaequalis*) and powdery mildew (*Podosphaera leucotricha*) in apples, and for control of black spot (*Venturia pirina*) in pears is supported.

Seguris Flexi Fungicide can be used safely if handled in accordance with the instructions on the product label and any other control measures described above.

7 ENVIRONMENTAL ASSESSMENT

7.1 Fate and behaviour in the environment

Fate and behaviour in soil

Photolysis of isopyrazam on soils was not a significant degradation pathway. Isopyrazam was fairly to very slightly degradable in soils under aerobic laboratory conditions at 20 °C, with the DT_{50} values in the range of 40–976 d. There was no clear relationship between persistence and soil pH, organic carbon content and texture. Isopyrazam degraded to two major metabolites, which were fairly to very slightly degradable with DT_{50} values of 65–1443 d and 40–190 d, respectively.

Isopyrazam was found to be persistent in soil under anaerobic conditions (DT50 >> 1 year). In field dissipation studies, isopyrazam was readily to very slightly degradable with normalised DT_{50} values ranging from 9–710 d at 20 °C and pF2. Isopyrazam was not as persistent in the loam soils mainly found in pome fruit orchards as it was in silty clay soil. Consequently, the DT_{50} of 173 days was used in the risk assessment. The rate of dissipation/degradation was consistent with the degradation in aerobic soils.

Isopyrazam has slight mobility in soils, with Koc values ranging from 2149–4588 L/kg. Based on the soil types that are in apple orchards, a Koc of 2766 L/kg and a Kd of 28.87 L/kg were used in the risk assessment. The isomers of isopyrazam did not show any significant difference in their adsorption/desorption properties. The two major metabolites were classified as medium to high and very high mobility, respectively.

Fate and behaviour in water

Isopyrazam was stable to hydrolysis. Isopyrazam was slightly degradable in water by direct photolysis and fairly degradable by indirect photolysis. In laboratory aquatic systems using river and pond water, isopyrazam dissipated rapidly from water to sediment with DT_{50} (dissipation) <3 d and <9 d under aerobic and anaerobic conditions, respectively. It was persistent in sediment with a total system DT_{50} (degradation) >> 1 year under aerobic and anaerobic conditions. In an outdoor microcosm study, isopyrazam dissipated rapidly in water (DT_{50} = 3.5 d) and degraded rapidly in the total system (DT_{50} (degradation) = 21.2 d). Isopyrazam degraded into three metabolites in water and sediment each with maximum levels for each metabolite being less than 10%.

Fate and behaviour in air

Due to the very low vapour pressure of isopyrazam (syn- and anti-isomers were 5.7×10^{-7} and 5.7×10^{-8} Pa, respectively at 25°C) it is unlikely to reach significant concentrations in the air as a result of volatilisation from dry soil or leaves. Additionally, volatilisation from spray droplets or moist soil surfaces is unlikely to occur to a significant extent because isopyrazam is only moderately to very slightly volatile from water (Henry's Law Constant H = 1.9×10^{-4} and 3.7×10^{-5} Pa•m^3/mole for syn- and anti-isomers, respectively).

7.2 Effects and associated risks to non-target species

Terrestrial vertebrates

Isopyrazam was practically non-toxic to birds and mammals on an acute basis and no ecologically relevant reproductive effects were observed at the highest doses tested. The environmental risk assessment concluded that the risks from the proposed use of the product is acceptable to terrestrial vertebrates.

Aquatic species

Isopyrazam dissipates rapidly from water to sediment so the risks to aquatic organisms and sediment dwellers were assessed. Isopyrazam was highly to very highly acutely toxic to fish. The most sensitive acute endpoint of an isomeric mixture of isopyrazam was carp (96 h LC_{50} = 25.8 µg ac/L). It had very high acute toxicity to *Daphnia magna*, low toxicity to green algae up to the limit of water solubility and no toxicity to higher aquatic plants at the highest tested concentration. The major metabolites were less toxic to fish, daphnids and algae compared to isopyrazam. Isopyrazam showed no biologically significant effect on midges, *Chironomus riparius,* over their full life cycle up to the highest concentration tested.

Isopyrazam is not expected to bio-accumulate as radioactive residues were rapidly eliminated from whole fish tissue (DT_{50} = 1.15 d) and the bio-concentration factor was low.

The risk to aquatic systems from spray drift was assessed using contemporary models and the current APVMA policy, and found to be acceptable as long as the maximum single application rate is 1.6 L product/ha (200 g ac/ha) and the no-spray zone of 40 m for the protection of aquatic environment is followed.

The risk resulting from the run-off following the proposed application rate in environmental water bodies was assessed using an OECD screening run-off model. The chemical characteristics such as solubility, mobility and degradability were taken into account. The concentrations of isopyrazam from use of Seguris Flexi Fungicide in environmental water bodies as a result of run-off showed an acceptable risk to aquatic organisms and sediment dwelling organisms based on rates of no more than 1.6 L product/ha (200 g ac/ha) per application.

