Australian Government

Australian Pesticides and Veterinary Medicines Authority

Public Release Summary

on the evaluation of the new active constituent metarylpicoxamid in the product GF-4898 Fungicide

APVMA product number 93003

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This publication is available from the APVMA website.

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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 GF-4898 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 9 December 2025 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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Canberra ACT 2601, Australia

Phone: +61 2 6770 2300
Email: casemanagement@apvma.gov.au.

Further information

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

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

Further information on Public Release Summaries can be found on the APVMA website.

Introduction

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of GF-4898 Fungicide, and approval of the new active constituent, metarylpicoxamid.

Applicant

CORTEVA AGRISCIENCE AUSTRALIA PTY LTD.

Purpose of application

CORTEVA AGRISCIENCE AUSTRALIA PTY LTD has applied to the APVMA for registration of the new product GF-4898 Fungicide, containing 150 g/L, as an emulsifiable concentrate (EC) formulation of the new active constituent metarylpicoxamid.

Proposed claims and use pattern

For the control of Asian soybean rust in soybean.

Mode of action

Metarylpicoxamid is a quinone inside (Qi) inhibitor.

Overseas registrations

The active metarylpicoxamid is registered in Paraguay as Haviza™ Active for control of Asian Soybean Rust and other fungal diseases in crops, especially soybeans.

Chemistry and manufacture

Active constituent

The active constituent metarylpicoxamid is manufactured overseas. Details of the chemical name, structure, and physicochemical properties of metarylpicoxamid are listed below in Tables 1 to 2.

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

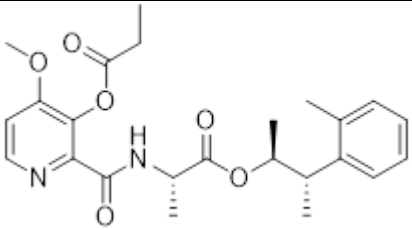
Common name (ISO):	Metarylpicoxamid
IUPAC name:	(2*S*,3*S*)-3-(2-Methylphenyl)butan-2-yl *N*-{[4-methoxy-3-(propanoyloxy)pyridin-2-yl]carbonyl}-*L*-alaninate
CAS registry number:	2376210-14-7
Molecular formula:	$C_{24}H_{30}N_2O_6$
Molecular weight:	442.5 g/mol
Structural formula:	

Table 2: Key physicochemical properties of the active constituent metarylpicoxamid

Physical form:	Powder
Colour:	White to light beige
Odour:	Odourless
Melting point:	89.5 – 92.5°C
Boiling point:	The initial onset of discoloration was at approximately 135 °C, becoming brown at approximately 220 °C and then appearing to boil at 256 °C.
Bulk density	0.65 g/mL for the poured bulk density; 0.72 g/mL for the tapped bulk density
Stability:	Metarylpicoxamid is expected to remain in compliance with its specifications for at least two years of storage under normal conditions and is unlikely to be adversely affected by the presence of metals or metal ions.
Safety properties:	Metarylpicoxamid is not considered highly flammable, auto-flammable, or explosive, and it has also no oxidising properties, indicating that it is a relatively safe chemical during transport and storage.
Solubility in water:	Essentially water insoluble: 3.6 mg/L in purified water; 3.1 mg/L in a pH 7 buffer solution
Organic solvent solubility:	Greater than 250 g/L in acetone, ethyl acetate, xylene and 1,2-dichloroethane 195 g/L in methanol 22 g/L in *n*-octanol: 0.86 g/L in *n*-hexane:
Dissociation constant (PK_a):	Two pK_a values were found for the purified active ingredient (PAI) The first one (pK_{a1}) was 2.05; and the second one (pK_{a2}) was 10.5
PH:	6.4 in a 1% water dispersion (oil-in-water emulsion) for the technical grade active ingredient (TGAI)
Octanol/water partition coefficient (K_{OW}):	Kow = 3.9 in pH 5, pH 7 or pH 9 buffer solutions
Vapour pressure:	4×10^{-7} Pa at 20 °C; 9×10^{-7} Pa at 25 °C for PAI
Surface tension	59.0 mN/m at 20°C for PAI (2.4 mg/L in purified water) 58.5 mN/m at 20°C for TGAI (2.4 mg/L in purified water)
UV/VIS absorption spectra:	See nested table below

Solution	Wavelength, λ_{max}	Molar extinction coefficient ε [L $mol^{-1}cm^{-1}$]
Acidic (pH 1.1)	243 nm 264 nm (shoulder)	8360 6030
Neutral (pH 5.3)	271 nm (shoulder)	2620
Basic (pH 13.0)	272 nm 340 nm	3390 11500

Formulated product

The product *GF-4898 Fungicide* will be manufactured overseas. Tables 3 and 4 outline some key aspects of the formulation and physicochemical properties of the product.

Table 3: Key aspects of the formulation of the product *GF-4898 Fungicide*

Distinguishing name:	GF-4898 Fungicide
Formulation type:	Emulsifiable concentrate (EC)
Active constituent concentration:	150 g/L metarylpicoxamid

Table 4: Physicochemical properties of the product *GF-4898 Fungicide*

Physical form:	Pale yellow/brown liquid with no particular odour
PH:	4.1 (1% w/v in water, an oil-in-water emulsion)
Specific density:	1.000
Viscosity:	19 mPa.s at 20°C
Emulsion characteristics:	< 1 mL cream after 2 hours, nil oil
Persistent foam:	8 mL foam after 1 minute in a 0.13% v/v oil-in-water emulsion; 5 mL foam after 1 minute in a 1.8% v/v oil-in-water emulsion
Safety properties:	The *GF-4898 Fungicide* product is a flammable, organic solution with a flashpoint of 91 °C and an autoflammability of 234 °C. It is not considered explosive, and it has also no oxidising properties
Storage stability:	The product should remain within specifications for at least 2 years, when stored under normal conditions.

Recommendations

The APVMA Chemistry section has evaluated the chemistry of the active constituent metarylpicoxamid and the associated product *GF-4898 Fungicide*, including the 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 formulated product (*GF-4898 Fungicide*) 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 *GF-4898 Fungicide*, and approval of the new active constituent metarylpicoxamid, are supported from a chemistry perspective.

Toxicological assessment

The submitted data package was sufficient to assess the toxicity of metarylpicoxamid and the formulated product, GF-4898 Fungicide.

Evaluation of toxicology

Chemical class

Metarylpicoxamid belongs to the picolinamide fungicides, and is a Fungicide Resistance Action Committee Group 21 fungicide (Quinone inside Inhibitors) inhibiting mitochondrial respiration in fungi by blocking electron transfer in the respiratory chain and binding to complex III (the bc1 complex) at the Qi site (the inner mitochondrial membrane). Florylpicoxamid is a related active constituent from the same class that is approved in Australia.

Pharmacokinetics

Systemic absorption following oral dosing of radiolabelled metarylpicoxamid was rapid in rats, mice and rabbits (T_{max} 0.5-3.1 hours). Estimated oral absorption ranged from 64.5- 92.2% in rats, depending on radiolabel and dose, and was sub-dose proportional between single oral doses of 10 and 100 mg/kg bw. The major route of elimination in rats was via bile (45-78% of the dose over 48 hours), followed by urine, with urinary elimination essentially complete by 24-48 hours. Residual tissue burden was negligible by 168 hours following dosing. There was no evidence of persistence or accumulation. Tissue distribution was widespread.

Metabolism was rapid and extensive *in vivo* and *in vitro*. Pre-systemic hydrolysis is expected to occur *in vivo*. Metarylpicoxamid was rapidly metabolised by propionic ester hydrolysis to form the primary metabolite X12644507, and then to other metabolites via pathways including ester hydrolysis, amide hydrolysis, O-demethylation, oxidation, glucuronidation, sulfate conjugation, and combinations. There were no human-specific major metabolites. Key metabolic enzymes were not identified.

Dermal absorption of metarylpicoxamid in the product GF-4898 Fungicide was 0.68% for the concentrated (neat) product (150 g/L metarylpicoxamid), 11% for 3 g/L spray (1:50 dilution), and 8.4% for 0.3 g/L spray (1:500 dilution) in a human skin *in vitro* dermal absorption study.

Acute toxicity (active constituent)

Metarylpicoxamid has low acute oral and dermal toxicity, and low to moderate inhalation toxicity. Based on the outcomes of *in vitro* and *in vivo* studies, metarylpicoxamid is not a skin irritant, is a slight eye irritant, and is a skin sensitiser (mouse LLNA).

Acute toxicity (product)

The formulated product (GF-4898 Fungicide) has moderate acute oral toxicity, low acute dermal toxicity, and low inhalation toxicity. Based on weight-of-evidence using mixture rules, *in vitro* studies, and *in vivo* studies,

GF-4898 Fungicide is considered a severe skin irritant, a severe eye irritant, and a skin sensitiser (mouse LLNA). The solvents in the formulation contribute to the severe skin and eye irritation of the product.

Repeat-dose toxicity

In short- and/or long-term repeat-dose toxicity studies with metarylpicoxamid in mice, rats, and dogs, the key adverse effects observed were reductions in bodyweight, bodyweight gain, food intake and/or food efficiency. Adverse effects on haematological parameters were also observed in rats. Non-neoplastic intestinal lesions (epithelial degeneration of the villous tip, villous atrophy, mucosal hyperplasia, luminal dilation, regenerative epithelial response) suggestive of a local effect were observed in mice in short- and long-term studies. This pro-carcinogenic effect (activation of enterothelial cell proliferation) occurred in mice in the absence of any evidence of carcinogenesis. This effect appears to be mouse-specific, based on the currently available data. This effect also has a threshold, non-genotoxic mode of action.

