



Australian Government
**Australian Pesticides and
Veterinary Medicines Authority**



Public Release Summary

on the evaluation of the new active cyclobutryfluram in the product TREFINTI Turf
Nematicide

APVMA product number 91438/132224

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Preface

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator responsible for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia. Before approving an active constituent and/or registering a product, the APVMA must be satisfied that the statutory criteria, including the safety, efficacy, trade, and labelling criteria, have been met. The information and technical data required by the APVMA to assess the statutory criteria of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined on the [APVMA website](#).

The APVMA has a policy of encouraging transparency in its activities and seeking community involvement in decision making. Part of that process is the publication of Public Release Summaries for products containing new active constituents. 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 advisory agencies, including other Australian Government agencies and State departments of primary industries. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience to encourage public comment.

About this document

This Public Release Summary indicates that the APVMA is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

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

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

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of TREFINTI Turf Nematicide 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 17 September 2024 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:

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

Please note: submissions will be published on the APVMA website unless you have asked for the submission to remain confidential, or if the APVMA chooses at its discretion not to publish any submissions received (refer to the [public consultation coversheet](#)).

Please lodge your submission using the [public consultation coversheet](#), which provides options for how your submission will be published.

Note that all APVMA documents are subject to the access provisions of the *Freedom of Information Act 1982* and may be required to be released under that Act should a request for access be made.

Unless you request for your submission to remain confidential, the APVMA may release your submission to the applicant for comment.

Written submissions should be addressed to:

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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](#).

Introduction

Applicant

Syngenta Australia Pty Limited is the applicant for the product TREFINTI Turf Nematicide and for the active, cyclobutrifluram.

Purpose of application

Syngenta Australia Pty Limited has applied to the APVMA for registration of the new product TREFINTI Turf Nematicide, containing 450 g/L cyclobutrifluram, as a suspension concentrate formulation of the new active constituent cyclobutrifluram.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of the product TREFINTI Turf Nematicide, and approval of the new active constituent cyclobutrifluram.

Proposed claims and use pattern

TREFINTI Turf Nematicide is intended for the control of Nematodes including Ring Nematode (*Macroposthonia* sp), Root-knot (*Meloidogyne* spp.), Southern Sting Nematode (*Ibipora loli*), Sting (*Belonolaius longicaudatus*), Stubby (*Paratrichodorus minor*), Dagger (*Xiphinema* spp) Sheath (*Hemicycliophora* spp) Spiral (*Helicotylenchus* spp) in Turf.

For Turf situations — including golf (tees, greens, fairways) professional sports fields, racetracks, parklands, commercial and residential lawns — the application rate is 275 – 550 mL/ha, up to 2 applications of 550 mL/ha or 4 applications of 275 mL/ha.

Mode of action

Cyclobutrifluram belongs to the pyridine-3-carboxamide chemical class. Its mode of action is as a selective inhibitor of succinate dehydrogenase (complex II) disrupting ATP production in nematode and fungal mitochondria (Insecticide Resistance Action Committee Group N-3 mode of action).

Overseas registrations

Cyclobutrifluram is currently in registered products in Argentina as VICTRATO® for control of Fusarium, charcoal stem rot (*Macrophomina phaseolina*), nematodes (*Meloidogyne* sp., *Pratelenchus* sp., *Heterodera glycines*), Septoriause in Soybean and VANIVA® for control of Fusarium, *Alternatia dauci*, *Cercospora carotae*, nematodes (*Nacobbus* sp, *Meloidogyne* sp., *Tylenchulus* sp., *Radophus similis* in Tomato, Potato; in Belize as VICTRATO® for control of Root-lesion nematodes (*Pratelenchus* sp.) in Corn; in Chile as A22011B VANIVA® for control of Root-knot nematodes (*Meloidogyne* sp.), cyst nematodes (*Globodera* sp.) in potato, tomato; in China as VANIVA® for control of Nematodes in Tomato; in Colombia as VANIVA® for

control of Root-knot nematodes (*Meloidogyne* sp.), cyst nematodes (*Globodera* sp.) in Tomato, peppers, potato; in El Salvador as VICTRATO® for control of Root-lesion nematodes (*Pratelenchus* sp.) in Corn; in Guatemala as TYMIRIUM® technology and as VANIVA® for control of Root-lesion nematodes (*Pratelenchus* sp.) in Zucchini, melons, tomato, banana; in Honduras as VANIVA® for control of Root-knot nematodes (*Meloidogyne* sp.) in Melon and as VICTRATO® for control of Lesion nematodes (*Pratelenchus* sp.) in Corn; in Paraguay as VICTRATO® for control of Fusarium, charcoal stem rot (*Macrophomina phaseolina*), nematodes (*Meloidogyne* sp., *Pratelenchus* sp., *Heterodera glycines*), Septoria in Soybean; in Philippines as VANIVA® for control of Fusarium wilt in Banana; in South Korea as TYMIRIUM® and VANIVA® for control of Root-knot nematodes in Chinese cabbage, oriental melon, and as A22011B VANIVA® for control of Root-knot nematodes in Cucumber, tomato, oriental melon, watermelon; in Vietnam as VANIVA® for control of Nematodes in Coffee; in Zambia as VICTRATO® for control of Root-knot nematodes (*Meloidogyne* sp.), Lesion nematodes (*Pratelenchus* sp.) in Soybean and Corn, and as VANIVA® for control of Nematodes tobacco, potatoes; and in Zimbabwe as VANIVA® for control of Root-knot nematodes (*Meloidogyne* sp.), Lesion nematodes (*Pratelenchus* sp.) in Tobacco.

Chemistry and manufacture

Active constituent

The active constituent cyclobutrifluram is manufactured overseas. Details of the chemical name, structure, and physicochemical properties of cyclobutrifluram are listed below (Tables 1 – 2).

Cyclobutrifluram is an off-white crystalline powdered solid that melts at 125°C, and further heating leads to decomposition at temperatures above 271°C. It has some solubility in water (33 mg/L at 20°C) but is more soluble in acetone, dichloromethane, ethyl acetate, and methanol. The vapour pressure ($<6.2 \times 10^{-6}$ Pa at 20°C) and the Henry's law constant (7.3×10^{-5} Pa·m³/mol) indicate that volatilisation is not expected to be a significant route of dissipation for cyclobutrifluram. The octanol/water partition coefficient (Log P_{ow}) is 3.2 at 20°C. There are no safety properties of concern (e.g. flammability, explosive, and/or oxidizing) regarding cyclobutrifluram. Cyclobutrifluram is expected to be stable for at least 12 months of storage under normal conditions.

Table 1: Nomenclature and structural formula of the active constituent cyclobutrifluram

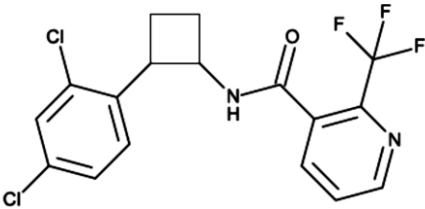
Common name (ISO):	Cyclobutrifluram
IUPAC name:	Mixture comprised of 80–100% <i>N</i> -[(1 <i>S</i> ,2 <i>S</i>)-2-(2,4-dichlorophenyl)cyclobutyl]-2-(trifluoromethyl)pyridine-3-carboxamide and 20–0% of the (1 <i>R</i> ,2 <i>R</i>)-enantiomer
CAS name:	<i>rel</i> - <i>N</i> -[(1 <i>R</i> ,2 <i>R</i>)-2-(2,4-dichlorophenyl)cyclobutyl]-2-(trifluoromethyl)-3-pyridinecarboxamide
CAS registry number:	1460292-16-3
Molecular formula:	C ₁₇ H ₁₃ Cl ₂ F ₃ N ₂ O
Molecular weight:	389.2 g/mol
Structural formula:	

Table 2: Key physicochemical properties of the active constituent cyclobutrifluram