Bees and other non-target arthropods

Isopyrazam was slightly to very-slightly acutely toxic to honeybees and was found to have low toxicity to non-target arthropods. The environmental risk assessment found that the risks from the proposed use of the product is acceptable to honey bees and other beneficial non-target arthropods.

Soil organisms

Isopyrazam was very slightly toxic to earthworms. Isopyrazam had no significant adverse effects on soil micro- and macro-organisms. Although isopyrazam is persistent in many soils, the risk to soil organisms such as collembolan, earthworms and soil micro-organisms over several years was assessed as acceptable.

Non-target terrestrial plants

Isopyrazam is not considered to be phytotoxic based on the submitted data. Risks to non-target terrestrial plants are considered to be acceptable.

7.3 Conclusions

The risk of Seguris Flexi Fungicide containing 125 g/L of isopyrazam was found to be acceptable provided the downwind no spray zone of 40 m is maintained on the label and the label states that no more than 1.6 L product/ha (200 g ac/ha) is applied per application.

The use of Seguris Flexi Fungicide meets the environmental safety criteria when used in accordance with the instructions on the product label.

7.4 List of endpoints

FATE AND BEHAVIOUR IN THE ENVIRONMENT

STUDY TYPE	ENDPOINTS
Hydrolysis	Isopyrazam is hydrolytically stable at pH 4, 5, 7 and 9 at 50 °C over 5 d. No degradation of isopyrazam at pH 5, 7 and 9 at 25 °C over 30 d.
Aqueous Photolysis	DT_{50} indirect photolysis in sterile natural water = 5–6 d (30–50°N) DT_{50} direct photolysis in pH 7 phosphate buffer = 60–64 d (30–50°N)
Aerobic and anaerobic aquatic degradation	DT_{50} River aerobic: Water 2.0 d (dissipation), Total System >>1 year (SFO) (degradation), Water 1.3 d (dissipation) (DFOP) DT_{50} River anaerobic: Water 8.8 d (dissipation), Total System >>1 year (SFO) (degradation) DT_{50} Pond aerobic: Water 2.6 d (dissipation), Total System >>1year (SFO) (degradation), Water 0.6 d (DFOP) (dissipation) DT_{50} Pond anaerobic: Water 7.1 d, Total System >>1 year (SFO) (degradation)
Degradation in Aquatic Microcosms	DT_{50} Water Column (Dissipation) = 3.5 d (SFO) DT_{50} (sediment) = 58 - 125 d (SFO) DT_{50} Total System (Degradation) = 21.2 d (SFO) Metabolites in water: CSCD662024 (10.9% at 29 days after treatment (DAT)); CSCD459488 (9.6% at 21 DAT), CSCD5636692 (9.9% at 21 DAT). Metabolites in sediment: CSCD5636692 (8.0% at 21 DAT), CSCD662024 (5.3% at 58 DAT) and CSCD459488 (6.5% at 21 DAT) At 7 DAT 45–47% radiolabelled material remained in the water.

STUDY TYPE	ENDPOINTS
Bioaccumulation	BCFss for total radioactive residues in whole fish tissues was 441, while BCFk was 406. DT_{90} = 1.15 d The chemical is not expected to bioconcentrate.
Atmospheric degradation	DT_{50} (Air) = 2.29 h
Soil photolysis	SFO DT50 = 68.2, 68.9 and 72 days (dry soil) and summer sunlight at latitude 30, 40 and 50°N. DT50 in moist soil > 1 year No degradation in dark Metabolites <8%
Soil photolysis	DT50 = 64.7, 65.3 and 68 d (SFO) No degradation in dark Metabolites <3%
Aerobic soil degradation (Study 1) in 4 soils	DT50 = 141, 149, 233 d and >1 year No clear relationship between persistence, soil pH, OC and texture. Metabolite CSCD459488 at a maximum of 23.6% and minor metabolites <4%.
Aerobic soil degradation (Study 2) in 4 soils at 20°C	DT50 = 121, 231, 349 and 592 days, (SFO) Metabolite CSCD459488 at a maximum of 20%
Aerobic soil degradation (Study 3) One soil at 20°C	DT50 = 40 d (SFO), loam sand DT90 = 133 d (SFO) Metabolite CSCD459488 at maximum of 22.3% Metabolite CSCD465008 at maximum of 11.5% Other metabolites were <5% and non-extractable residues were at maximum 58.3% AR Radiolabelled CO2: maximum 22.7% AR
CSCD459488 aerobic degradation in 3 soils at 20°C	DT50 = 65, 782 and 1443 d (SFO) Soils = Sandy loam, silty clay loam and sandy clay loam, respectively
CSCD465008 aerobic degradation in 3 soils	DT50 = 40.4, 98.6, 157 d (SFO) for sandy clay loam, sandy loam and silty clay loam, respectively