In a 21-day dietary study in rats, the LOAEL was 71 mg/kg bw/d (1000 ppm), based on decreased bodyweight gain, food intake, food efficiency, and non-regenerative decreases in red blood cell parameters. As the LOAEL occurred at the lowest dose tested, a NOAEL was not established.

In a 90-day dietary study in mice, the NOAEL was 93 mg/kg bw/d (700 ppm), based on intestinal lesions suggestive of a local effect at the next highest dose (283 mg/kg bw/d; 2100 ppm). The test substance was negative for micronucleus induction.

In a 90-day dietary study in rats, the NOAEL was 30 mg/kg bw/d (500 ppm), based on decreased bodyweight and non-regenerative decreases in red blood cell parameters at the next highest dose (82 mg/kg bw/d; 1500 ppm).

In a 90-day oral (capsule) study in dogs, the NOAEL was 30 mg/kg bw/d, based on decreased bodyweight and food consumption at the next highest dose (60 mg/kg bw/d).

Chronic toxicity and carcinogenicity

Metarylpicoxamid did not demonstrate carcinogenic potential in chronic toxicity and carcinogenicity studies in mice and rats.

In a 18-month dietary study in mice, the LOAEL for toxicity was 28 mg/kg bw/d (200 ppm), based non-neoplastic intestinal lesions. As the LOAEL occurred at the lowest dose tested, a NOAEL was not established. The NOAEL for carcinogenicity was 255 mg/kg bw/d (2100 ppm) in males and 664 mg/kg bw/d (4200 ppm) in females, the highest doses tested. Metarylpicoxamid did not have carcinogenic potential in mice under the conditions of this study. Although activation of enterothelial cell proliferation occurred in the mice, this was in the absence of any evidence of carcinogenesis. This effect was concluded to be mouse-specific, given the lack of evidence of a similar effect in other species.

In a 2-year dietary study in rats, the NOAELs for toxicity and carcinogenicity were 42.5 mg/kg bw/d (1000 ppm), the highest dose tested.

Reproductive and developmental toxicity

Metarylpicoxamid did not demonstrate reproductive or developmental toxicity potential in rats and/or rabbits.

In a 2-generation, reproductive toxicity study in rats, the NOAEL for parental/systemic toxicity was 28 mg/kg bw/d (500 ppm), based on reductions in body weight and food intake parameters in the P1/F1 generations at the next highest dose (89 mg/kg bw/d; 1500 ppm). The NOAEL for reproductive and offspring toxicity was 89 mg/kg bw/d (1500 ppm), the highest dose tested.

In a developmental toxicity study in rats, the NOAEL for maternal toxicity was 72 mg/kg bw/d (1000 ppm), based on decreased maternal bodyweight, particularly over gestational days 6-7 (correlated with reduced food intake over gestational days 6-7 and 7-8) at the next highest dose (174 mg/kg bw/d; 2500 ppm). The NOAEL for developmental toxicity was 174 mg/kg bw/d (2500 ppm), the highest dose tested.

In a developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 192 mg/kg bw/d (5,500 ppm), based on decreased maternal bodyweight gain, particularly over gestational days 7-10 (correlated with reduced food intake over gestational days 7-10, with an adverse reduction in food intake continuing through to gestational day 20) at the next highest dose (542 mg/kg bw/d; 17,000 ppm). The NOAEL for developmental toxicity was 542 mg/kg bw/d (17,000 ppm), the highest dose tested.

Genotoxicity

Metarylpicoxamid was examined for its genotoxic potential in an adequate range of *in vitro* and *in vivo* tests, and all were found to be negative.

The formulated product, GF-4898 Fungicide, was negative for genotoxicity in two *in vitro* genotoxicity studies (Ames test and mammalian cell micronucleus test).

Neurotoxicity/immunotoxicity

Metarylpicoxamid did not demonstrate neurotoxicity (motor activity, functional observational battery tests, neurohistopathology) or immunotoxicity (immune response to sheep red blood cells) in the 90-day dietary study in rats at the highest dose tested (82 mg/kg bw/d; 1500 ppm).

Mode of action (toxicology)

No studies provided.

Toxicity of metabolites and/or impurities

There are no metabolites of toxicological concern.

The technical grade active constituent proposed for approval in Australia does not contain impurities of toxicological concern.

Reports related to human toxicity

Products containing metarylpicoxamid have not yet been commercialised. No reports relating to human toxicity were provided.

Health-based guidance values and poisons scheduling

Poisons Standard

Metarylpicoxamid is included in Schedule 5 of the Poisons Standard, with no exceptions.

The product, GF-4898 Fungicide, contains 180 g/L N,N-dimethyldecanamide, which is in Schedule 6 of the Poisons Standard without a concentration cut-off. Therefore, GF-4898 Fungicide is a Schedule 6 product and requires the signal heading 'POISON' on the product label.

Health-based guidance values

Acceptable daily intake

An acceptable daily intake (ADI) of 0.4 mg/kg bw/d is established for metarylpicoxamid, based on a NOAEL of 42.5 mg/kg bw/d (the highest dose tested) in the 2-year rat combined toxicity and carcinogenicity study and an uncertainty factor of 100. The NOAEL from this study was considered suitable for establishing the ADI, as the effects seen in the mouse study were considered to be species-specific.

Acute reference dose

An ARfD for metarylpicoxamid was considered unnecessary on the basis of its low acute toxicity, and the absence of any developmental toxicity or other toxicologically relevant effect that would occur following acute exposure.

Recommendations

There are no objections on human health grounds to the approval of the new TGAC, metarylpicoxamid, when complying with the declaration of composition (DoC) provided by the applicant.

There are no objections on human health grounds to the registration of the product GF-4898 Fungicide containing 150 g/L metarylpicoxamid when used in accordance with the directions for use (DFU) and adhering to the recommended label statements.

Residues assessment

As part of the residues assessment of metarylpicoxamid, plant and target animal metabolism studies, supervised residue trial data for soyabean, analytical methodology, fate in storage and processing data, and residues in trade information were considered.

Metabolism

Plant Commodities:

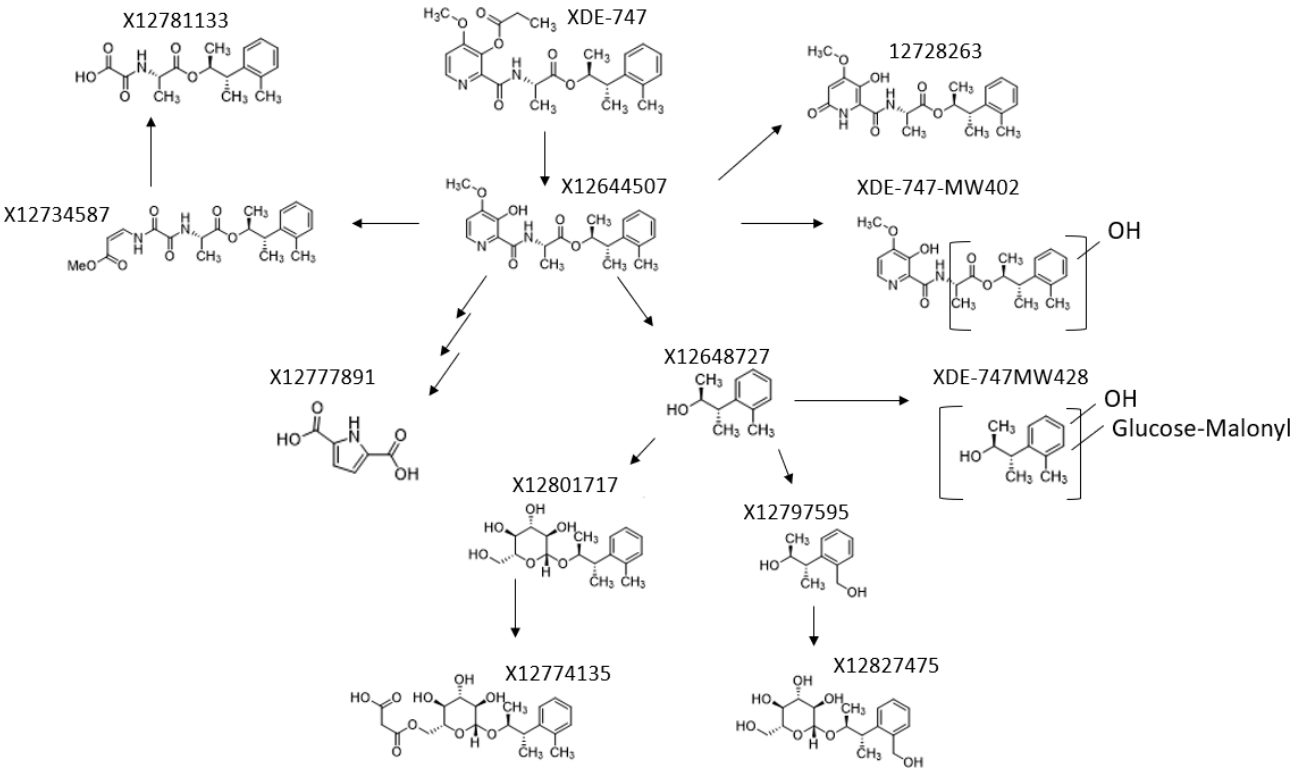
The metabolism of metarylpicoxamid (XDE-747) was investigated in soybean following foliar spray applications with [^{14}C] PH-XDE 747 (PH) or [^{14}C] PY-XDE 747 (PY) formulated as an *emulsifiable concentrate* at a target maximum seasonal rate of 180 g a.i./ha (3 x 60 a.i./ha). XDE-747 was extensively metabolized in soybean. In food and feed raw agricultural commodities (RACs, e.g., forage, hay, and mature seeds) the residue which approached or exceeded 10% TRR (total radioactive residue) was the parent metarylpicoxamid, referred as XDE-747 (8-51% TRR) whereas metabolites detected were X12644507 (3-9% TRR), a malonyl- glucose conjugate of X12648727 identified as X12774135 (1-10% TRR), and X12777891 (13% TRR, a naturally occurring compound in mature seeds only).