Physical form:	Solid crystalline powder
Colour:	Off-white
Odour:	Odourless
Melting point:	124.6 – 125.4°C
Relative density	1.39 – 1.46 g/cm ³ at 20°C
Stability:	At ambient temperature, cyclobutrifluram is stable over the period of at least one year without decomposition. The average weight % of cyclobutrifluram stored was 100.1% (w/w) at time zero, and 99.6% (w/w) for HDPE, 99.8% (w/w) for a laminated paper/aluminium/PETP/PE, 99.9% (w/w) for a PE bag, and 99.9% (w/w) for a varnished steel drum after storage for 12 months at 20°C. The percentage total weight change observed was <0.3% (w/w) (on dried basis).
Safety properties:	Not considered flammable. Not explosive. Slightly corrosive against tin plate, galvanised sheet metal and sheet steel but weight changes are ≤ 0.01 g.
Solubility in water:	33 mg/L at 20°C (PAI) 19 mg/L at 20°C (TGAI)
Organic solvent solubility:	Acetone: >500 g/L Methanol: 420 g/L Ethyl acetate: 390 g/L Dichloromethane: 430 g/L Octanol: 69 g/L Toluene: 53 g/L n-hexane: 0.27 g/L
PH:	pH (1% w/v) = 6.34 at 20°C (TGAI)
Octanol/water partition coefficient (Log K _{ow} /K _{ow}):	Log P _{ow} = 3.2 at 20°C
Vapour pressure:	<6.2 × 10 ⁻⁶ Pa at 20°C and 25°C
Henry's law constant:	K = 7.3 × 10 ⁻⁵ Pa·m ³ /mol
UV/VIS absorption spectra:	ε = 12817 L·mol ⁻¹ ·cm ⁻¹ (λ = 225 nm) (acidic solution) ε = 12970 L·mol ⁻¹ ·cm ⁻¹ (λ = 225 nm) (basic solution) ε = 11792 L·mol ⁻¹ ·cm ⁻¹ (λ = 225 nm) (neutral solution)
Hydrolysis in water:	Stable at pH 4, 7 and 9 at 50°C, 60°C and 70°C in the absence of light.
Photochemical oxidation degradation:	The estimated half-life in pH 7 buffer solution is 11 to 24 days summer sunlight of UK and USA, in a continuous irradiated system.

Formulated product

TREFINTI Turf Nematicide product containing cyclobutrifluram will be manufactured overseas. Tables 3 to 4 outline some key aspects and physicochemical properties of TREFINTI Turf Nematicide. TREFINTI

TREFINTI Turf Nematicide will be available in 500 mL to 20 L in HDPE or HDPE/PA and/or PET containers.

Table 3: Key aspects of the formulation of the product TREFINTI Turf Nematicide

Distinguishing name:	TREFINTI Turf Nematicide
Formulation type:	Suspension concentrate (SC)
Active constituent concentration:	450 g/L cyclobutrifluram

Table 4: Physicochemical properties of the product TREFINTI Turf Nematicide

Physical form:	Beige liquid
pH:	7.6 (1% aqueous dilution) 7.4 (neat)
Relative density:	1.173 g/cm ³ at 20°C
Kinematic viscosity:	99.4 mPa ^s at 20°C and 92.2 mPa ^s at 40°C
Pourability:	Poured residue = 2.9%; rinsed residue = 0.12%
Wet Sieve test:	<0.01% retained in a 75 µm sieve
Persistent foaming:	0 mL foam (1% dilution and 0.1% dilution) after 1 minute
Spontaneity of dispersion:	100% in 5% v/v aqueous dilution after 5 minutes
Suspensibility:	98% (1% dilution and 0.1% dilution)
Corrosion of metal:	Slightly corrosive on tin plate, sheet steel and galvanised steel metal
Safety properties:	No flash point below 101°C. Auto-ignition temperature is 480°C. Not classified as a flammable liquid or an explosive and/or as an oxidising substance.
Storage stability:	There was sufficient data to conclude that the product is expected to remain within specifications for at least two (2) years when stored under normal conditions

Recommendations

The APVMA Chemistry section has evaluated the chemistry of the active constituent cyclobutrifluram and TREFINTI Turf Nematicide containing cyclobutrifluram — including the physicochemical properties, manufacturing process, quality control procedures, stability, batch analysis results and analytical methods — and found them to be acceptable. The available storage stability data indicate that the TREFINTI Turf Nematicide is expected to remain stable for at least 2 years when stored under normal conditions.

Based on a review of the chemistry and manufacturing details, the registration of TREFINTI Turf Nematicide TREFINTI and approval of the active constituent cyclobutrifluram, are supported from a chemistry perspective.

Toxicological assessment

The submitted data on cyclobutrifluram and TREFINITI Turf Nematicide was of adequate scope and quality for assessment. Where appropriate, the submitted studies were conducted in accordance with GLP and were validated by the appropriate use of controls.

Evaluation of toxicology

Chemical class

Cyclobutrifluram belongs to the pyridine-3-carboxamide chemical class. Its mode of action is as a selective inhibitor of succinate dehydrogenase (complex II) disrupting ATP production in nematode and fungal mitochondria (Insecticide Resistance Action Committee Group N-3 mode of action). In this regard, it shares a similar mode of action to fluopyram and possesses a similar chemical structure. Cyclobutrifluram is a mixture of 1S,2S (SYN547386) and 1R,2R (SYN548941) enantiomers and contains a minimum of 80% of the 1S,2S isomer.

Pharmacokinetics

Following a single oral or intravenous dose in the rat, cyclobutrifluram was extensively and rapidly absorbed at 5 mg/kg bw. At higher doses (500 mg/kg bw), absorption was more limited, implying saturation of oral absorption. Blood-to-plasma ratios of radioactivity suggested that total radioactivity remained predominantly in plasma rather than the cellular component of whole blood at earlier time points. The blood-to-plasma ratio appeared to increase at later time points, becoming either evenly distributed or greater in the cellular fraction. Overall, there were no consistent, biologically important, sex-related toxicokinetic differences.

Metabolism of cyclobutrifluram in the rat was complex and extensive. It primarily consisted of hydroxylation \pm glucuronide, sulphate and S-cysteine conjugation, amide bond cleavage, hydrolysis of the amide bond and oxidative cleavage of the cyclobutane moiety. The key metabolic enzymes involved in the metabolism were not identified. No information on comparative inter-species metabolism studies were provided. Excretion of radioactivity derived from cyclobutrifluram was essentially complete at 72 to 168 hours following dosing. The major route of excretion was via bile, followed by urinary elimination. There was no evidence of radiation derived from cyclobutrifluram accumulating in the body. There were no biologically relevant sex or radiolabel position-dependent effects on the disposition.

Acute toxicity (active constituent)

Cyclobutrifluram has low acute oral, dermal, and inhalation toxicity. It is a slight eye irritant but not a skin irritant or a skin sensitiser.

Acute toxicity (product)

TREFINITI Turf Nematicide has low toxicity by oral, dermal and inhalation routes; is a slight eye irritant but is neither a skin irritant nor a skin sensitiser.

Repeat-dose toxicity

Following repeat daily dietary exposure at up to 1771 mg/kg bw/d the major target organs/systems were red blood cells and their precursors, liver, and the thyroid gland. Effects on body weight parameters (often correlated with effects on food consumption parameters) also occurred.

In a 28-day mouse dietary study, no overall No Observed Adverse Effect Level (NOAEL) could be determined due to increased incidence of splenic haemopoiesis in females at ≥ 62 mg/kg bw/d, and other haematological and clinical chemistry effects (often exceeding the biological normal range) at ≥ 62 mg/kg bw/d. The overall study Lowest Observed Adverse Effect Level (LOAEL) was 62 mg/kg bw/d. In a 90-day mouse dietary study, the NOAEL was 16.8 mg/kg bw/d due to increased blood triglycerides, correlated with decreased blood cholesterol in males. The changes in blood triglycerides and cholesterol at doses ≥ 93.8 mg/kg bw/d in males fell outside of the relevant normal biological range (implying an adverse disturbance of normal lipid metabolism) and were accompanied by increases in serum liver enzymes (generally within biological normal range). Similar changes occurred in females. Notably, a similar pattern of dyslipidaemia occurred in the 28-day study in male mice at doses ≥ 338 mg/kg bw/d. Reduced serum cholesterol (without triglyceridaemia) occurred in the 28-day rat study.

In a 28-day rat dietary study, the NOAEL was 32 mg/kg bw/d due to increased serum fibrinogen in males exceeding the biologically normal range by 19.1 and 23.1 % at 2000 and 4000 ppm, respectively. No other evidence of clotting disorders was detected. In a 90-day rat dietary study, the NOAEL was 51.1 mg/kg bw/d based on reduced body weight gain (correlated with reduced food utilisation) at 4000/6000 ppm.