STUDY TYPE	ENDPOINTS
CSCD465008 aerobic degradation in 3 soils at 20°C	DT50 = 78, 129, 190 d (SFO) for sandy clay loam, sandy loam and silty clay loam, respectively
CSCD459488 2nd study on this metabolite – aerobic degradation	DT50 = 197 d (SFO) for sandy loam soil
CSCC210616 aerobic soil degradation in 4 soils	DT50 = 4.1, 2.5, 1.7, 3.5 d (SFO) Soils = Silty clay loam, sandy loam, sandy clay loam and sandy loam, respectively
Modelling study of aerobic soil degradation based on FOCUS	Isopyrazam DT_{50} (Geometric mean): Sandy loam: 39.8, 121, 141 days (87.9) Sandy clay loam: 592, 976 days (760) Silty clay loam: 231, 149 days (186) Sandy loam: 349, 233 days (285) Isopyrazam overall geometric mean = 244 days CSCD459488 DT_{50}: Sandy loam: 32.2, 153, 178, 65.0, 197 days (102). In other soils DT_{50} >>1 year CSCD465008 DT_{50}: Sandy loam: 103, 129, 98.7 days (109) Sandy clay loam: 78.9, 40.1 days (56.2) Silty clay loam: 190, 157 days (173 days) CSCD465008 overall geometric mean = 102 d
Anaerobic soil degradation	No degradation (DT_{50} >>1 year)

STUDY TYPE	ENDPOINTS
Modelling study of Field dissipation studies – Based on FOCUS Normalised to 20°C and pF2 Single first order (SFO) DT_{50} presented	**Isopyrazam SFO DT_{50} (X^2):** DT_{50} = 18.6 (15.2) d (sandy loam, pH = 7.7) DT_{50} = 124 (11.6) d (sandy loam, pH = 6.6) DT_{50} = 164 (16.9) d (clay loam, pH = 5.9) DT_{50} = 41.7 (21.4) d (silt loam, pH = 6) DT_{50} = 45.7 (14) d (silt loam, pH = 8.2) DFOP DT_{50} = 173 (3.6) d (silty clay loam, pH = 6.2) DT_{50} = 52.9 (21.8) d (sandy loam, pH = 8.6) DT_{50} = 710 (13.8) d (silty clay, pH = 7.8) DT_{50} = 109 (14.7) d (silty clay loam, pH=7.9) DT_{50} = 88.8 (17.2) d (sandy loam, pH = 6.3) DT_{50} = 9.11 (22.0) d (sandy loam, pH = 6.6) DT_{50} = 41.3 (13.9) d (sandy loam, pH = 7.8) DT_{50} = 83.7 (8.3) d (silt loam, pH =7.5) Arithmetic mean DT_{50} = 129 d Geometric mean DT_{50} = 72 d Median DT_{50} = 84 d **CSCD459488:** DT_{50} = 72.6 (13.6) d (sandy loam) DT_{50} = 151(20.4) d (clay loam)
Modelling study of Field dissipation studies – Based on FOCUS Un-Normalised SFO DT50 presented	Isopyrazam SFO DT50 (X2): Thirteen soils tested Arithmetic mean DT50 = 119 d Geometric mean DT50 = 59 d Median DT50 = 55 d
Calculation Half-life and formation fraction of Metabolite CSCD459488	DT50 = 1,000 days Formation fraction of CSCD459488: 0.03 (Median) and 0.09 (Average).

STUDY TYPE	ENDPOINTS
Adsorption/Desorption Isopyrazam in six soils	Kd, Koc L/kg (1/n, pH, %OM): Sandy clay loam: 73.35, 2874 (50.92, 5.40, 4.40); Sandy loam: 14.2, 3060 (0.95, 6.00, 0.80); Sand: 13.31, 4588 (0.97, 7.00, 0.50); Loam: 43.62, 2149 (0.95, 7.10, 3.50); Silty clay: 68.91, 2898 (0.93, 7.20, 4.10); Silty clay loam: 28.87, 2766 (0.93, 7.70, 1.80)
Adsorption of CSCD459488 to six soils	Kd, Koc L/kg (1/n, pH, %OM): Silty clay loam: 2.84, 114 (0.9588, 6.7, 4.3); Silty clay: 2.16, 178 (0.9089, 7.2, 2.1); Loam: 4.24, 159 (0.9212, 5.5, 4.6); Sand: 0.50, 106 (0.9887, 6.0, 0.8); Sandy loam: 0.49, 170 (0.9860, 7.0, 0.5); Sandy clay loam: 3.78, 159 (0.9881, 7.2, 4.1)
Adsorption of CSCD465008 to three soils	Koc mL/kg (OC, pH, 1/n): Loam: 0.71 (2.44, 7.3, 0.6742); Silty clay: 1.94 (1.04, 8.2, 0.9015); Sandy clay loam: 3.70 (2.78, 5.8, 0.9804).)