In mature seeds sampled 21 days after the final application, parent XDE-747 was detected at 16.13% TRR (0.006 mg/kg) in the PH label and at 7.59% TRR (0.011 mg/kg) in the PY label. All individual metabolite residues were <0.010 mg eq/kg in the mature seed except the naturally occurring X12777891 (0.020 mg eq/kg). A few minor metabolites (<10% TRR) detected in hay or immature forage include X12644507, and X12781133. Additionally, several low-level metabolites (<3% TRR) such as X12827475, X12797595, X12801717, X12648727, X12728263, and X12734587 were tentatively identified. Chiral analysis of the radiolabeled test material and representative soybean samples confirmed no significant changes in stereoisomeric ratio for XDE-747, and X12644507 throughout the study. The metabolic pathway of XDE-747 in soybean proceeds *via* several routes, including pyridine ring opening, hydrolysis, hydroxylation, oxidation, conjugation, and incorporation into plant natural products.

In addition, the metabolism of XDE-747 was investigated in confined rotational crops (lettuce, radish, oilseed rape, and wheat) with [^{14}C] PH-XDE 747 (PH) or [^{14}C] PY-XDE 747 (PY) applied to bare soil at a target maximum seasonal application rate of 180 g a.i./ha, with plant-back intervals (PBI) of 29, 120, and 300 days. In the rotational crops, the parent XDE-747 was not detected. XDE-747 was extensively metabolized to very low-level residues, the majority of which were unknown polar metabolites, and incorporation into starch (*ca.* 20-48% TRR) and oils (*ca*.38-44% TRR). None of the metabolites were greater than 0.01 mg eq/kg. The tentatively assigned, known metabolite X12728263 was the most abundant, representing 16% TRR (<0.01 mg eq/kg) in the wheat grain. X12764267 was tentatively identified in the 29-day, and 120-day wheat straw extracts in the phenyl label, at <10% TRR and <0.01 mg eq/kg. X12728845 was tentatively identified in the oilseed rape seed sample (PH label) at <10% TRR and <0.01 mg eq/kg.

A consistent metabolic profile for XDE-747 was observed following foliar applications to soybean, and in soil-treated confined rotational crops.

Figure 1: Example figure Metabolic pathway of metarylpicoxamid in soybean.



Animal commodities:

Metabolism of [^{14}C]-XDE-747 in livestock was studied in laying hens and lactating goat.

In the poultry metabolism study, laying hens were dosed with approximately 14.1 mg XDE- 747/kg dry feed for 14 days. Most of the radioactivity was excreted (89-93%). Less than 0.3% of the administered dose was recovered in edible tissues (0.004-0.448 mg eq/kg) and less than 0.2% in the eggs. Eggs reached a total radioactive residue plateau at 9-12 days, of 0.024-0.058 mg eq/kg. The highest radioactive residues levels were detected in the liver (0.448 mg eq/kg) and abdominal fat (0.125 mg eq/kg). The major metabolites identified were X12771309 (42% TRR or 0.065 mg eq/kg in skin with fat), X12644507 (62% TRR or 0.020 mg eq/kg in abdominal fat) and X12851221 (17% TRR or 0.013 mg eq/kg in abdominal fat). XDE-747 (<0.01 mg/kg) and many unidentified minor metabolites were also detected but did not exceed 10% TRR in any tissue. The metabolism of XDE-747 in poultry is similar to ruminant and rat.

In ruminant (goat) metabolism study, lactating goats were dosed with the Phenyl- or Pyridine-labeled XDE-747 at approximately 9.7 mg XDE-747/kg DM in the diet or 0.308-0.320 mg a.i./kg body weight/day for 7 days. Approximately 56% of the dose was recovered in urine and *ca* 29% in faeces. While a combination of approximately 10% of the dose was recovered from the GI tract, GI contents, blood, bile, and cage rinse.

No more than 0.03% of the dose was recovered in the milk and less than 0.16% dose in edible tissues. Milk reached a total residue plateau of *ca* 0.004 mg eq/kg within 1 to 4 days of dosing. The highest radioactive residues were detected in kidney at a level of 0.097-0.381 mg eq/kg. Residues in milk, muscle, and fat samples were less than <0.010 mg eq/kg after the last dose indicating no bioaccumulation potential.

No parent XDE-747 was detected in edible tissues over 0.002 mg eq/kg. The major residues in the liver are X12485473 (17.07% TRR, 0.021 mg eq/kg) and X12826475 (14.75% TRR, 0.018 mg eq/kg), while the major residues in the kidney are X12485473 (69.35% TRR, 0.264 mg eq/kg) and X12771593 (29.12% TRR, 0.028 mg eq/kg), which were identified by LC- MS/MS with authentic reference standards. Several low-level metabolites identified include X12764795, X12745065, XDE-747-MW-418, X12644507 and X12777919.

Chiral analysis of selected poultry and ruminant samples demonstrated that XDE-747 and X12644507 did not undergo any significant stereoisomeric interconversion.

The metabolism of XDE-747 in ruminant is consistent with that of rat studies.

Analytical methods and storage stability

Commodities of plant origin

All the methods followed a similar methodology. Generally, residues were extracted from homogenized samples (seed, forage, hay, stubble) with acetonitrile/water with QuEChERS citrate salts. After shaking and centrifugation, an aliquot of the acetonitrile layer is taken and cleaned up using dispersive SPE. Following this clean-up step, an aliquot is taken and diluted with water/acetonitrile + formic acid, prior to injection and quantitation via LC-MS/MS.

The method was appropriately validated with satisfactory validation recoveries for XDE-747 and X12644507 in lettuce, soya bean, corn and lemon. For each analyte the limits of detection (LOD) and quantitation (LOQ) were proposed at the initiation of the study at 0.003 mg/kg and 0.010 mg/kg, respectively. The average recoveries at each fortification level (10× LOQ and 100× LOQ) fell within the range of 70 to 110%. Relative standard deviations at each fortification level were all less than 20%.

Commodities of animal origin

The multi-residue analytical method based on QuEChERS was employed. Animal matrix samples (milk, muscle, kidney, fat, eggs, and honey) were extracted with a combination of acetonitrile and water, with the aid of QuEChERS citrate salts After shaking and centrifugation, an aliquot of the acetonitrile layer is taken and cleaned up using dispersive SPE. Following this clean-up step, an aliquot is taken and diluted with HPLC water, prior to injection and quantitation via LC-MS/MS.

Residues of XDE-747 and X12644507 were extracted from samples using a QuEChERS method, followed by a dispersive solid-phase extraction (d-SPE) clean-up procedure. Final determination is by high performance liquid chromatography coupled with positive-ion electrospray tandem mass spectrometry (LC-MS/MS).

The analytical method was satisfactorily validated at 10× LOQ and 100× LOQ to demonstrate the suitability of the method for the determination of XDE-747 and metabolite X12644507 in six animal matrices (milk, kidney, muscle, fat, eggs and honey) at a limit of quantification (LOQ) of 0.01 mg/kg.

Mean recoveries at the 100× LOQ level (1.0 mg/kg), for each analyte were considered acceptable if they were within the range of 70 – 110% with relative standard deviations (RSDs) of ≤15%.

The storage stability studies were conducted on plant and animal matrices for the parent and metabolites and were found to be satisfactory for the purpose of the risk assessment.

Residue definition

Plant Commodities

Soybean

Soya bean mature seed: The parent metarylpicoxamid (XDE-747) in soya bean seed accounted for 7-16% TRR, 0.011 mg/kg.

Metabolites: The metabolites X12644507 and X12774135 accounted for <10% TRR, <0.01 mg/kg and were not detected (ND) in soybean seeds (food commodity) at the intended PHI of 21 days (proposed harvest WHP).

Metabolite X12777891 is an endogenous compound, naturally occurring in soybeans. Low residue levels, up to 0.019 mg/kg in untreated seed samples and up to 0.026 mg/kg in treated seed samples, of X12777891 were observed in soybean seeds.

Soybean forage

In soya bean immature forage, the parent (XDE-747) component in the TRRs (%) ranged from 39-51% (0.397-0.567 mg eq/kg), whereas for metabolite X12644507 TRRs ranged from 6.70-7.08% (0.069-0.078 mg eq/kg) and for X12774135, TRRs were 9.70% (0.099 mg eq/kg).

Soybean hay

In soya bean hay, the parent (XDE-747) TRRs ranged from 22.47-28.54% (0.838-1.009 mg eq/kg), whereas for the metabolite X12644507, TRRs ranged from 6-6.65% (0.224-0.235 mg eq/kg) and for X12774135, TRRs were 10.35% (0.386 mg eq/kg).