In a 28-day oral dog study, the NOAEL was 300 mg/kg bw/d based on minimal/marginal serum chemical evidence consistent with cholestasis/biliary injury at 600 mg/kg bw/d. These effects occurred in the absence of any changes in serum bilirubin and were not correlated with any anatomic pathology evidence of cholestasis or biliary injury. Accordingly, this NOAEL is considered to be conservative.

In a 13-week oral dog study, the NOAEL was 30 mg/kg bw/d based on reduced body weight gain in males at 100 mg/kg bw/d (exceeding -10% (MTD)).

Chronic toxicity and carcinogenicity

Cyclobutrifluram was not carcinogenic in mice and rats.

In an 80-week carcinogenicity study in mice, the NOAEL was established for toxicity and carcinogenicity at 47.8 mg/kg bw/d, the highest dose tested. Cyclobutrifluram is a strong activator of murine CAR and there is sufficient evidence that any carcinogenic actions in the murine liver occur via a phenobarbital-like (CAR xenosensor activation) mode of action that is not relevant to humans (see discussion of human relevance in the mode of action evaluation section below).

In a 104-week combined chronic/carcinogenicity study in rats, dietary exposure to cyclobutrifluram at ≥ 6.8 mg/kg bw/d resulted in reduction ($\geq 10\%$ cf. controls) in body weight gain in male rats. The overall study NOAEL is 7.7 mg/kg bw/d due to reduced body weight gain in male rats at the next highest dose. Within the context of this study, this NOAEL is conservative.

Reproductive and developmental toxicity

Cyclobutrifluram did not adversely affect reproduction or development survival in a rat multigenerational study at doses up to 43.1 mg/kg bw/d. Cyclobutrifluram was neither teratogenic nor maternotoxic in a prenatal development study in rats at oral doses up to 250 mg/kg bw/d. Cyclobutrifluram was not teratogenic in a rabbit prenatal development study at doses up to 125 mg/kg bw/d. Maternotoxicity manifesting as reduced (about -35% cf. control) gestational day 6-27 body weight gain occurred following dosing at 125 mg/kg bw/d.

Genotoxicity

Cyclobutrifluram was not genotoxic in an appropriately validated genotoxicity test battery.

Neurotoxicity

Cyclobutrifluram was not an acute neurotoxicant in rats. No developmental neurotoxicology studies were undertaken and such studies were not considered necessary at this time.

Mode of action (toxicology)

Toxicity of metabolites and/or impurities

The following food/feed specific metabolites present at $\geq 10\%$ of the total radioactive residue were identified: SYN510260 (CA5442), SYN552202, SYN552415, SYN552430, SYN552439, SYN552441, SYN552442, trifluoroacetic acid (CSCA000397). Based on QSAR analysis, all these food/feed metabolites are classified as Cramer Class III, and do not have structural alerts for genotoxicity (detected alerts are the same structures identified for cyclobutrifluram, which is not genotoxic). The lack of genotoxicity of SYN510260 (CA5442) was confirmed by a battery of *in vitro* genotoxicity studies.

SYN510275 is a major metabolite in rats and is thus considered to be adequately tested in the toxicology studies of cyclobutrifluram (covered by the health-based guidance value(s)). Its lack of genotoxicity was confirmed by studies on the purified compound.

Health-based guidance values and poisons scheduling

Poisons Standard

Cyclobutrifluram is included in Appendix B, clause 1.3 of the Poisons Standard, a fungicide not requiring control of use by scheduling.

Health-based guidance values

Acceptable daily intake (ADI)

The ADI of 0.08 mg/kg bw/d for cyclobutrifluram was established from a NOAEL of 7.7 mg/kg bw/d (rounded up to 8 mg/kg bw/d) in a 104-week dietary toxicity and carcinogenicity study in rats, based on an $\approx 10\%$

reduction in body weight gain in body weight gain in males in the carcinogenesis study phase of the study. Within the context of this study, this point of departure is regarded as being conservative. An intraspecies uncertainty factor of 10 and an interspecies uncertainty factor of 10 have been used. Overall, the ADI value is regarded as being conservative.

Acute reference dose

No acute reference dose (ARfD) has been established for cyclobutrifluram. An ARfD was considered unnecessary due to its low oral toxicity, and the absence of any neurological effects or developmental toxicity after a single dose.

Recommendations

There are no objections on human health grounds to the approval of the new active constituent cyclobutrifluram (950 g/kg) TGAC.

There are no objections on human health grounds to the registration of the product TREFINTI Turf Nematicide containing 450 g/L of cyclobutrifluram when used in accordance with the directions for use (DFU) and adhering to the recommended safety directions.

Residues assessment

Metabolism

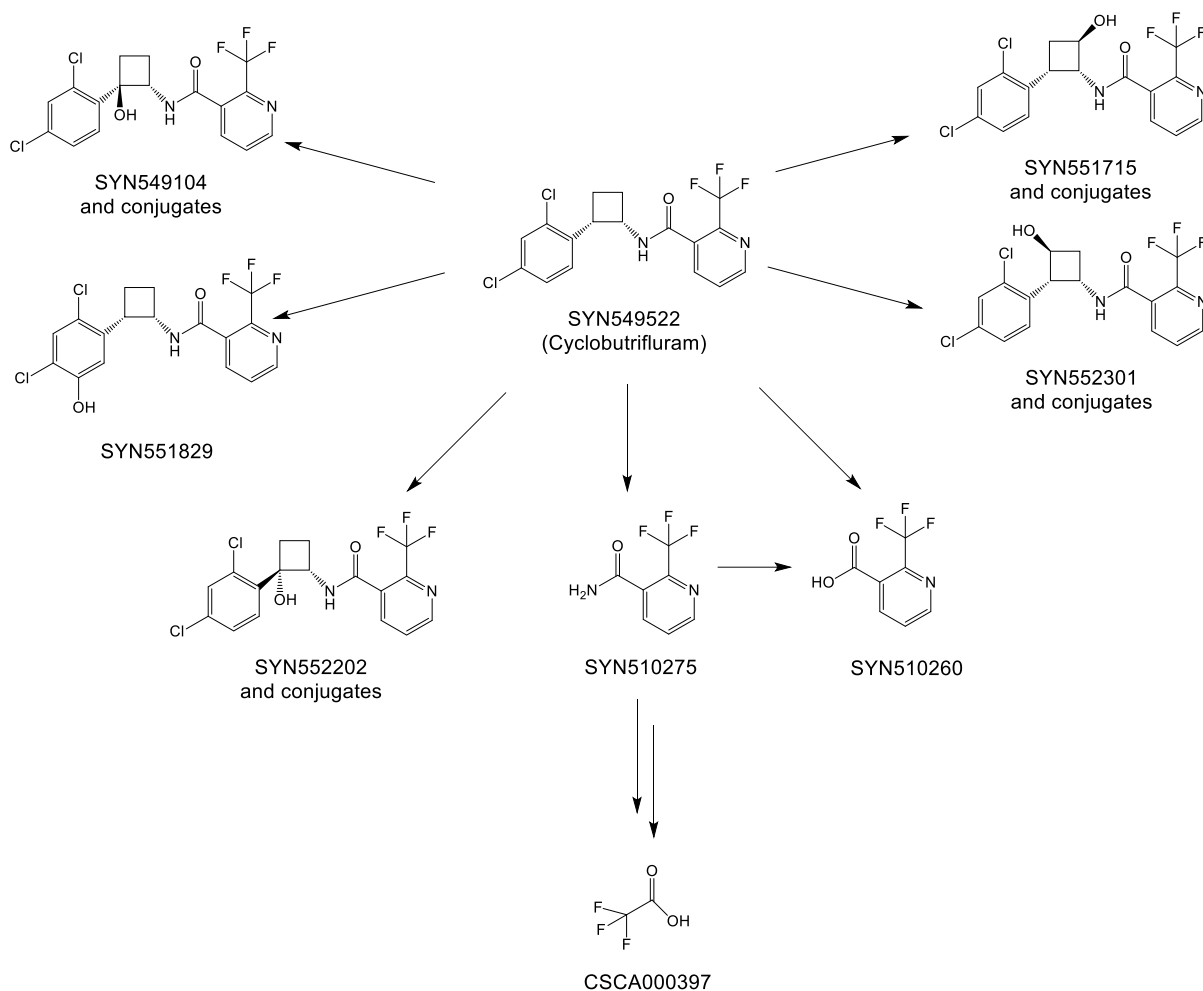
Plant commodities

Plant metabolism studies conducted on wheat, soybeans and potatoes with phenyl- $U-^{14}C$ -(PH) and pyridinyl- $2-^{14}C$ -(PY) labelled cyclobutrifluram that were provided by Syngenta, showed the metabolism and distribution of cyclobutrifluram in food and animal feed commodities.