EFFECTS ON NON-TARGET SPECIES

SPECIES	TEST TYPE	ENDPOINTS
TERRESTRIAL VERTEBRATES		
Northern bobwhite (*Colinus virginianus*)	Acute oral	Technical active, syn:anti isomer ratio 95:05: LD_{50} >2,000 mg ac/kg bw
		EC formulation, syn:anti isomer ratio 70:30: LD_{50} >2,000 mg product/kg bw/d (>250 mg ac/kg bw/d)
	Acute dietary	Technical active, syn:anti isomer ratio 70:30: 5 d LC_{50} >5,620 mg ac/kg feed
	Reproduction	Technical active, syn:anti isomer ratio 70:30: 21 wks NOEC 480 mg ac/kg feed (32.5 mg ac/kg bw/d) (reduced bw of hatchlings and 14 d-old survivors and reduced 14 d-old survivors as % of hatchlings at 1200 ppm or 83.5 mg ac/kg bw/d)
Mallard duck (*Anas platyrhynchos*)	Acute dietary	Technical active, syn:anti isomer ratio 70:30: 5 d LC_{50} >5,620 mg ac/kg feed
	Reproduction	Technical active, syn:anti isomer ratio 70:30: 21 wks NOEC 3000 mg ac/kg feed (369 mg ac/kg bw/d) (no effect at highest dose)
Rat (*Rattus norvegicus*)	Acute oral	Technical active, syn:anti isomer ratio 93:07: LD_{50} >2,000 mg ac/kg bw
		Technical active, syn:anti isomer ratio 70:30: LD_{50} 2,000 mg ac/kg bw
	Reproduction	Technical active, syn:anti isomer ratio 93:07: NOAEL 3000 mg ac/kg feed (217 mg ac/kg bw/d) (no ecologically relevant adverse effects at highest dose)

SPECIES	TEST TYPE	ENDPOINTS
AQUATIC ORGANISMS		
Rainbow trout (*Oncorhynchus mykiss*)	Acute flow through	Technical active, syn:anti isomer ratio 70:30: 96 h LC_{50} 66.1 µg ac/L
		Technical active, syn:anti isomer ratio 90:10: 96 h LC_{50} 63 µg ac/L
		100% syn-isomer: 96 h LC_{50} 46.9 µg ac/L
		100% anti-isomer: 96 h LC_{50} 9.20 µg ac/L
		EC formulation, syn:anti isomer ratio 70:30: 96 h LC_{50} 0.32 mg product/L (0.040 mg ac/L)
Bluegill sunfish (*Lepomis macrochirus*)	Acute flow through	Technical active, syn:anti isomer ratio 70:30: 96 h LC50 181 µg ac/L
Carp (*Cyprinus carpio*)	Acute flow through	Technical active, syn:anti isomer ratio 70:30: 96 h LC_{50} 25.8 µg ac/L
Zebrafish (*Danio rerio*)	Acute flow through	Technical active, syn:anti isomer ratio 70:30: 96 h LC_{50} 300 µg ac/L
Fathead minnow (*Pimephales promelas*)	Acute flow through	Technical active, syn:anti isomer ratio 70:30: 96 h LC_{50} 26.3 µg ac/L
		Technical active, syn:anti isomer ratio 90:10: 96 h LC_{50} 34 µg ac/L
		100% syn-isomer: 96 h LC_{50} 81.7 µg ac/L
		100% anti-isomer: 96 h LC_{50} 10.7 µg anti-isomer/L

SPECIES	TEST TYPE	ENDPOINTS
	Chronic, early life stage flow-through	Technical active, syn:anti isomer ratio 70:30: 32 d NOEC 2.87 µg ac/L (reduced fry survival at 5.49 µg ac/L**)**
Sheepshead minnow (*Cyprinodon variegatus*)	Acute flow through	Technical active, syn:anti isomer ratio 70:30: 96 h LC_{50} 314 µg ac/L
Waterflea (*Daphnia magna*)	Acute static	Technical active, syn:anti isomer ratio 70:30: 48 h EC_{50} 44 µg ac/L
		Technical active, syn:anti isomer ratio 90:10: 48 h EC_{50} 130 µg ac/L
		EC formulation, syn:anti isomer ratio 70:30: 48 h EC50 0.35 mg product/L (0.44 mg ac/L)
	Chronic, reproduction, semi-static	Technical active, syn:anti isomer ratio 70:30: 21 d NOEC 13 µg ac/L 21 d EC50 53 µg ac/L
11 aquatic insects	Acute static	Technical active, syn:anti isomer ratio 95:05: 48 h EC_{50} >730 to >1000 µg ac/L
Chironomid *(Chironomus riparius)*	Chronic, static spiked water	Technical active, syn:anti isomer ratio 70:30: 27 d NOEC 1 mg ac/L (no effect at highest dose)
	Chronic, static spiked sediment	Technical active, syn:anti isomer ratio 95:05: 28 d NOEC 56 mg ac/kg dry weight (no effect at highest dose)
Green algae (*Pseudokirchneriella subcapitata*)	Acute static	Technical active, syn:anti isomer ratio 90:10: 72 h ErC50 >4 mg ac/L 96 h ErC50 >4 mg ac/L