Rotational crops

In *rotational* crops (canola, wheat, lettuce, radish), the parent XDE-747 was not detected. XDE-747 was extensively metabolized to very low-level residues, the majority of which were unknown polar metabolites and incorporation into starch (ca. 20-48% TRR) and oils (ca.38-44% TRR). None of the metabolites were greater than 0.01 mg eq/kg.

A consistent metabolic profile for XDE-747 was observed following foliar applications to soybean and in soil-treated confined rotational crops.

The residues data from soya bean field trials shows that residues of the parent (XDE-747) were <LOQ in soya bean seed, however detectable residues of the parent and metabolites X12644507, and X12774135 were found in animal feeds soya bean forage and hay/stubble.

The recommended residues definition for enforcement and dietary risk assessment for commodities of plant origin is Metarylpicoxamid (XDE-747).

Animal commodities

The metabolism studies in laying hen and goat showed markedly different residue profiles in terms of nature and magnitude of metabolites detected in these species.

Poultry

Poultry metabolism data shows that residues of the parent or metabolites (X12644507, X12771309, and X12851221) were detected in low amounts at a dosing rate of 10 mg/kg dry feed. Parent XDE-747 was poorly absorbed; it was nearly absent from the edible tissues and eggs, detected only in the PH-labeled abdominal fat at 0.66% TRR (0.001 mg eq/kg).

X12644507 was the most abundant metabolite in terms of %TRR (5-62%) in fats, though it never exceeded, 0.050 mg eq/kg in any tissue. It ranged from about 5-62% TRR in the fats. In other tissues and the eggs, X12644507 ranged from less than 1% TRR (≤0.001 mg eq/kg) in the liver and muscles up to about 5% TRR (0.001 mg eq/kg) in eggs. X12771309 was the only metabolite to exceed both 10% TRR and 0.050 mg eq/kg in any tissue or egg sample, ranging from 4.02% TRR (0.018 mg eq/kg) in the liver to 42.46% TRR (0.065 mg eq/kg) in the skin with fat. X12851221 ranged from 0.42% TRR (<0.001 mg eq/kg) in the breast muscle up to 16.05% TRR (0.012 mg eq/kg) in the abdominal fat, the only tissue in which it exceeded 10% TRR.

In soya bean seed meal (poultry feed), the parent residues (XDE-747) were not detected at the proposed GAP. Taking into account poultry metabolism and residues data, it is considered unlikely that residues of the parent or the metabolites will be present in edible poultry commodities from the proposed use.

Ruminant (lactating goat)

In a goat metabolism study, animals were dosed at ~10 ppm (dry feed) for seven days, no parent XDE-747 was detected in edible tissues except in the liver at 0.002 mg eq/kg. Residues in milk were <0.010 mg. eq./kg.

The main metabolites detected were X12485473 and X12826475 in kidney and liver.

For the metabolite, X12485473, the TRRs in kidney were up to 69% (0.264 mg eq. kg), whereas in liver, TRRs were up to 17% (0.021 mg eq. kg).

For the metabolite, X12826475, the TRRs in kidney were up to 24.54% (0.024 mg eq. kg), whereas in liver, TRRs were up to ~15% (0.021 mg eq. kg).

In lactating cow feeding study, residues of the parent were not detected in any treatment group dosed at 1, 10 and 20 ppm in tissues or milk/cream. The metabolites X12644507 and X12485473 were detected (0.05 mg/kg) in liver and kidney at 10 or 20 ppm dose.

Residues of X12644507 and X12485473 above the LOQ of 0.01 mg/kg were found in liver samples from cows in the 20 mg/kg treatment group (up to 0.011 and 0.017 mg/kg, respectively) and residues of X12485473 above the LOQ of 0.01 mg/kg were found in kidney samples from cows in the 10 mg/kg (up to 0.017 mg/kg) and 20 mg/kg (up to 0.038 mg/kg) treatment groups.

Residues of the parent or metabolites in tissues or the milk/by-products are unlikely to be detected when adjusted to the estimated dietary burden arising from the consumption of soya bean forage and straw following the proposed GAP.

Residues definition

The APVMA's health assessment report discussed the toxicological aspects of the parent metarylpicoxamid. The metabolite X12644507 was observed in soya bean hay, poultry fat and whole egg at significant levels. The toxicological aspects of X12644507 are covered by the parent as informed by the health assessment team.

For other significant metabolites X12485473, X12826475 and X12771593 observed in ruminant tissues, their toxicological aspects are not clearly understood. The TTC (Threshold of Toxicological Concern) approach is adopted in food safety assessment when there are limited chemical-specific toxicity data and can be used for substances with or without structural alerts for genotoxicity and for cancer and non-cancer endpoints. Therefore, for these metabolites dietary exposure assessment is conducted by employing TTC approach.

Residue definitions for dietary risk assessment are linked to an endpoint and point of departure that are specific to the compounds covered by the residue definition; therefore, metabolites that are assessed by TTC cannot be included in the residue definition for dietary risk assessment of a given compound.

It is therefore not necessary to consider these metabolites for the risk assessment definition for animal commodities for the current assessment. Should further uses be considered in the future, these conclusions may need to be re-evaluated.

Based on the available information, it is recommended that: for commodities of animal origin the residues definition for enforcement and dietary risk assessment be the: Sum of metarylpicoxamid and (2S,3S)-3-(2-methylphenyl)butan-2-yl N- {[3-hydroxy)-4-methoxypyridin-2-yl}-L-alaninate (X12644507), expressed as metarylpicoxamid.

Residues in food and animal feeds

Soyabean seed

In Australian trials at the proposed harvest WHP of 21 days, residues of metarylpicoxamid (as per the recommended residues definition for commodities of plant origin) in soya bean dried seeds following two foliar

applications of metarylpicoxamid (XDE-747) made at growth stages ranging from BBCH57-85 at ~1× the proposed rate was <LOD (n=3; LOD=0.003 mg/kg).

In Brazilian trials at the proposed harvest WHP of 21 days residues of metarylpicoxamid in soya bean dried seeds following three foliar applications of metarylpicoxamid (XDE-747) made at growth stages ranging from BBCH60-81 at ~1× the proposed rate was <LOQ (n=8; LOQ=0.01 mg/kg).

In Argentinian trials at the proposed harvest WHP of 21 days residues of metarylpicoxamid in soya bean dried seeds following three foliar applications of metarylpicoxamid (XDE-747) made at growth stages ranging from BBCH60-85 at ~1× the proposed rate was <LOQ (n=6; LOQ=0.01 mg/kg).

*Based on the available information, a permanent MRL of *0.01 mg/kg for metarylpicoxamid for VD 0541 Soya bean (dry) is considered appropriate for the proposed use in conjunction with a 21-day harvest WHP.*

Processing fraction (Oil)

Since residues of metarylpicoxamid (XDE-747) were <0.01 mg/kg in processed fractions such as refined or crude oil as shown in the processing study at exaggerated rates (4× the proposed rate), no separate MRL for edible oil is considered necessary for the proposed use.

Animal feed

The proposed grazing WHP is 14 days, however, residues data at 14 days is limited. Therefore, residues data at 21 days are considered here for this proposed use.

Soya bean forage

Residues of metarylpicoxamid in soya bean forage in Australian and overseas trials addressing the GAP are in rank order: <LOQ (4), 0.02, 0.03, 0.03, 0.04, 0.06, 0.10, 0.14, 0.14, 0.20, 0.29 and 0.31 mg/kg on a dry weight basis (n=15; STMR=0.04 mg/kg). The OECD calculator recommends an MRL (rounded) of 0.5 mg/kg for the proposed, use based on forage data set.

Stubble/Hay

Residues of metarylpicoxamid in soya bean stubble/hay in Australian and overseas trials addressing the GAP are in rank order: <LOQ (n=7),0.02, 0.03, 0.04, 0.04, 0.06, 0.13, 0.13, 0.15 and 0.19 mg/kg. The OECD calculator recommends an MRL of 0.3 mg/kg for stubble/hay (STMR=0.025 mg/kg).

At a PHI of 21 days, combined data set for forage and stubble/hay from Australian and overseas trials for estimation of MRL is in rank order: <LOQ (11), 0.02, 0.02, 0.03, 0.03, 0.03, 0.04, 0.04, 0.04, 0.06, 0.06, 0.10, 0.13, 0.13, 0.14, 0.14, 0.15, 0.19, 0.20, 0.29 and 0.31 mg/kg The OECD calculator recommends a combined MRL (rounded) of 0.5 mg/kg (STMR=0.03 mg/kg) for soyabean forage and fodder.

Noting most of the available residues data on animal feeds addresses 21-day grazing WHP, it is recommended that the proposed grazing WHP of 14 days should be amended to 21 days.

Based on the available information, a Table 4 entry of 0.5 mg/kg for AL 1265 for Soya bean forage and fodder for metarylpicoxamid is considered appropriate in conjunction with 21 days grazing WHP.

Animal commodities and MRLs

Ruminant: The animal feeding study demonstrates that at a dosing level of 1 ppm (parent), finite residues of the parent, or any other metabolite, are not expected to be detected in edible mammalian tissue, milk, or its by-products. The estimated maximum residues in animal feed after the proposed GAP is 0.3 mg/kg (parent).

Based on the animal feeding studies, quantifiable residues of the parent or metabolites are not expected in mammalian meat commodities, or their by-products, at the proposed GAP. It is recommended that animal commodity MRLs, as per the recommended residues definition for commodities of animal origin, be established at *0.02 mg/kg (parent plus metabolite X12644507, based on the validated analytical method in mammalian tissue or milk) for Edible offal (mammalian, MO 0105); Meat (mammalian, MO0105); and Milks (ML 0106) be established for the proposed use.