In wheat, a seed treatment application of labelled cyclobutrifluram was made at 120.2 g a.c./ha for both labels. Parent cyclobutrifluram was identified in forage at 65–72% total radioactive residue (TRR) (0.493–0.539 mg/kg); in hay at 77% TRR (1.106–1.175 mg/kg); in straw at 23–34% TRR (0.944–1.442 mg/kg); and in grain at 4–27% TRR (0.002–0.007 mg/kg).

Of the other components in wheat matrices at >10% TRR, SYN549104 at 15–18% TRR (0.585–0.781 mg eq./kg); SYN552301 at 7–11% TRR (0.284–0.457 mg eq./kg); SYN552202 at 8–13% TRR (0.312–0.557 mg eq./kg); and SYN510275 at 24% TRR (0.973 mg eq./kg) were identified in straw, while both SYN510260 at 34% TRR (0.019 mg eq./kg) and trifluoroacetic acid (TFA) at 12% TRR (0.006 mg eq./kg) were identified in wheat grain.

Figure 1: Proposed metabolic pathway for cyclobutrifluram in wheat



In soybean, a seed treatment application of labelled cyclobutrifluram was made at ≥ 48.0 g a.c./ha for both labels. Parent cyclobutrifluram was identified in forage at 75–89% TRR (0.098–0.319 mg/kg); in hay at 67–89% TRR (0.468–0.497 mg/kg); in straw at 34–79% TRR (0.059–0.108 mg/kg); and in grain at 7–14% TRR (0.001–0.003 mg/kg).

Of the other components in soybean matrices at >10% TRR, SYN510275 was identified in forage at 10% TRR (0.013 mg eq./kg); in hay at 27% TRR (0.200 mg eq./kg); in straw at 22% TRR (0.038 mg eq./kg); and in grain at 34% TRR (0.013 mg eq./kg). SYN549104 was identified in grain at 7–12% TRR (0.001–0.003 mg eq./kg) and was also observed at $\leq 6\%$ TRR in the other three matrices. TFA was identified in straw at 24% TRR (0.042 mg eq./kg) and at $\leq 8\%$ TRR in the other three matrices.

The metabolism of labelled cyclobutrifluram was investigated in potatoes after a nominal 250 g a.c./ha single furrow application, followed by a 250 g a.c./ha application to the whole soil area of the same containers (actual total rates across the two applications 492.1–495.5 g a.c./ha). Parent cyclobutrifluram was identified in immature tubers at 77% TRR (0.021–0.024 mg/kg); in mature tubers at 61–68% TRR (0.018–0.022 mg/kg); in immature foliage at 57–63% TRR (0.299–0.319 mg/kg); and in mature foliage at 30–37% TRR (0.363–0.407 mg/kg).

Of the other components in potato matrices at >10% TRR, SYN549104 was identified in immature tubers at 10–11% TRR (0.003 mg eq./kg); in mature tubers at 11–12% TRR (0.003–0.004 mg eq./kg); in immature foliage at 16–19% TRR (0.090–0.091 mg eq./kg); and in mature foliage at 19–24% TRR (0.238–0.259 mg eq./kg), while SYN510275 was identified in immature foliage at 15% TRR (0.083 mg eq./kg) and in mature foliage at 20% TRR (0.278 mg eq./kg) and in immature and mature tubers at 5% TRR (0.001 mg eq./kg) and 8% TRR (0.003 mg eq./kg) respectively.

The metabolism of cyclobutrifluram was also investigated in rotational crops (spinach, spring wheat, and radish) after application to soil. Parent was observed in all matrices at all plant-back intervals, often at significant levels. A number of compounds were observed at >10% TRR. Of these compounds, SYN510275 and SYN549104 were major metabolites across a range of matrices.

Animal commodities

Animal metabolism studies conducted on hens and goats with phenyl-U-¹⁴C-(PH) and pyridinyl-2-¹⁴C-(PY) labelled cyclobutrifluram, showed the metabolism and distribution of cyclobutrifluram in animal commodities.

Parent cyclobutrifluram was a minor identified component in goat liver at 0.2–0.4% TRR (0.016–0.019 mg/kg), muscle at 0.7% TRR (0.001 mg/kg), and skin and fat at 2–3% TRR (0.006 mg/kg). Parent was not observed in goat kidney, milk, or in any hen matrix.

SYN510275 was observed in all goat matrices at >10% TRR: in milk at 90% TRR (0.250 mg eq./kg); liver at 66% TRR (5.803 mg eq./kg); kidney at 52% TRR (1.53 mg eq./kg); muscle at 88% TRR (0.942 mg eq./kg); and skin and fat at 42% TRR (0.144 mg eq./kg). It was also observed in all hen matrices at >10% TRR: in liver at 45% TRR (0.549 mg eq./kg); egg yolk at 45% TRR (0.318 mg eq./kg); egg white at 61% TRR (0.314 mg eq./kg); muscle at 83% TRR (0.227 mg eq./kg); and in skin and fat at 60% TRR (0.132 mg eq./kg).

Of the other metabolites observed at >10% TRR, SYN549104 was observed in milk at up to 11% TRR (0.004 mg eq./kg); in goat muscle at up to 12% TRR (0.010 mg eq./kg); and in liver and skin and fat at ≤9% TRR. It was observed in egg yolk at 9–11% TRR (0.060–0.062 mg eq./kg) and in egg white at 11–34% TRR (0.054–0.064 mg eq./kg).

A conjugated compound of metabolite SYN549104, Metabolite C (SYN549104 glucuronide) was observed in goat kidney at 14–25% TRR (0.289–0.420 mg eq./kg) and in goat muscle at up to 12% TRR (0.010 mg eq./kg). It was not observed in any hen matrix.

No other metabolite was observed at >10% TRR in both goat and hen matrices.

Residue definition

Plant commodities

Overall, the metabolic pathway is consistent between the three crops, with the primary component being parent. Based on the available information, parent cyclobutrifluram is considered to be the appropriate residue definition for commodities of plant origin for enforcement.

SYN549104 and SYN510275 were observed in all three primary crops at >10% TRR and were also dominant components in a number of matrices in the confined rotational study so will be included in the risk

assessment definition. Suitable analytical methods have been validated to determine residues of parent cyclobutrifluram and the metabolites SYN549104 (including conjugates) and SYN510275, in plant and processed commodities.

As the submitted analytical method GRM076.08A converts SYN549104 to its epimer SYN552202, which was observed itself at up to 13% TRR in wheat straw, this metabolite will also be included in the cyclobutrifluram risk assessment definition for plant commodities.

The sum of parent cyclobutrifluram, SYN510275, SYN549104 (free and conjugated), and SYN552202 and expressed as cyclobutrifluram, is therefore considered to be the appropriate residue definition for commodities of plant origin for dietary risk assessment, noting that SYN510275 and SYN549104 are covered by the health-based guidance values for cyclobutrifluram.

Animal commodities

Based on the available information, a residue definition of parent cyclobutrifluram and SYN510275 is considered to be appropriate for commodities of animal origin for enforcement.

Suitable analytical methods have been validated to determine residues of parent cyclobutrifluram, SYN510275 and SYN549104 (including conjugates such as Metabolite C) in animal commodities.

The sum of parent cyclobutrifluram, and the metabolites SYN510275 and SYN549104 (free and conjugated) and expressed as cyclobutrifluram, is considered to be the appropriate residue definition for commodities of animal origin for dietary risk assessment.

Residues in food and animal feeds

The proposed grazing restraint “DO NOT GRAZE TREATED TURF OR FEED TURF CLIPPINGS FROM ANY TREATED AREA TO POULTRY OR LIVESTOCK” will ensure there are no residues in animal feeds from the use of this product.

Residues in animal commodities

The recommended grazing restraint will also ensure there are no residues in animal commodities from animals following consumption of turf or turf clippings resulting from the use of this product.

Recommendations

The following amendments are required to be made to the APVMA MRL Standard (Table 5).