SPECIES	TEST TYPE	ENDPOINTS
		EC formulation, syn:anti isomer ratio 70:30: 72 h ErC50 43 mg formulation/L (5.4 mg ac/L) 96 h ErC50 33 mg formulation/L(4.1 mg ac/L)
Duckweed *(Lemna gibba)*	Acute semi-static	Technical active, syn:anti isomer ratio 90:10: 7 d EC_{50} >500 µg ac/L
BEES AND OTHER NON-TARGET ARTHROPODS		
Honey bee *Apis mellifera*	Acute oral and contact	Technical active, syn:anti isomer ratio 90:10: 48 h LD_{50} (oral) >95.5 µg ac/bee 48 h NOEC (oral) 95.5 µg ac/bee 48 h LD_{50} (contact) >100 µg ac/bee 48 h NOEC (contact) 100 µg ac/bee
		Technical active, syn:anti isomer ratio 70:30: 48 h LD_{50} (oral) >192.27 µg ac/bee, 48 h NOEC (oral) 111.5 µg ac/ bee 48 h LD_{50} (contact) >200 (contact) µg ac/bee 48 h NOEC (contact) 200 µg ac/bee
		EC formulation, syn:anti isomer ratio 70:30: 48 h LD_{50} (oral) 230.9 µg ac/bee 48 h NOEC (oral) 38.78 µg ac/bee 48 h LD_{50} (contact) 63.64 µg ac/bee 48 h NOEC(contact) 25 µg ac/ bee
Parasitic wasp (*Aphidius rhopalosiphi)*	Lab (glass plate)	EC formulation, syn:anti isomer ratio 70:30: 48 h LR_{50} 329.6 mL product/ha (41.2 g ac/ha)
	Extended lab (barley plant)	EC formulation, syn:anti isomer ratio 70:30: 48 h LR_{50} >3,240 mL product/ha (>405 g ac/ha)
Predatory mite, (*Typhlodromus pyri)*	Lab (glass plate)	EC formulation, syn:anti isomer ratio 70:30: 7 d LR_{50} 1398 mL product/ha (174.75 g ac/ha)

SPECIES	TEST TYPE	ENDPOINTS
	Extended lab (bean leaf)	EC formulation, syn:anti isomer ratio 70:30: 7 d LR_{50} >3,240 mL product/ha (>405 g ac/ha)
Rove beetle *(Aleochara bilineata)*	Extended lab (soil)	EC formulation, syn:anti isomer ratio 70:30: 28 d LR_{50} >3,240 mL product/ha (>405 g ac/ha)
Green lacewing, *Chrysoperla carnea*	Extended lab (bean leaf)	EC formulation, syn:anti isomer ratio 70:30: LR_{50} >3,240 mL formulation/ha (>405 g ac/ha)
SOIL ORGANISMS		
Earthworm *(Eisenia foetida)*	Acute	Technical active, syn:anti isomer ratio 90:10: 14 d LC_{50} >1,000 mg ac/kg soil dw
		Technical active, syn:anti isomer ratio 70:30: 14 d LC_{50} >1,000 mg ac/kg soil dw
		EC formulation, syn:anti isomer ratio 70:30: 14 d LC_{50} >248 mg ac/kg soil dw
	Chronic reproduction	Technical active, syn:anti isomer ratio 90:10: 56 d NOEC 60 mg ac/kg soil dw (no effect at highest dose)
		Technical active, syn:anti isomer ratio 70:30: 56 d NOEC 120 mg ac/kg soil dw (no effect at highest dose)
		EC formulation, syn:anti isomer ratio 70:30: 56 d NOER = 450 g ac/ha (no effect at highest dose)
Collembola *(Folsomia candida)*	Chronic reproduction	EC formulation, syn:anti isomer ratio 70:30: 28 day NOEC = 15 mg ac/kg dw soil (no effect at highest dose)