For poultry, since parent residues were not detected in soya bean meal, it is expected that residues of the parent or metabolites would not be detected in poultry meat or eggs, after the proposed use. Nevertheless, based on the validated analytical method and residue study in poultry, the following MRLs at *0.02 mg/kg for poultry commodities: Eggs (PE0112), Poultry, edible offal of (PO 0111) and Poultry meat (PM 0110) are recommended.

Crop rotation

The metabolism of XDE-747 was investigated in rotational crops (lettuce, radish, oilseed rape and wheat) with [14C] PH-XDE 747 (PH) or [14C] PY-XDE 747 (PY) applied to bare soil, at a target maximum seasonal application rate of 180 g a.s./ha, and with plant-back intervals (PBI) of 29, 120 and 300 days.

In the rotational crops, the parent XDE-747 was not detected. XDE-747 was extensively metabolized to very low-level residues, the majority of which were unknown polar metabolites, and incorporation into starch (ca. 20-48% TRR) and oils (ca.38-44% TRR). None of the metabolites were greater than 0.01 mg eq/kg. The tentatively assigned known metabolites, X12728263 was the most abundant, representing 16% TRR (<0.01 mg eq/kg) in the wheat grain. X12764267 was tentatively identified in the 29-day and 120-day wheat straw extracts in the phenyl label, at <10% TRR and <0.01 mg eq/kg. X12728845 was tentatively identified in the oilseed rape seed sample (PH label) at <10% TRR and <0.01 mg eq/kg.

A consistent metabolic profile for XDE-747 was observed following foliar applications to soybean and in soil-treated confined rotational crops.

Conclusion on rotational crop residues

The residues of the parent compound or its metabolites are based on the confined rotational crop study at the proposed rate (180 g ai/ha total seasonal rate), and are expected to be <0.01 in rotational crops (for both food and animal feed commodities). Therefore, a plant back interval for managing residues in succeeding crops are not considered necessary for the proposed use.

Residues in animal commodities

Soya bean forage can form up to 100% of the diet of the cattle (beef) and 40% of the diet of dairy cattle, the estimated dietary burden resulting from the proposed use is presented below.

BEEF CATTLE - for MRLs							
Commodity	CC	Residue (mg/kg)	Basis	DM (%)	Residue dw (mg/kg)	AU Diet content (%)	AU Residue Contribution (ppm)
						AU	AU
Soybean forage	AL	0.3	HR	100	0.3	100	0.3
Total						100	0.3

Ruminant: The estimated maximum residues in animal feed after the proposed GAP is 0.3 mg/kg (parent). The animal feeding study demonstrates that at a dosing level of 1 ppm (parent), finite residues of the parent or any other metabolite are not expected to be detected in edible mammalian tissue or milk or its by-products.

Based on the animal feeding studies, quantifiable residues of the parent or metabolites are not expected in mammalian meat commodities, or their by-products, at the proposed GAP It is therefore recommended that animal commodity MRLs, as per the recommended residues definition for commodities of animal origin, be established at *0.02 mg/kg (parent plus metabolite X12644507, based on the validated analytical method in mammalian tissue or milk) for Edible offal (mammalian, MO 0105); Meat (mammalian, MO0105); and Milks (ML 0106) be established for the proposed use.

For poultry, since residues of the parent in soya bean meal were not detected, it is expected that residues of the parent or metabolites would not be detected in poultry meat or eggs after the proposed use. Nevertheless, based on the validated analytical method and residue study in poultry, the following MRLs at *0.02 mg/kg for poultry commodities: Eggs (PE0112), Poultry, edible offal of (PO0111) and Poultry meat (PM0110) are recommended.

Dietary risk assessment

The chronic dietary exposure to metarylpicoxamid 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 2011-12 National Nutritional and Physical Activity Survey. The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for metarylpicoxamid is equivalent to <1% of the ADI. Exposure to the metabolites (X12485473, X12826475 and X12771593) observed in livestock not covered by

the ADI would also be acceptable (<10% of TTC) using a Threshold of Toxicological Concern[1] (TTC) approach for a Cramer class III structure (TTC = 1.5 µg/kg bw/day).

It is concluded that the chronic dietary exposure of metarylpicoxamid 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 with 97.5th percentile food consumption data derived primarily from the 2011-12 National Nutritional and Physical Activity Survey. NESTI calculations are conservative estimates of short-term exposure (24 hour period) to chemical residues in food.

The ARfD for metarylpicoxamid is considered to be unnecessary due to its low oral toxicity and the absence of any developmental toxicity after a single dose. Thus, acute dietary exposure assessment is considered unnecessary.

Recommendations

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

Table 5: Amendments to the APVMA MRL Standard

Amendments to Table 1			
Compound		**Food**	**MRL (mg/kg)**
Add:			
Metarylpicoxamid			
MO	0105	Edible offal (mammalian)	*0.02
PE	0112	Eggs	*0.02
MM	0095	Meat (mammalian)	*0.02
ML	0106	Milks	*0.02
PO	0111	Poultry, Edible offal of	*0.02
PM	0110	Poultry meat	*0.02
VD	0541	Soya bean (dry)	*0.01

[1] European Food Safety Authority (EFSA) Guidance document on Threshold of Toxicological Concern approach in food safety assessment, EFSA website, accessed June 2025

Amendments to Table 1		
Compound	**Food**	**MRL (mg/kg)**
Amendments to Table 3		
Compound	**Residue**	
Add:		
Metarylpicoxamid	Commodities of plant origin for enforcement and dietary exposure assessment: Metarylpicoxamid (XDE-747)	
	Commodities of animal origin for enforcement and dietary exposure assessment:-Sum of metarylpicoxamid and (2S,3S)-3-(2-methylphenyl)butan-2-yl N- {[3-hydroxy)-4-methoxypyridin-2-yl}-L-alaninate (X12644507), expressed as metarylpicoxamid	
Amendments to Table 4		
Compound	**Animal feed commodity**	**MRL (mg/kg)**
Add:		
Metarylpicoxamid		
	Soya bean forage and fodder	0.5

Assessment of overseas trade aspects of residues in food

Potential risk to trade

Soya bean is not considered a major trade commodity and quantifiable residues are not expected to arise in animal products (major trade commodities) produced from consumption of treated animal feed as a result of the proposed use. The risk to international trade associated with the proposed use is considered to be low.

Work health and safety assessment

Occupational risk assessment is based on both acute exposure to the product formulation and repeat exposure to the active constituents. Workers may be exposed repeatedly to the product through the 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

GF-4898 Fungicide has moderate acute, oral toxicity, low dermal, and inhalation toxicity, severe skin and eye irritation potential, and is a skin sensitiser. The solvents in the formulation contribute to the severe skin and eye irritation of the product.

Occupational exposure

GF-4898 Fungicide, containing 150 g/L metarylpicoxamid in an emulsifiable concentrate (EC) formulation, is intended for use as a fungicide in soybeans. The product is intended for professional use and will be applied mechanically by ground boom to crops, with no more than 3 sprays per crop, applied at 14-day intervals. Therefore, the pattern of exposure is considered to be of short- to intermediate-term duration.

The point of departure (POD) used for the occupational exposure scenarios was the same as the NOAEL for the 2-year combined toxicity and carcinogenicity study in rats, 42.5 mg/kg bw/day. This is the highest dose tested without adverse effects that may be relevant to occupational exposure scenarios. Given the likely duration of exposure in the various occupational exposure scenarios, this point of departure is considered to be conservative.

As GI absorption was greater than 80% in rat metabolism studies (range 64.5-92.2%), no adjustment of the NOAEL was required for extrapolation from oral to systemic exposure. In the absence of inhalational absorption data, a default value of 100% for inhalational absorption was used (EFSA 2014). A dermal absorption value of 0.7% was used for the neat product (for mixing/loading) and 8.4% was used for the spray dilution (for application). These values were obtained from a human skin *in vitro* dermal absorption study using the formulated product neat and diluted 1:500 (equivalent to label dilution rate).

Exposure during use

The US EPA Occupational Pesticide Handler Exposure Calculator (OPHEC) was used to estimate worker exposure during M/L/A (US EPA 2021a). Margins of Exposure (MOEs) were calculated by dividing PODs by the corresponding exposure estimates.

MOEs ≥ 100 were considered acceptable. This value is based on a 10-fold uncertainty factor (UF) for intra-species and 10-fold UF for inter-species differences in susceptibility to effects.

Acceptable MOEs were found with all endpoints selected for users complying with the recommended safety directions while handling GF-4898 Fungicide according to the proposed directions for use.

Exposure during re-entry or rehandling

Workers performing post-application activities in soybean crops may be exposed to metarylpicoxamid residues from dermal contact with foliage. Re-entry exposure for workers undertaking activities associated with soybean maintenance was estimated using the US EPA Occupational Pesticide Re-entry Exposure Calculator (OPREC) (2021b).

Acceptable MOEs were found on day 0 (of application) for workers conducting all post-application activities. There is no requirement to wear specific protective equipment. However, based on the acute toxicological properties of the active and product, a re-entry restriction is recommended.

Public exposure

Bystander risk from spray drift

Application of GF-4898 Fungicide by ground boom may lead to unintended bystander exposure via chemical spray drift. This may be in the form of a single, random exposure, or repeat exposures of residents who reside adjacent to areas being treated with the product. Risks from spraying activities were estimated based on potential risks to toddlers (as the most sensitive sub population) using the APVMA (2019) Spray Drift Risk Assessment Tool (SDRAT).