Table 5: Amendments to Table 3 of the APVMA MRL Standard

Amendments to Table 3	
Compound	Residue
Add:	
Cyclobutrifluram	<p>Commodities of plant origin for enforcement: Cyclobutrifluram</p> <p>Commodities of plant origin for dietary exposure assessment: Sum of cyclobutrifluram, 2-trifluoromethyl-nicotinamide (SYN510275), N-[(1S, 2R)-2-(2, 4-dichlorophenyl)-2-hydroxy-cyclobutyl]-2-(trifluoromethyl)pyridine-3-carboxamide (SYN549104, free and conjugated) and N-[(1S, 2S)-2-(2, 4-dichlorophenyl)-2-hydroxy-cyclobutyl]-2-(trifluoromethyl)pyridine-3-carboxamide (SYN552202) expressed as cyclobutrifluram</p> <p>Commodities of animal origin for enforcement: Sum of cyclobutrifluram and 2-trifluoromethyl-nicotinamide (SYN510275), expressed as cyclobutrifluram</p> <p>Commodities of animal origin for dietary exposure assessment: Sum of cyclobutrifluram, 2-trifluoromethyl-nicotinamide (SYN510275) and N-[(1S, 2R)-2-(2, 4-dichlorophenyl)-2-hydroxy-cyclobutyl]-2-(trifluoromethyl)pyridine-3-carboxamide (SYN549104, free and conjugated) expressed as cyclobutrifluram</p>

Work health and safety assessment

Occupational risk assessment is based on both acute exposure to the product and repeat exposure TREFINTI Turf Nematicide containing cyclobutrifluram at 450 g/L. Workers may be exposed repeatedly to the product from dermal and/or inhalation routes during mixing, loading, and application (M/L/A) and dermal exposure during post-application activities. Minor or accidental ocular exposure may also occur.

Health hazards

TREFINTI Turf Nematicide has low toxicity by oral, dermal, and inhalation routes; is a slight eye irritant; but is neither skin irritant nor a skin sensitiser.

Occupational exposure

Exposure during use

TREFINTI Turf Nematicide containing 450 g/L of cyclobutrifluram in a suspension concentrate (SC) formulation is intended for the control of nematodes in turf. TREFINTI Turf Nematicide will be available in 500 mL – 20 L HDPE/HDPE/PA or PET containers.

TREFINTI Turf Nematicide will be used by professionals and will be applied mechanically using either a ground rig with a low boom spray or a knapsack/backpack sprayer. The product will be used at the rate of 275 – 550 mL/ha for golf courses, sports fields, racetracks, parklands and commercial and residential lawns.

TREFINTI Turf Nematicide is to be applied up to 2 times at 550 mL/ha rate and up to 4 times at 275 mL/ha rate at intervals of 14–28 days where required.

A detailed dermal exposure risk assessment is not required in the absence of systemic toxicity effects in a repeat-dose dermal toxicity study at a limit dose of 1000 mg/kg bw/d. Cyclobutrifluram showed no signs of systemic toxicity in the rat 28-day semi-occlusive dermal exposure study. Further, as pharmacokinetic steady state was achieved in the study, a detailed dermal exposure risk assessment was not required. Given the proposed methods of application, only a small fraction of total exposure will occur via the respiratory route. Overall, there are no worker health and safety (WHS) exposure scenarios that may result in a risk that is unacceptable.

Exposure during re-entry or rehandling

As the repeat-dose dermal toxicity study showed no systemic toxicity effects at the limit dose of 1000 mg/kg bw/d, a re-entry exposure assessment was not considered necessary, and no re-entry statement will be required on the product label.

Public exposure

The product is not intended for use by the general public. Based on cyclobutrifluram's low toxicity and low dermal absorption, re-entry of members of the public onto treated turf is not of concern.

Exposure to cyclobutrifluram through food residues is not expected. There are currently no approved registrations for the use of cyclobutrifluram on food crops.

Recommendations

The following first aid instructions, safety directions and precautionary (warning) statements are recommended for the product label.

First aid instructions

First aid is not generally required. If in doubt, contact a Poisons Information Centre (phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor.

Safety directions

May irritate the eyes. Avoid contact with eyes. Wash hands after use.

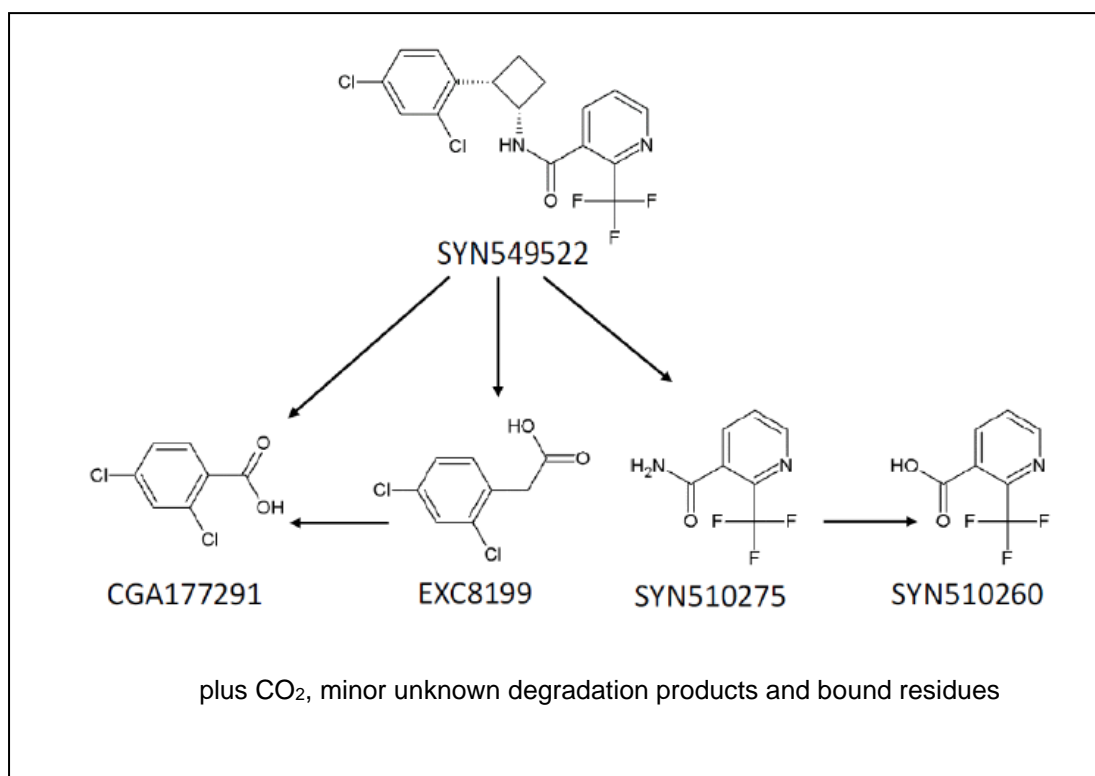
Precautionary (warning) statements/Restrictions/Re-handling statements

Not required.

Environmental assessment

Fate and behaviour in the environment

Figure 2: Proposed photo-degradation pathway in soil



Soil

A laboratory study under photolytic conditions showed that cyclobutrifluram degradation was faster in moist soil (DT₅₀ 14.7 days) than in dry soil (DT₅₀ 52.8 days). Three major degradation products of cyclobutrifluram (SYN549522) were identified in moist soil; the predominant product was SYN510275 (maximum of 47.7% AR), with other products CGA177291 and EXC8199 identified at lower levels (maxima of 14.0% and 11.5% AR respectively). In laboratory studies under dark aerobic conditions, degradation of cyclobutrifluram was slow with a geomean DT₅₀ of 456 days (6 soils). In field dissipation studies, model DT₅₀ values ranged from 27.1 to 248 days in cropped and bare soil plots (geomean DT₅₀ 64.1 days, 6 estimates), and from 86.4 to 89.5 days in two total systems in grassed areas (grass + thatch/sod + soil).

Freundlich adsorption coefficients (K_F) for cyclobutrifluram ranged from 3.39 to 9.53 L/kg (9 soils) with K_{FOC} values from 210 to 585 L/kg (mean K_{FOC} 333 L/kg) indicating moderate mobility in soil; sorption was dependent on 1/n values (mean 1/n 0.87) and was weakly correlated with the organic carbon concentration.

Water

Cyclobutrifluram was found to be hydrolytically stable at pH 4, 7, and 9 at temperatures of 50, 60, and 70°C. Cyclobutrifluram was found to hydrolyse under photolytic conditions, with degradation by direct photolysis in pH 7 buffer being relatively fast with a DT₅₀ of 11 to 24 days under summer sunlight (UK/US).