SPECIES	TEST TYPE	ENDPOINTS
Soil microorganisms	Chronic	EC formulation, syn:anti isomer ratio 70:30: NOEC 1.67 mg ac/kg soil dw (no effect on respiration or nitrogen metabolism at highest dose)
Organic matter decomposers	Litter bag test	EC formulation, syn:anti isomer ratio 70:30: Mass loss relative to controls was 12.9% and 11.9% at 0.114 and 0.359 mg ac/kg, respectively.
NON-TARGET TERRESTRIAL PLANTS		
4 monocot and 6 dicot crop species	Seedling emergence	EC formulation, syn:anti isomer ratio 70:30: ER_{25} >150 g ac/ha ER_{50} >150 g ac/ha
	Vegetative vigour	EC formulation, syn:anti isomer ratio 70:30: ER_{25} >150 g ac/ha ER_{50} >150 g ac/ha

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed use pattern

For both apples and pears Seguris Flexi Fungicide is to be applied as a protectant against development of black spot (scab) (*Venturia inaequalis*) and powdery mildew (*Podosphaera leucotricha*) in apples and black spot (scab) (*Venturia pirina*) in pears. Application is proposed to begin at green tip with further applications at 7–10 day intervals with a maximum of 3 sprays per season and no more than 2 consecutive sprays per season.

Seguris Flexi Fungicide is to be applied as a dilute foliar spray at a product rate of 80 mL/100 L (10 g ai/100 L) for black spot (scab) control in both apples and pears, and at the same rate in apples for control of primary infections of powdery mildew. The shorter application intervals are used under higher disease pressure and periods of rapid tree growth.

8.2 Summary of efficacy and crop safety

Efficacy

The Applicant presented results from nineteen Australian field trials (2011–2014) comparing the efficacy and crop safety of Seguris Flexi Fungicide and other industry standard fungicides for the control of black spot/scab (*Venturia inaequalis*) and powdery mildew (*Podosphaera leucotricha*) in apples and black spot/scab (*Venturia pirina*) in pears. The trials were conducted on the commonly grown apple cultivars Red Delicious, Jonathan, Granny Smith, Red Fuji, Royal Gala and Cripps Pink/Pink Lady and pear cultivars, Packham's Triumph (Packham), William bon Chretien and Beurre Bosc.

The trials conducted in orchards in Queensland, New South Wales, Victoria and Tasmania, provided sites that were representative of commercial situations, under natural disease pressures with common apple and pear varieties with different susceptibilities to disease. The trials were based on randomised complete block designs, with four replicates and the spray rates used included those as proposed on the draft label. All results were analysed appropriately by an analysis of variance and means separated by the least significant difference at 5% level and Fisher’s unprotected LSD test.

Seguris Flexi Fungicide was trialled with up to ten applications at rates of 50–150 g product/100 L (6.3–18.8 g ai/100 L), at 7–14 day intervals from green tip stage onwards and on various stages of flower and fruit development. The spray regimes were tested at different spray volumes with most trials using dilute sprays ranging from 680–2500 L/ha (noting concentrate spraying is not being sought under this current submission). Efficacy of Seguris Flexi Fungicide was assessed at regular intervals by comparing the incidence and severity of disease symptoms on leaves and fruit against untreated controls and the industry standard fungicides.

The trial data support that Seguris Flexi Fungicide, applied at 7–10 day intervals, as a dilute foliar spray at rates of 60–160 mL/100 L significantly reduced the incidence and severity of black spot and powdery mildew compared to untreated controls and provided similar efficacy to the industry standard fungicides tested.

Crop safety

Crop safety assessments were conducted in all of the efficacy trials. Crop safety was assessed at regular intervals by recording any signs of blossom damage, discolouration, fruit russeting or phytotoxicity of fruit and leaves at regular intervals during the trials.

Seguris Flexi Fungicide was demonstrated to be safe to use on apple and pear cultivars at rates of up to 160 mL/100 L and multiple applications at 7–10 day intervals from green tip stage, when applied as a dilute foliar spray.

Resistance management

Isopyrazam has an inhibitory mode of action on the enzyme succinate dehydrogenase (complex II) within the fungal mitochondrial respiration chain. For resistance management purposes, the Fungicide Resistance Action Committee (FRAC), a specialist technical group of CropLife International, has designated Isopyrazam as a Group 7 fungicide.

The proposed uses in apples for control of Black spot/scab *(Venturia inaequalis*) and pears for the control of Black spot/scab (*Venturia pirina*) are subject to CropLife Australia Fungicide Resistance Management strategies.

8.3 Conclusions

Trial data support that Seguris Flexi Fungicide will provide acceptable control against black spot (scab) (*Venturia inaequalis*) and powdery mildew (*Podosphaera leucotricha*) in apples and black spot (scab) (*Venturia pirina*) in pears when used according to the label instructions. The product is not expected to result in phytotoxicity in the target crop when used as directed.

The directions for use are appropriate and consistent with fungicide use in commercial agriculture in Australia.

The application for the registration of Seguris Flexi Fungicide is supported on efficacy and crop safety grounds when used in accordance with label instructions.