Assessment was conducted against the oral NOAEL of 42.5 mg/kg, using a dermal absorption factor of 8.4%, which was taken from an *in vitro* dermal absorption study with human skin using a 0.3 g/L diluted aqueous spray (equivalent to label dilution rate). The resulting RALs (regulatory acceptable levels) were 0.019 and 0.025 mg/cm^2 or 1940 and 2483 g/ha for 1- to 2-year-old and 2- to 3-year-old toddlers, respectively.

Results from the APVMA Spray Drift Risk Assessment Tool indicate that no buffer zones are required for mechanical ground spraying of soybean crops with boom heights of 1.0 m or lower for bystander areas

Recommendations

The following first aid instructions, safety directions, restraints and re-entry statements are recommended for the product label. The safety directions manage the risks associated with the acute hazards of the product (moderate oral toxicity, severe skin and eye irritation, skin sensitisation) and repeat exposure with occupational use.

First aid instructions

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 0800 764 766. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

Safety directions

Harmful if swallowed. Will damage eyes and skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If clothing becomes contaminated with product, remove clothing immediately. If product on skin, flush with water for at least 20 minutes. Take care to avoid hypothermia. If product sprayed in mouth, rinse mouth with water. When using together with other products, consult their label safety directions. When opening the container and preparing spray (closed system), wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow-length chemical-resistant gloves, face shield and chemical resistant footwear. When using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing). Wash hands after use. After each day's use, wash gloves, face shield and contaminated clothing. Do not re-use footwear until thoroughly aired.

Restraints

DO NOT use open mixing and loading.

DO NOT apply more than three (3) applications per season.

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

DO NOT apply unless the wind speed is between three (3) and twenty (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 aircraft.

Boom sprayers

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

• Spray droplets are not smaller than a MEDIUM spray droplet size category.

Re-entry statements

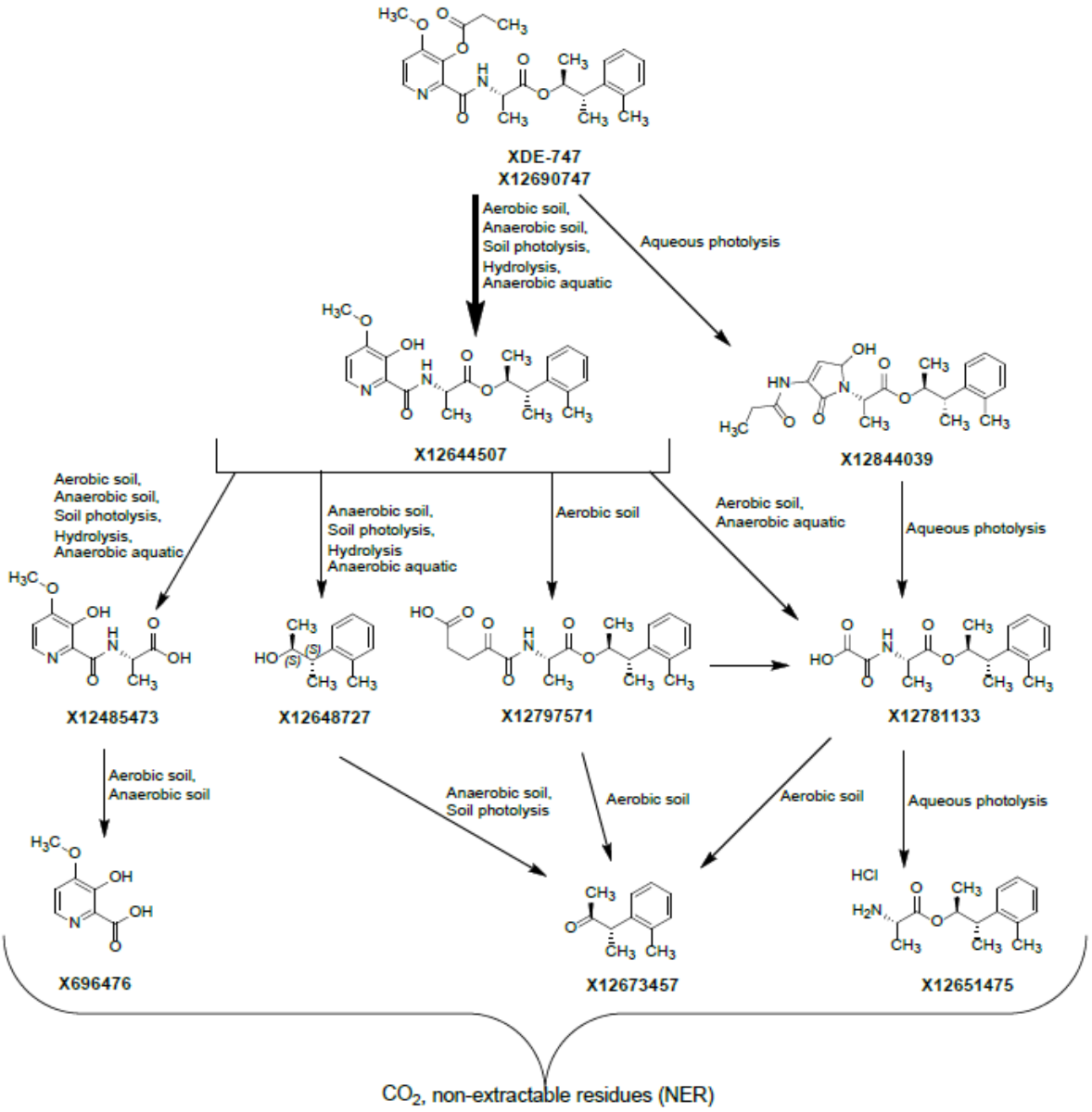
DO NOT enter treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

Environmental assessment

Fate and behaviour in the environment

The overall route of degradation in the environment within different matrices (aerobic and anaerobic soil and aquatic) and via different mechanisms (microbial, hydrolysis, photolysis) is depicted in Figure 2 below:

Figure 2 : Route of degradation of metarylpicoxamid in the environment



Soil

In a soil photolysis study, the DT_{50}s of metarylpicoxamid under dark and irradiated conditions were 8.4 and 5.8 hours respectively.

Under aerobic conditions in soil (n = 4), metarylpicoxamid quickly degraded to form a major metabolite, X12644507 (49.2-83.4% AR). Subsequently, X12485473 (5.7-14.5% AR) was formed from the pyridine labelled X12644507, which further degraded to X696476 (6.3-31.4% AR). Metabolite X12797571 was also formed from X12644507, and further degraded to form X12781133 and other minor products. Following ester hydrolysis, the phenyl moiety further degraded to multiple volatile degradation products consisting of small non-polar compounds such as X12673457. Finally, non-extractable residues (16.7-55.8% AR) and mineralization to CO_2 (4.7-62.7% AR) were the terminal degradation products of metarylpicoxamid in soil. Metarylpicoxamid rapidly degraded in soil under aerobic conditions (DT_{50} 0.18-0.48 days; following first order kinetics in 3 soils and biphasic in one soil), while its major metabolite X12644507 had a moderate degradation rate (DT_{50} 13.8-58 days; following first order kinetics in one soil and biphasic in 3 soils).

Under anaerobic conditions in soils (n = 4), the initial transformation of metarylpicoxamid to X12644507 was observed via hydrolysis (51.8-73.5% AR). Other major transformation products observed were X12485473 (22.6-52.2% AR), X12648727 (23.2-37.6% AR) and X12673457 (8.7-12.8% AR). Metarylpicoxamid rapidly degraded under anaerobic conditions in soil (DT_{50} 0.14-0.63 days, first order kinetics), while the metabolites were more persistent, i.e. X12644507 (DT_{50} 76-122 days, n = 2) and X12648727 (DT_{50} 47-95 days, n = 3).

In soil mobility studies, Freundlich adsorption coefficients (K_F) for metarylpicoxamid were in the range of 4.2-23 L/kg and K_{FOC} values ranged from 84 to 499 L/kg (n = 7). Metarylpicoxamid's sorption was slightly concentration dependent (mean 1/n = 0.90) and correlated with organic carbon (OC); the extrapolated K_F for 1% OC soil was 3.6 L/kg. In the same soils, the metabolite X12644507 was more strongly bound with K_F values in the range of 12-84 L/kg and K_{FOC} values ranging from 497 to 1657 L/kg (n = 7). The sorption of X12644507 was not concentration dependent (mean 1/n = 0.99) but was correlated with the OC; the extrapolated K_F for 1% OC was 9.5 L/kg.

Water

Hydrolysis of radiolabelled metarylpicoxamid was studied in the dark at 10, 25, and 40ºC in sterile aqueous buffered solutions at pH 2, 4, 7 and 9 for 41 days. Metarylpicoxamid was very stable in pH 4 buffer, with 66.9-64.6% AR of the radioactivity in the parent compound remaining at the end of the study at 25°C. The half-lives of metarylpicoxamid were 6.3, 68, 42 and 0.93 days at pH 2, 4, 7 and 9, respectively at 25°C. The major transformation products detected were X12644507 (maximum 85.7% AR at pH 2 and 40°C, 10 DAT); X12648727 (maximum 92.3% AR at pH 9 and 40°C, 41 DAT) and X12485473 (maximum 90.3% AR at pH 9 and 40°C, 41 DAT). Degradation fits for X12644507 were largely unacceptable because no decline was observed by the end of the study.