The routes and rates of degradation of [¹⁴C]-cyclobutrifluram were investigated in two water-sediment systems (sediments of silt loam and sand) under laboratory conditions. Aerobic degradation was investigated under dark and illuminated conditions, and anaerobic degradation was investigated under dark conditions. In the aerobic sediment systems, no difference was observed between dark and illuminated systems. Cyclobutrifluram dissipated relatively quickly from the water layer above the silt loam sediment (model DT₅₀ 21.7 to 25.3 days), but more slowly from water above the sand sediment (DT₅₀ 57.8 to 58.1 days). Total system degradation was slow in both test systems, ranging from 593 to 777 days (geomean DT₅₀ 697 days).

In the anaerobic water sediment test system, dissipation from the water layer was faster above the silt loam sediment (model DT₅₀ 94.1 days) than the sand sediment (DT₅₀ 161 days) and the whole system degradation was slow (DT₅₀ 676 to >1000 days).

Air

Standard modelling was undertaken to predict the atmospheric half-life of cyclobutrifluram through reaction with hydroxyl radicals. Based on a global annual average 24-hour concentration of 1.5×10^6 OH-radicals /cm³ and a 12-hour day, the atmospheric DT₅₀ was calculated to be 1.73 days.

Effects and associated risks to non-target species

Terrestrial vertebrates

Cyclobutrifluram has low acute toxicity to mammals (LD₅₀ >5000 mg a.c./kg bw, *Rattus norvegicus*) and birds (LD₅₀ >2000 mg a.c./kg bw, three species). In short-term dietary testing, continual exposure in the diet over 5 days did not result in toxicity to birds at the highest administered diet concentration of 5620 mg a.c./kg (LD₅₀ >1264 mg a.c./kg bw/d, *Colinus virginianus*).

Following long-term dietary administration in reproduction studies, there were no effects on two bird species (*Colinus virginianus*, *Anas platyrhynchos*) at the highest concentration tested (2013 mg a.c./kg diet); at this concentration, the lowest observed daily dose was for *Colinus virginianus* (NOEL 173 mg a.c./kg bw/d). In mammals, a 2-generation study with the rat (*Rattus norvegicus*) resulted in a NOEL of 43.1 mg a.c./kg bw/d. Risks for the proposed uses of TREFINTI Turf Nematicide to terrestrial vertebrates were determined to be acceptable.

The octanol-water partition coefficient for cyclobutrifluram (log K_{ow} of 3.2) indicates a potential for bioaccumulation. A food chain assessment indicated that any accumulated residues in earthworms or fish will not reach levels harmful to predators under the proposed conditions of use. Cyclobutrifluram has low potential for accumulation in mammalian and fish tissue; therefore, it is expected that there will be no biomagnification up the food chain.

Evaluation of reproduction data in several non-mammalian species did not reveal evidence of endocrine disrupting effects of cyclobutrifluram.

Aquatic species

Cyclobutrifluram is moderately toxic to fish with a lowest reported LC₅₀ of 11 mg a.c./L (*Pimephales promelas*; 4 species tested), and moderately toxic to aquatic invertebrates with the most sensitive EC₅₀ of 0.33 mg a.c./L based on shell deposition (*Cassostrea virginica*; 3 species tested). Cyclobutrifluram is moderately toxic to algae (4 species tested) with the most sensitive E_rC₅₀ being 9.5 mg a.c./L (*Raphidocelis subcapitata*). A single test on aquatic macrophytes resulted in no observed effects at the highest concentration tested (E_rC₅₀ >16 mg a.c./L, *Lemna gibba*). A protection statement is advised to identify the toxicity of cyclobutrifluram to aquatic invertebrates.

The soil metabolite SYN510275 was tested on one fish, one aquatic invertebrate and one algal species, and was not toxic at the highest tested concentration of 100 mg metabolite/L.

Early life stage testing of cyclobutrifluram on two fish species indicated decreased length/growth at 4.7 mg a.c./L (most sensitive NOEC of 1.9 mg a.c./L, *Pimephales promelas*).

Tests of chronic exposure on two species of aquatic invertebrates are available. Based on decreased length/growth, the most sensitive result was a No Observed Effect Concentration (NOEC) of 1.3 mg a.c./L (*Americamysis bahia*). Three acute (10 day) spiked sediment studies are available for sediment organisms. The most sensitive species was *Chironomus dilutes* with an LC₅₀ of 57.7 mg a.c./kg dry sediment.

Cyclobutrifluram is not considered to be bioaccumulative, with a whole fish BCF of 31 L/kg.

For the proposed uses of TREFINTI Turf Nematicide, acceptable risks were determined for all aquatic species except for acute risks to aquatic invertebrates. Refinement of risks to aquatic species were considered through runoff and spray drift assessments. Runoff risks were determined to be acceptable provided the product is not applied when a runoff event is expected soon after application. Spray drift buffer zones were determined not to be required for protection of aquatic organisms when boom sprayers are used with spray droplets no smaller than VERY COARSE size. As a result, only general runoff and spray drift restraints are required to mitigate risks to aquatic species.

Bees and other non-target arthropods

Cyclobutrifluram has low toxicity to adult bees (*Apis mellifera*) by contact exposure (LD₅₀ >200 µg a.c./bee) and acute oral exposure (LD₅₀ >72 µg a.c./bee), and low acute toxicity to bee larvae (LD₅₀ >30 µg a.c./larva).

Following chronic exposure to cyclobutrifluram, sub-lethal effects were observed at 3.39 µg a.c./bee/day in adult bees in a 10-day continuous feeding study (No Observed Effect Dietary Dose (NOEDD) 1.48 µg a.c./bee/day), while a treatment-related effect for adult emergence could not be excluded at the highest dose of 6.15 µg a.c./larva/day in bee larvae exposed to spiked diet over 4 days in a 22-day exposure test (NOEDD 2.46 µg a.c./larva/day). Chronic risks to adult bees and larvae could not be determined to be acceptable for proposed broadcast uses of TREFINTI Turf Nematicide, therefore protection statements are required for bees and other insect pollinators to mitigate chronic risks.

A representative SC formulation of cyclobutrifluram was not toxic to the indicator species for predatory or parasitic arthropods ($LR_{50} > 572$ g a.c./ha, *Typhlodromus pyri* and *Aphidius rhopalosiphii*) in Tier 1 (glass plate) laboratory toxicity tests. Risks for the proposed uses of TREFINTI Turf Nematicide to beneficial arthropods were determined to be acceptable, assuming direct contact exposure to fresh-dried residues on foliage or soil within the treatment area at the maximum use rate. No protection statements are therefore required for beneficial arthropods.

Soil organisms

Cyclobutrifluram has low acute toxicity to earthworms ($LC_{50 \text{ corrected}} > 500$ mg a.c./kg dry soil, *Eisenia andrei*). Chronic exposure tests using a representative SC formulation indicated low chronic toxicity (EC_{10} 129 mg a.c./kg dry soil, *Eisenia andrei*), with reduced reproduction observed at 212 mg a.c./kg dry soil.

Testing of the soil-dwelling mite *Hypoaspis aculeifer* using a flowable concentrate (FS) formulation showed no observed effects at the highest tested concentration of 414 mg a.c./kg dry soil.

Cyclobutrifluram had no adverse effects on soil nitrification or carbon transformation by soil microorganisms at the highest concentration tested, with a NOEC of 4.15 mg a.c./kg dry soil.

Risks for the proposed uses of TREFINTI Turf Nematicide to soil organisms were therefore determined to be acceptable, and no protection statements are required.

Non-target terrestrial plants

A representative SC formulation of cyclobutrifluram had low toxicity to non-target terrestrial plants in both pre-emergent exposure (seedling emergence tests) and post-emergent exposure (vegetative vigour tests). In both instances the ER_{25} or ER_{50} was > 900 g a.c./ha for 10 tested species. A screening level assessment for the proposed uses of TREFINTI Turf Nematicide considering a worst-case scenario of direct exposure at the maximum use rate indicated potential risks to non-target terrestrial plants; refinement of risks was considered through a spray drift assessment. Spray drift assessment indicated that buffer zones are not required for protection of non-target terrestrial plants. Therefore, no protection statements are required for non-target terrestrial plants.

Recommendations

In considering the environmental safety of the proposed use of the product TREFINTI Turf Nematicide, the APVMA had regard to the toxicity of the active constituent and its residues, including degradation products, in relation to relevant organisms and ecosystems.