9 LABELLING REQUIREMENTS

POISON

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

DIRECTIONS FOR USE

Restraints

DO NOT apply by aircraft

DO NOT apply if heavy rains or storms are forecast within 3 days

DO NOT apply more than 1.6 L product/ha (200 g ac/ha) per application.

Spray Drift Restraints:

DO NOT apply when the wind speed is less than 3 or more than 20 kilometres per hour as measured at the application site.

DO NOT apply during surface temperature inversion conditions at the application site.

DO NOT direct the spray above trees during airblast applications.

TURN OFF outward pointing nozzles at row ends and outer rows during airblast applications.

Users of this product **MUST make an accurate written record** of the details of each spray application within 24 hours following application and **KEEP** this record for a minimum of 2 years. The spray application details that must be recorded are: **1.** date with start and finish times of application; **2.** location address and paddock/s sprayed; **3.** full name of this product; **4.** amount of product used per hectare and number of hectares applied to; **5.** crop/situation and weed/pest; **6.** wind speed and direction during application; **7.** air temperature and relative humidity during application; **8.** nozzle brand, type, spray angle, nozzle capacity and spray system pressure measured during application; **9.** name and address of person applying this product. (Additional record details may be required by the state or territory where this product is used.)

Mandatory No-Spray Zones

DO NOT apply if there are aquatic and wetland areas including aquacultural ponds, surface streams and rivers within **40 metres** downwind from the application area.

Crop	Disease	Rate	Critical Comments
Apples	Powdery mildew (*Podosphaera leucotricha*), Black spot (scab) (*Venturia inaequalis*)	80 mL per 100 L of water	Apply as a protectant spray. Apply by dilute spraying equipment. Begin applications at green tip and make further applications at 7–10 day intervals. Use the shorter interval under higher disease pressure and periods of rapid tree growth. **This use is subject to a CropLife Australia Fungicide Resistance Management strategy.** DO NOT apply more than 3 sprays of SEGURIS FLEXI or other Group 7 fungicides per season. DO NOT apply more than 2 sequential sprays of SEGURIS FLEXI or other Group 7 fungicides. If two sequential sprays are applied, they must be followed by at least two fungicide sprays from a different mode of action group before a Group 7 fungicide is applied again, either in the current or following season.
Pears	Black spot (scab) (*Venturia pirina*)	80 mL per 100 L of water	Apply as a protectant spray. Apply by dilute spraying equipment. Begin applications at green tip and make further applications at 7-10 day intervals. Use the shorter interval under higher disease pressure and periods of rapid tree growth. **This use is subject to a CropLife Australia Fungicide Resistance Management strategy.** DO NOT apply more than 3 sprays of SEGURIS FLEXI or other Group 7 fungicides per season. DO NOT apply more than 2 sequential sprays of SEGURIS FLEXI or other Group 7 fungicides. If two sequential sprays are applied, they must be followed by at least two fungicide sprays from a different mode of action group before a Group 7 fungicide is applied again, either in the current or following season.

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

WITHHOLDING PERIOD:

Harvest: DO NOT HARVEST FOR 21 DAYS AFTER APPLICATION

Grazing: DO NOT ALLOW LIVESTOCK TO GRAZE TREATED ORCHARDS OR CUT FOR STOCK FOOD

EXPORT OF TREATED PRODUCE

Where this product will be used on apples or pears destined for export market, seek advice from your industry or Syngenta Australia Pty Ltd representative to ensure product will meet the requirements of the intending import country.

WARNING:

In some situations, SEGURIS FLEXI may cause petal burning when applied over flowering. Fruit finish will not be affected.

GENERAL INSTRUCTIONS

Mixing

SEGURIS FLEXI is an Emulsifiable Concentrate (EC) formulation that mixes readily with water and is applied as a spray.

1. Partly fill the spray tank with water.
2. Start the agitation.
3. Add the correct amount of product to the spray tank with the agitation system running.
4. Continue agitation while topping up the tank with water and while spraying.
5. Use the spray mix as soon as possible after preparation.

Application

Ground Application Only

Ensure thorough coverage of foliage and fruit. Apply by high volume (dilute) sprayer.

Dilute Spraying

Use a sprayer designed to apply high volumes of water up to the point of runoff and matched to the crop being sprayed. Set up and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient water to cover the crop to the point of runoff. Avoid excessive runoff. The required water volume may be determined by applying different test volumes, using different settings on the sprayer, from industry guidelines or expert advice. Add the amount of product specified in the Direction for Use table for each 100 L of water. Spray to the point of runoff. The required dilute spray volume will change and the sprayer set up and operation may also need to be changed, as the crop grows.

The chosen spray volume, amount of product per 100 L of water, and the sprayer set up and operation may need to be changed as the crop grows. For further information on spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow industry Best Practices.