In an aqueous photolysis study performed at pH 4 (the most stable level of pH from hydrolysis results), the quantum yield of metarylpicoxamid was calculated as 6.55×10^{-2} molecules degraded/photon. The predicted environmental DT_{50} derived from the calculated quantum yield was determined to be 0.74 day at 40°N latitude in summer sunlight, and the expected DT_{90} was 2.46 days.

An aerobic biotransformation study of phenyl- and pyridyl-labelled forms of metarylpicoxamid was undertaken in two water/sediment river systems. Degradation proceeded via hydrolysis of the pyridine propyl ester moiety to form metabolite X12644507. Metarylpicoxamid rapidly degraded under both systems with half-lives <1.3 day in both water and the total system. Mineralisation was at a maximum of 24% AR after 100 days, while non-extractable residues in sediment ranged from 11-29% AR after 100 days. The major transformation product detected in both the water and sediment phases was X12644507 (maximum 30% AR in the water phase after 1 day; maximum 68% AR in the sediment phase at the 7th DAT; maximum 81% AR in the total system at the 7th DAT). The metabolite X12673457 was observed at maximum 10% AR at 1st day in the water phase and at maximum 16% AR in the total system. The half-lives of X12644507 in the water, sediment and total system ranged from 4.6-7.7 days, 169-351 days and 116-121 days, respectively.

An anaerobic biotransformation study of phenyl- and pyridyl-labelled forms of metarylpicoxamid was undertaken in two water/sediment river systems. Metarylpicoxamid rapidly degraded under both systems with half-lives <0.5 days in both water and the total system. Mineralisation was not significant (maximum 5.1% AR after 100 days) while non-extractable residues in sediment ranged 20.8-66% AR after 100 days. The major transformation product detected in both the water and sediment phases was X12644507 (maximum 64% AR in the water phase at 1 DAT; maximum 52.7% AR in the sediment phase at the 44th DAT; maximum 81.6% AR in the total system at the 30th DAT). In the phenyl-labelled samples, the metabolite X12648727 was observed in the water phase (maximum 17.7% AR at 3rd day), sediment phase (maximum 9.6% AR at 100th day) and total system (maximum 22.1% AR). The half-lives of X12644507 in the water, sediment and total system ranged 4.7-8.0, 68.3-233 and 77-80 days, respectively.

Air

The half-life in air was modelled using a standard approach. The rate constant for metarylpicoxamid reaction with OH radicals is 24 × 10^{-12} cm^3/mol/second and the atmospheric half-life is calculated to be 0.44 days (12-hour day). The rate constant for X12644507 reaction with OH radicals is 29 × 10^{-12} cm^3/mol/second and the atmospheric half-life is calculated to be 0.37 days (12-hour day).

Effects and associated risks to non-target species

Terrestrial vertebrates

Following gavage administration, metarylpicoxamid had low acute toxicity to mammals (LD_{50} >2000 mg ac/kg bw, *Rattus norvegicus*) and birds (LD_{50} >609 mg ac/kg bw, *Anas platyrhynchos*). The lowest LD_{50} in bird acute testing was the highest tested rate where regurgitation was not observed. In short term dietary testing, continual exposure in the diet over 5 days did not result in toxicity to birds at the highest diet concentration of nominal 5000 mg/kg (LDD_{50} >1330 mg ac/kg bw/d, *Colinus virginianus*). In a two-generation study in rats, decreased bodyweight and food intake were observed in P1 and F1 animals (males and females) at 89 mg/kg bw/d (NOAEL of 28 mg ac/kg bw/d, *Rattus norvegicus*). Following long-term reproduction studies in birds, there were no effects on the two standard test species at the highest concentration tested of 1850-1970 mg ac/kg diet (141 mg ac/kg bw/d, *Colinus virginianus*). The screening level assessment concluded acceptable risks to birds and mammals. As a result, no protection statements are required for terrestrial vertebrates.

The octanol-water partition coefficient for metarylpicoxamid (log K_{ow} of 3.9 at pH 7.0) indicated a potential for bioaccumulation. A food chain assessment concluded that any accumulated residues in earthworms or fish are not expected to reach levels harmful to predators under the proposed conditions of use. As there was no evidence of accumulation in the toxicokinetic studies, it is expected that there will be no biomagnification of metarylpicoxamid or its metabolites in the food chain. Further, no endocrine disrupting properties have been noted from currently available data, hence metarylpicoxamid is not expected to be an endocrine disrupting agent.

Aquatic species

Metarylpicoxamid was highly toxic to fish (lowest LC_{50} 0.0055 mg ac/L, *Pimephales promelas*), aquatic invertebrates (lowest LC_{50} 0.011 mg ac/L, *Americamysis bahia*) and aquatic plants (E_rC_{50} >0.37 mg ac/L, *Lemna gibba*), and toxic to algae (lowest E_rC_{50} 1.7 mg ac/L, *Skeletonema costatum*). A representative EC formulation of metarylpicoxamid was also highly toxic to fish (LC_{50} 0.013 mg ac/L, *Oncorhynchus mykiss*), aquatic invertebrates (lowest LC_{50} 0.0089 mg ac/L, *Americamysis bahia*), algae (lowest E_rC_{50} 0.50 mg ac/L, *Navicula pelliculosa*), and toxic to aquatic plants (E_rC_{50} 4.5 mg ac/L, *Lemna gibba*). Based on the high toxicity of metarylpicoxamid to many aquatic species, a protection statement is required on the label.

Following long-term exposure of metarylpicoxamid, increased duration were required to swim up and hatching in fish under an early life stage (ELS) study at concentrations as low as 0.0013 mg ac/L (NOEC 0.00051 mg ac/L, *Pimephales promelas*), and a reduced number of offspring per female was observed for an aquatic invertebrate at 0.0022 mg ac/L (NOEC 0.0012 mg ac/L, *Americamysis bahia*). Following long-term exposure to sediment dwellers, no effects were observed at the highest tested concentration (NOEC 1.4 mg ac/L, *Chironomus riparius*) in a study using spiked water, but adverse effects on emergence and emergence ratio were considered likely to have been observed at 30 mg ac/kg dw (NOEC 6.7 mg ac/kg dry sediment, *Chironomus riparius*) in a study using spiked sediment.

Metarylpicoxamid and its metabolites are not considered bioaccumulative with a whole fish BCF = 97 L/kg.

There are no aquatic toxicity data for the major metabolite X12644507 which is formed at >80% in the soil and total aquatic systems. The risk assessments for X12644507 were based on consideration that the metabolite exhibits the same toxicity as the parent compound, while utilising knowledge of their respective environmental fate properties. Metarylpicoxamid dissipates quickly from the water, but X12644507 is persistent in sediment and the total aquatic system. Therefore, the endpoints for fish and aquatic invertebrates were adjusted to account for the expected dissipation under natural conditions, ie. adjusted endpoints for fish and aquatic invertebrates were time weighted averages (TWAs) considering the study exposure periods and a water DT_{50} of 0.98 days. Screening level assessments for metarylpicoxamid and metabolite X12644507 concluded unacceptable risks for fish, aquatic invertebrates and aquatic plants, and hence required further refinement using spray drift and runoff assessments.

A spray drift assessment according to APVMA's updated approach to spray drift management considered the RAC of 0.0017 mg ac/L and boom spray with a MEDIUM droplet size at 60 g ac/ha, and recommended a buffer zone of 5 metres for the protection of natural aquatic areas.

Runoff assessments according to APVMA's method to refine estimates of pesticide runoff to waterways considered the RAC of 0.0017 mg ac/L and assumed a runoff event occurs three days after the last

application. The runoff risks were considered acceptable at Tier-1 level for metarylpicoxamid and X12644507.

Bees and other non-target arthropods

Metarylpicoxamid had low acute toxicity to adult bees by contact (LD_{50} >200 µg ac/bee, *Apis mellifera*) and by oral exposure (LD_{50} >55 µg ac/bee, *Apis mellifera*). A representative EC formulation of metarylpicoxamid also had low acute toxicity to adult bees by contact (LD_{50} 102 µg ac/bee, *Apis mellifera*) and by oral exposure (LD_{50} 61 µg ac/bee, *Apis mellifera*). The metabolite X12644507 had low acute toxicity to adult bees by contact (LD_{50} >200 µg ac/bee, *Apis mellifera*) and by oral exposure (LD_{50} of 30 µg ac/bee, *Apis mellifera*). Following long-term dietary exposure to metarylpicoxamid there was increased mortality at 22 µg ac/bee/d after exposure for 10 days (NOEDD was 8.3 µg ac/bee/d, *Apis mellifera*). Metarylpicoxamid also had low acute oral toxicity to larvae (LD_{50} >23 µg ac/larva, *Apis mellifera*). Chronic toxicity to bee larvae was tested with larvae exposed to spiked diet over 4 days (days 3-6 of the study), however, there were no effects at the highest tested dietary concentration (NOEDD >16 µg ac/larva/d, *Apis mellifera*). A screening level risk assessment indicated acceptable risks to bees; hence no protection statements are required.

In a Tier 1 laboratory test exposure of indicator species of predatory mites to fresh-dried residues of a representative EC formulation on glass plates resulted in an LR_{50} of 414 g ac/ha (*Typhlodromus pyri*); adult mortality was more sensitive than reproduction. In two Tier 1 laboratory studies exposure of indicator species of parasitic wasps to fresh-dried residues of a representative EC formulation on glass plates resulted in an empirically estimated ER_{50} of 17.3 g ac/ha (*Aphidius rhopalosiphi*). Two extended laboratory studies using a representative EC formulation and predatory arthropods, i.e. green lacewing (*Chrysoperla carnea*) and rove beetle (*Aleochara bilineata*), resulted in an ER_{50} >138 g ac/ha for both species (highest rate tested).