Available information indicates that cyclobutrifluram is persistent in soil and sediment, but not in air, and is not bioaccumulative. The chronic toxicity of cyclobutrifluram is considered relevant for persistent substances, and data for aquatic organisms indicate cyclobutrifluram is moderately toxic. However, given it is not bioaccumulative in the aquatic environment cyclobutrifluram does not show ecotoxicity that indicates potential for damage to the environment with respect to aquatic organisms. Based on the outcome of the risk assessment, the APVMA can be satisfied that the proposed use of the product meets the environmental safety criteria when used according to the label directions.

Efficacy and safety assessment

Syngenta Australia Pty Ltd has applied to the APVMA for registration of the new product TREFINTI Turf Nematicide, containing 450 g/L cyclobutrifluram, as a Suspension Concentrate (SC) formulation for use as a Group N-3 nematicide and Group 7 fungicide to control plant parasitic nematodes in managed turf as a preventative or early curative treatment at 275-550 mL/ha (no more than 2 applications of 550 mL/ha or 4 of 275 mL/ha).

Proposed product use pattern

TREFINTI Turf Nematicide is intended for the control of Nematodes including Ring Nematode (*Macroposthonia* sp), Root-knot (*Meloidogyne* spp.), Southern Sting Nematode (*Ibipora lolii*), Sting (*Belonolaius longicaudatus*), Stubby (*Paratrichodorus minor*), Dagger (*Xiphinema* spp) Sheath (*Hemicycliophora* spp) Spiral (*Helicotylenchus* spp) in Turf

For Turf situation in golf (tees, greens, fairways) professional sports fields, racetracks, Parklands, commercial and residential lawns, the application rate is 275 – 550 mL/ha, up to 2 applications of at 550 mL/ha or 4 applications of 275 mL/ha.

Efficacy and target crop/animal safety

Ten Australian small plot, replicated trials conducted from 2019-2021 and two USA trials conducted in 2017 were submitted to demonstrate the efficacy and safety of TREFINTI Turf Nematicide (a 450 g/L cyclobutrifluram SC formulation) for the proposed use pattern.

The product was tested at the proposed label rates in addition to lower rates in the early trials. Trials were small plot trials of randomised complete block (RCB) design with four or five replicates applied to areas of turf with nematode problems. The trials included variety of nematodes: dagger, cyst, sheath, sting, spiral, ring, lance, root-knot nematodes, southern sting nematodes, and stubby root nematodes.

Efficacy was assessed as a numerical decrease in the nematode populations or as the percentage control achieved.

Samples (8, 9, or 12) were randomly taken within a plot to a depth of 80 mm with a 10 mm core and combined for each plot. Parasitic nematode species were extracted from a 200 g soil sample. Nematodes were extracted from soil for 2 days at 25-30°C using Whitehead tray or misting technique and counted and were identified to genus level. Statistical analyses were included for each trial and analysis was made using ANOVA, LSD ($p < 0.050$) using Fisher's Least Significant Difference (LSD) test.

For crop safety, turf colour and quality were assessed visually in the trials on couchgrass (*Cynodon dactylon*), hybrid couch varieties (*C. dactylon* x *C. transvaalensis*), bentgrass varieties (*Agrostis stolonifera*) and kikuyu (*Pennisetum clandestinum*). Turf quality was visually assessed on a 1–9 scale. Turf colour was measured on a 1–9 scale.

Efficacy

Efficacy was assessed as a numerical decrease in the nematode populations or as the percentage control achieved. The performance of TREFINTI was compared to a registered nematicide product and untreated controls. TREFINTI Turf Nematicide was tested at rates of 140, 250, 275, 550, and 1,100 mL/ha as a single application; two applications at 275 and 550 mL/ha; and four applications of 275 mL/ha at 28-day intervals in small plot trials conducted on multiple turf varieties located on golf courses or in turf nurseries.

Efficacy of TREFINTI Turf Nematicide as a preventative or early curative treatment for mixed populations of nematodes in managed turf was demonstrated when used at the proposed label rates of 275–550 mL/ha with repeat applications at 28 days.

Control achieved was similar to that obtained with the industry standard nematicide and ranged from 80–90%. In some trials control achieved was lower but was still comparable to that of the industry standard nematicide.

Crop safety

Safety was demonstrated at 2 x highest rate for preventative treatment or 1,100 mL/ha or 495 g a.c./ha assessed as turf colour and quality in the trials. TREFINTI was safe to use on couchgrass (*Cynodon dactylon*), hybrid couch varieties (*Cynodon dactylon* x *Cynodon transvaalensis*), bentgrass varieties (*Agrostis stolonifera*), and kikuyu (*Pennisetum clandestinum*) at up to 2 x 550 mL/ha.

Resistance management

TREFINTI Turf Nematicide (a 450 g/L cyclobutrifluram formulation) is a Group N-3 nematicide.

Recommendations

The data provided justifies the claims of efficacy against common plant parasitic nematode species found in turf. The data provided justifies the claims of safety for preventative or early curative treatment in turf.

Spray drift assessment

Regulatory Acceptable Levels (RALs) were used in the APVMA Spray Drift Assessment Tool (SDRAT), by each risk area, in order to calculate the appropriate spray drift buffer zones for TREFINITI Turf Nematicide.

Human health

A buffer zone to mitigate any potential bystander exposure is not considered necessary.

Residues and trade

In the animal transfer study provided by Syngenta, feeding cyclobutrifluram at 7 ppm in the diet gave a maximum residue of parent and SYN510275 metabolite of 0.250 mg/kg (in parent equivalents) in liver.

Cyclobutrifluram has not been considered by Codex. In addition, no overseas MRLs have been established for cyclobutrifluram.

The feeding level for residues of parent cyclobutrifluram and SYN510275 in liver (and other tissues) to be at the LOQ (0.03 mg/kg in parent equivalents) is 0.84 ppm. A RAL of 0.84 ppm is therefore appropriate for the spray drift assessment for protection of livestock areas with respect to international trade.

If a RAL of 0.84 ppm is used in the APVMA Spray Drift Risk Assessment Tool with a very coarse droplet size (as suggested on the label template) at the maximum label rate with a boom height 0.5 metre or lower, livestock buffer zones are not required.

Environment

Cyclobutrifluram has low toxicity to adult bees (*Apis mellifera*) by contact exposure ($LD_{50} > 200 \mu\text{g a.c./bee}$). Spray drift risks to bees are therefore considered to be acceptable and no buffer zones for pollinators are required.

Based on the aquatic RAL of 0.033 mg a.c./L (acute toxicity to aquatic invertebrates) spray drift risks were determined to be acceptable, and buffer zones were determined not to be required for protection of aquatic organisms.

Cyclobutrifluram has low toxicity to non-target terrestrial plants (pre-emergent and post-emergent exposure tests), with ER_{25} and ER_{50} values $> 900 \text{ g a.c./ha}$ for 10 tested species; spray drift assessment indicated that buffer zones are not required for protection of non-target terrestrial plants.

Table 6: Summary of RALs for TREFINTI Turf Nematicide

Sensitive area	Regulatory Acceptable Level	
	Level of active	Units
Bystander	N/A	g/ha
Livestock	0.84	ppm
Aquatic	33	µg/L
Pollinator	33333	g/ha
Vegetation	90	g/ha

Labelling requirements

READ SAFETY DIRECTIONS BEFORE OPENING OR USING



syngenta®

ACTIVE CONSTITUENT: 450 g/L CYCLOBUTRIFLURAM

GROUP **N-3** NEMATICIDE

For the control of Nematodes in Turf as per the Directions for Use

500 mL – 20 L

Syngenta Australia Pty Ltd
Level 1, 2 Lyonpark Road, Macquarie Park NSW 2113

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

APVMA Approval No: 91438/132224

SC

Formulation type
Suspension
Concentrate

®

DIRECTIONS FOR USE

Restrains

DO NOT apply with aircraft

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

DO NOT irrigate to the point of runoff for at least 3 days after application

DO NOT apply more than two consecutive applications of a Group N-3 nematicide

DO NOT apply more than 250 g a.c./ha (550 mL product/ha) in a single application, or more than a total of 500 g a.c./ha/year (1110 mL product/ha/year).

SPRAY DRIFT RESTRAINTS

Specific definitions for terms used in this section of the label can be found at apvma.gov.au/spraydrift.

DO NOT allow bystanders to come into contact with the spray cloud.

DO NOT apply in a manner that may cause an unacceptable impact to native vegetation, agricultural crops, landscaped gardens and aquaculture production, or cause contamination of plant or livestock commodities, outside the application site from spray drift. Wherever possible, correctly use application equipment designed to reduce spray drift and apply when the wind direction is away from these sensitive areas.