Compatibility

SEGURIS FLEXI is compatible with a range of commonly used fungicides, insecticides, herbicides and fertilizers, including BOGARD 100 WG. Always consult your Syngenta representative before mixing SEGURIS FLEXI with other products. As formulations of other manufacturer's products are beyond the control of Syngenta, and the quality of water may vary with location, all mixtures should be tested prior to mixing commercial quantities.

Fungicide Resistance Warning

GROUP	7	FUNGICIDE

SEGURIS FLEXI Fungicide is a Group 7, SDHI fungicide. Some naturally occurring individual fungi resistant to SEGURIS FLEXI and other Group 7 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungi population if these fungicides are used repeatedly. These resistant fungi will not be controlled by SEGURIS FLEXI and other Group 7 fungicides, thus resulting in a reduction in efficacy. Since the occurrence of resistant fungi is difficult to detect prior to use, Syngenta Australia Pty Ltd accepts no liability for any losses that may result from the failure of SEGURIS FLEXI to control resistant fungi.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

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

STORAGE AND DISPOSAL

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

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

SAFETY DIRECTIONS

Harmful if inhaled or swallowed. Will damage eyes. Will irritate the skin. Avoid contact with eyes and skin. Do inhale spray mist. When opening the container and preparing the spray, wear:

– cotton overalls buttoned to the neck and wrist (or equivalent clothing)
– elbow-length chemical-resistant gloves
– goggles

If product on skin, immediately wash area with soap and water. If product spray in eyes, wash it out immediately with water.

Wash hands after use. After each day's use wash gloves, goggles and contaminated clothing.

FIRST AID

If poisoning occurs contact a doctor or Poisons Information Centre. Phone 131 126.

SAFETY DATA SHEET

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

ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
d	day
DAT	Days After Treatment
DFOP	Double first order in parallel (dissipation kinetics)
DT_{50}	Time taken for the concentration of a chemical in a defined compartment (eg soil, water) to decline by 50 %
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
EGI	Export Grazing Interval
ESI	Export Slaughter Interval
EUP	End Use Product
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice

h	hour
ha	hectare
Hct	Heamatocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram

NHMRC	National Health and Medical Research Council
NOAEL	No Observed Adverse Effect Limit
NOEC/NOEL	No Observed Effect Concentration/ Level
OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SFO	Single First Order (dissipation kinetics)
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period

GLOSSARY

Abiotic degradation	Degradation of a chemical via physical or chemical mechanisms such as hydrolysis or photolysis.
Absorption	Movement of a chemical from the environment across a biological membrane into an organism.
Active constituent	The substance that is primarily responsible for the effect produced by a chemical product.
Aerobic	Living or occurring only in the presence of oxygen.
Anaerobic	Living or occurring only in the absence of oxygen.
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer.
Chronic	Of long duration.
Codex MRL	Internationally published standard maximum residue limit.
Desorption	Removal of a material from or through a surface.
Emulsifiable concentrate	Liquid formulation containing emulsifiers in an organic solvent that disperse when added to water.
Emulsifier	Surfactant used to aid the preparation of a colloidal dispersion of one liquid in another which is not miscible.
Efficacy	Production of the desired effect.
Formulation	A combination of both active and inactive constituents to form the end use product.
Genotoxicity	The ability to damage genetic material.
Inhalation	Drawing of air into the lungs.
Hydrolysis	The chemical process of decomposition involving the cleaving of a molecule and the insertion of a water molecule.
Hydrophobic	Repels water.
Isomerism	The existence of more than one substance having a given molecular composition and molecular mass but differs in constitution or structure. Different identifiers are called isomers.
K_{oc}	Chemicals vary in how well they are adsorbed to soil particles. K_{oc} measures the affinity for pesticides to sorb to organic carbon. The higher the value, the stronger the tendency to attach to and move with soil.
Leaching	Removal of a compound by use of a solvent.
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW.

MRL	Maximum concentration of a residues legally permitted or recognised as acceptable in food, agricultural commodities or animal feedstuffs.
Metabolism	The chemical processes that maintain living organisms.
Micronucleus Assay	A toxicological test used in screening for potential genotoxic compounds
Mutagenicity	Ability of a chemical to produce a detectable and heritable change in genetic material which may be transmitted to offspring from one generation to the next.
Photo-degradation	Breakdown of chemicals due to the action of light.
Photolysis	Breakdown of chemicals due to the action of light.
Unscheduled DNA Synthesis (USD) Assay	This assay measures a cell's ability to perform DNA synthesis repair after excision and removal of a stretch of DNA containing a region of damage induced by chemical and physical agents.
Subcutaneous	Under the skin.
Toxico-kinetics	The study of the movement of toxins through the body.
Toxicology	The study of the nature and effects of poisons.