DO NOT apply unless the wind speed is between three and 20 kilometres per hour at the application site during the time of application.

DO NOT apply if there are hazardous surface temperature inversion conditions present at the application site during the time of application. Surface temperature inversion conditions exist most evenings one to two hours before sunset and persist until one to two hours after sunrise.

DO NOT apply by a boom sprayer unless the following requirements are met:

- Spray droplets are not smaller than a VERY COARSE spray droplet size category.
- Boom height no greater than 0.5m.

Situation	Disease	Rate	Critical Comments
Turf golf (tees, greens, fairways) professional sports fields, racetracks, Parklands, commercial and residential lawns	Turf Parasitic Nematodes including: Ring Nematode (<i>Macroposthonia</i> spp.), Root-knot (<i>Meloidogyne</i> spp.) Southern Sting Nematode (<i>Ibipora loli</i>), Sting (<i>Belonolaius longicaudatus</i>), Stubby (<i>Paratrichodorus minor</i>) Dagger (<i>Xiphinema</i> spp.) Sheath (<i>Hemicycliophora</i> spp.) Spiral (<i>Helicotylenchus</i> spp.) Cyst (<i>Heterodera</i> spp.) Sheath (<i>Hemicycliophora</i> spp.) Root lesion (<i>Pratylenchus</i> spp.)	275 – 550 mL/ha	<p>Apply TREFINTI® preventatively when conditions become favourable for root growth or in an early curative situation (after appropriate nematode extraction, identification, and counts).</p> <p>Wash application in with 3 to 6 mm of irrigation or rain within 24 hours of application.</p> <p>Apply up to 2 applications of TREFINTI® at 550 mL/ha or 4 applications of 275 mL/ha.</p> <p>Make repeat applications at 28 days if required.</p> <p>Best results will be obtained were TREFINTI® is used as part of an integrated program aimed at reducing overall nematode populations.</p> <p>Refer to Application section for detailed information.</p>

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

GENERAL INSTRUCTIONS

Mixing

TREFINTI® is a Suspension Concentrate (SC) formulation that mixes readily with water and is applied as a spray. Measure the required amount of TREFINTI®, add to the partly filled spray tank, and then add the remainder of the water.

Application

Applications should be in sufficient water volume to ensure that the product reaches the root zone. Where lower application volumes are used, washing in should commence as soon as possible after application. For best results, use very coarse droplets (e.g. Air Induction 08 nozzles) and a minimum application volume of 800 L/ha. Irrigate with 3 to 6 mm of water commencing within 1 hour of application. DO NOT irrigate to the point of run off.

Compatibility

TREFINTI® is compatible with a range of commonly used fungicides, insecticides, herbicides and fertilizers. Always consult your Syngenta representative before mixing TREFINTI® 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.

Nematicide Resistance Warning

GROUP	N-3	NEMATICIDE
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Although resistance in nematode populations has not been proven, repeated exclusive use of any product may lead to a reduction in control. Rotation with nematicides with a different mode of action is recommended. TREFINTI® should be used as part of an Integrated Pest Management (IPM) program to control nematodes. IPM programs using cultural practices, farm hygiene, planting of resistant varieties to reduce infestations caused by nematodes, monitoring or other detection methods, proper pest identification and rotation of nematicides with different modes of action will help prevent economic pest damage.

TREFINTI® may be subject to TREFINTI® resistance management strategies. To help prevent the development of resistance to TREFINTI®, use TREFINTI® in accordance with the current CropLife resistance management strategies. For further information contact your local Syngenta representative, CropLife Australia, farm chemical supplier, local Department of Agriculture or Primary Industries or consultant.

Integrated Pest Management

The possible effects of TREFINTI® on integrated pest management (IPM) strategies in the turf industry have not been studied at the proposed rates. However, based on available information, it cannot be ruled out that TREFINTI® may have an adverse effect on non-target beneficial turfgrass invertebrates where such IPM is practiced.

PRECAUTIONS

DO NOT graze treated areas or feed turf clippings from treated areas to animals including poultry.

Re-entry Period

DO NOT allow entry in treated areas until the spray has dried.

PROTECTION OF HONEY BEES AND OTHER INSECT POLLINATORS

A risk is identified for bees foraging in treated turf or in hives and non-target areas which are oversprayed. Bee brood development may be harmed by exposure to residues transported into the hive by foraging bees or overspray. DO NOT apply where bees from managed hives are known to be foraging, and weeds are in flower at the time of spraying.

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 treatment 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 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

May irritate the eyes. Avoid contact with eyes.

Wash hands after use.

FIRST AID

First aid is not generally required. If in doubt, contact a Poisons Information Centre (phone 131126) or a doctor.

SAFETY DATA SHEET

If additional hazard information is required refer to the Safety Data Sheet. For a copy visit our website at www.syngentaturf.com.au or www.syngenta.com.au or use the QR code on this label.

DISCLAIMER

This product complies with the specifications in its statutory registration. Implied terms and warranties are excluded. Syngenta's liability for breach of the express or any non-excludable implied warranty is limited to product replacement or purchase price refund. The purchaser must determine suitability for intended purpose and take all proper precautions in the handling, storage and use of the product including those on the label and/or safety data sheet failing which Syngenta shall have no liability.

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the SYNGENTA Logo and the PURPOSE ICON
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Acronyms and abbreviations

Acronyms and abbreviations Shortened term	Full term
ACCS/ACMS	Advisory Committee for Chemicals Scheduling/Advisory Committee for Medicines Scheduling
ac	Active constituent
ADI	Acceptable daily intake (for humans)
ai	Active ingredient
ANOVA	Analysis of Variance
ARfD	Acute reference dose
ATP	Adenosine triphosphate
bw	Bodyweight
CAR	constitutive androstane receptor
d	Day
DFU	Directions For Use
DT ₅₀	Time taken for 50% of the concentration to dissipate
EC ₅₀	Concentration at which 50% of the test population are immobilised
ED ₁₀	Concentration at which 10% of the population shows an adverse effect
E _r C ₅₀	Concentration at which the rate of growth of 50% of the test population is impacted
eq	equivalent
FS	Flowable Concentrate
g	Gram
GLP	Good laboratory practice
h	Hour
ha	Hectare
HDPE	High-density polyethylene
IPM	Integrated pest management
iv	Intravenous

Acronyms and abbreviations Shortened term	Full term
<i>in vitro</i>	Outside the living body and in an artificial environment
IUPAC	International Union of Pure and Applied Chemistry
ISO	International Organization for Standardization
kg	Kilogram
K _F	Freundlich adsorption coefficients
K _{FOC}	Organic carbon normalized Freundlich distribution 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
Log K _{OW}	Log to base 10 of octanol water partitioning co-efficient, synonym P _{OW}
LOQ	Limit of Quantitation – level at which residues can be quantified
LOAEL	Lowest Observed Adverse Effect Level
LSD	Fisher's Least Significant Difference
mg	Milligram
mL	Millilitre
MRL	Maximum residue limit
MSDS	Material Safety Data Sheet
MTD	Maximum Tolerated Dose
NOAEL	No observed adverse effect level
OC	Organic carbon
PAI	Purified active ingredient
PET	Polyethylene Terephthalate
Ph	Potential of Hydrogen - referred to as acidity or basicity
po	Oral
ppb	Parts per billion
ppm	Parts per million

Acronyms and abbreviations Shortened term	Full term
QSAR	Quantitative structure–activity relationship
RAL	Regulatory acceptable level
RCB	Randomised Complete Block
REI	Re-entry interval
s	Second
sc	Subcutaneous
SC	Suspension concentrate
SDRAT	Spray Drift Risk Assessment Tool
TFA	Trifluoroacetic Acid
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
TRR	Total radioactive residue
TTC	Threshold of toxicological concern
µg	Microgram
UV/VIS	Ultra-violet visible (UV-vis) spectroscopy
WHS	Worker Health and Safety

Glossary

Term	Description
Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration
Carcinogenicity	The ability to cause cancer
CAS	a unique and unambiguous identifier for a specific substance
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	Repels water
Leaching	Removal of a compound by use of a solvent
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

References

Agricultural and Veterinary Chemicals Code Act (1994) (Cth)

APVMA (2018). Spray Drift Risk Assessment Tool (SDRAT) – Version 1.0. Australian Pesticides and Veterinary Medicines Authority. <https://apvma.gov.au/node/28086>