The Tier 1 screening assessment indicated an unacceptable risk to parasitic arthropods, while Tier 1 and Tier 2 screening assessment concluded acceptable risks to predatory arthropods. As no further higher tier information is available to refine the assessment for parasitic arthropods, the proposed use is considered not to be compatible with integrated pest management (IPM) programs utilising parasitic arthropods. Given the effects on reproduction at low application rates to parasitic wasps, and the identified in-field risk, a risk mitigation statement is required on the label.

Soil organisms

Metarylpicoxamid was not acutely toxic to soil macro-organisms ($LC_{50\ CORR}$ >500 mg ac/kg soil dw *Eisenia andrei*), however, a representative EC formulation was more acutely toxic to earthworms ($LC_{50\ CORR}$ 65 mg ac/kg soil dw, *Eisenia andrei*). In chronic testing, reduced reproduction was observed in earthworms at 155 mg ac/kg soil dw ($EC_{10\ CORR}$ 87 mg ac/kg soil dw, *Eisenia andrei*), while a representative EC formulation reported reduced reproduction at 13 mg ac/kg soil dry soil ($EC_{10\ CORR}$ 5.0 mg ac/kg soil dw, *Eisenia andrei*). Chronic tests with technical active and other soil macro-organisms showed no adverse effects at highest tested concentrations (NOEC 1000 mg ac/kg soil dw, *Folsomia candida* and *Hypoaspis aculeifer*), while a representative EC formulation showed reduced reproduction in collembolans at 38 mg ac/kg soil dw (EC_{10} 22.1 mg ac/kg soil dw, *Folsomia candida*) and reduced reproduction in soil mites at 152 mg ac/kg soil dw (NOEC 85 mg ac/kg soil dw, *Hypoaspis aculeifer*).

In soil microorganism testing, metarylpicoxamid had no significant effects on soil nitrification or carbon transformation at 0.82 mg ac/kg soil dw, and its representative EC formulation was similarly lacking in observable effects (NOEC 0.80 mg ac/kg soil dw).

The metabolite X12644507 had an acute toxicity of $LC_{50\ CORR}$ >50 mg/kg dw to earthworms (*Eisenia andrei*) and no significant effects on nitrogen or carbon transformation at 1.33 mg/kg soil dw.

Acceptable risks could be concluded at the screening level for metarylpicoxamid and the metabolite X12644507, and therefore no protection statements are required for soil organisms.

Non-target terrestrial plants

The effects of an EC formulation of metarylpicoxamid were examined following a pre-emergent (seedling emergence, n = 9) and post-emergent (vegetative vigour, n = 10) spray application. The highest tested rate was 0.80 L product/ha (120 g ac/ha). In both studies, there were no effects on the quantitative endpoints relating to survival or growth (plant height and weight) over the course of the tests. In the seedling emergence study, there were no treatment-related visual (phytotoxicity) effects observed for any species (ER_{25} >122 g ac/ha). In the vegetative vigour study, there were no treatment-related visual (phytotoxicity) effects observed for 9 of the 10 tested species. However, a dose/response was observed in radish with respect to phytotoxicity at days 14 and 21 (end of study). The visual injury ER_{25} at day 21 was calculated to be 1.04 L product/ha (extrapolated) equating to 157 g ac/ha. Acceptable risks could be concluded at the screening level, and therefore no protection statements are required.

Recommendations

In considering the environmental safety of the proposed use of the product GF-4898 Fungicide, the APVMA had regard to the toxicity of the new active constituents and its residues, including metabolites and degradation products, in relation to relevant organisms and ecosystems. 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

Proposed product use pattern

GF-4898 Fungicide is a new novel fungicide containing 150 g/L metarylpicoxamid proposed for the control of Asian soybean rust (*Photophore pachyrhizi*) in soybean.

Efficacy and target crop safety

Efficacy and crop safety trials conducted both in Australia and overseas were provided to support a label claim of control of Asian soybean rust (*Photophore pachyrhizi*) in soybean. The overseas trials were conducted in Brazil and Paraguay having a predominantly subtropical to tropical climate with more consistent rainfall and higher temperatures, which helped to achieve higher disease pressures. Although the climates are not identical with Australia, there are similarities in the soybean growing seasons, particularly due to their locations in the Southern Hemisphere. The trials were carried out according to acceptable scientific practices appropriate for measuring efficacy for the control of disease development for Asian soyabean rust (ASR) by measuring disease plot severity or disease incidence and severity over time and crop safety as phytotoxicity or yield loss in soyabeans. In the trials, GF-4898 Fungicide was applied according to label recommendations under moderate to high disease pressure of ASR. Application rates included proposed label rate of 60g ai/ha with an adjuvant in a water volume of 150 to 200 L/ha with a minimum of three to eight applications, at 14 days intervals. All trial work examined both efficacy and crop safety over time, using a replicated (n=4) RCBD trial design. Crop safety trials also included application at double label rate at 14-day intervals at the correct crop growth stages (GS 60+) to determine potential negative crop safety effects.

Efficacy

The trials were sufficient to demonstrate efficacy for the control of ASR of between 95 to 99%. Therefore, based on the evidence provided using the proposed new metarylpicoxamid formulation, a label claim for the control of Asian soybean rust is accepted.

Crop safety

All trials considered did not show crop safety issues when applied at the proposed label recommendations for this application at 0.4 L/ha (60 g ai/ha) as well as when applied at two times (2x) the proposed label rate (120g ai/ha). Thus, the trials demonstrated crop safety in soyabeans up to two times the proposed label rate and were supportive of a label claim of crop safety for the new metarylpicoxamid product.

Recommendations

Based on the trials and evidence provided, a label claim for the control of Asian soybean rust in soyabeans when applied according to the label recommendations using the proposed new product GF-4898 Fungicide is supported. The trial work also supported label claims for crop safety of GF-4898 Fungicide in soyabeans.

Spray drift assessment

Regulatory Acceptable Levels (RALs) were established using the APVMA Spray Drift Assessment Tool (SDRAT), or Spray Drift Management Tool (SDMT), by each risk area, in order to calculate the appropriate spray drift buffer zones for GF-4898 Fungicide.

Human health

Bystander risks from spraying activities were estimated based on potential risks to toddlers (as the most sensitive sub population) using the APVMA (2019) Spray Drift Risk Assessment Tool (SDRAT).

Assessment was conducted against the oral NOAEL of 42.5 mg/kg, using a dermal absorption factor of 8.4%, which was taken from an *in vitro* dermal absorption study with human skin using a 0.3 g/L diluted aqueous spray (equivalent to label dilution rate). The resulting RALs (regulatory acceptable levels) were 0.019 and 0.025 mg/cm^2 or 1940 and 2483 g/ha for 1- to 2-year-old and 2- to 3-year-old toddlers, respectively.

Residues and trade

The estimated maximum residues in animal feed after the proposed GAP is 0.3 mg/kg (parent). Animal feeding study demonstrates that at a dosing level of 1 ppm (parent), finite residues of the parent or any other metabolite are not expected to be detected in edible mammalian tissue or milk or its by-products.

Environment

Spray drift risks to aquatic species are driven by the high toxicity of metarylpicoxamid to fish. Based on the aquatic RAC of 0.0017 mg ac/L (adjusted LC_{50} 0.017 mg ac/L for *Pimephales promelas* and an assessment factor of 10), a buffer zone of 5 metres is advised for a MEDIUM spray quality and 1 metre boom height.

Metarylpicoxamid and a representative EC formulation had low acute toxicity to adult bees (*Apis mellifera*) by contact exposure with a LD50 >200 µg ac/bee and 102 µg ac/bee, respectively. Based on the pollinator RAL of 17000 g ac/ha for the formulation (contact LD50 102 µg ac/bee and a conversion factor of LOC 0.4/ExpE2.4 * 1000), spray drift risks to bees are considered to be acceptable and no buffer zones for pollinators are required.

Using the lowest RAL of 61 g ac/ha for metarylpicoxamid to non-target terrestrial plants (pre-emergent ER_{25} >122 g ac/ha and an assessment factor of 2), spray drift risks are considered to be acceptable and no buffer zones for protection of non-target terrestrial plants are required.

Table 6: Summary of RALs for GF-4898 Fungicide (150 g/L metarylpicoxamid)

Sensitive area	Regulatory Acceptable Level	
	Level of active	Units
Bystander	1940	g/ha
Livestock	1	ppm
Aquatic	1.7	µg/L
Pollinator	17000	g/ha
Vegetation	61	µg/L

Buffer zones calculated by the SDRAT or SDMT, using the above RALs, were incorporated into the GF-4898 Fungicide label spray drift instructions (see *Labelling requirements* below).

Labelling requirements

Product Name: GF-4898 Fungicide

APVMA Approval No: 93003/137590

Label Name:	GF-4898 Fungicide

Signal Headings:	POISON KEEP OUT OF REACH OF CHILDREN READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Constituent Statements:	ACTIVE CONSTITUENT: 150 g/L METARYLPICOXAMID SOLVENT: 180 g/L N,N-Dimethyldecanamide

Mode of Action:	GROUP 21 FUNGICIDE

Statement of Claims:	An emulsifiable concentrate for the control of Asian soybean rust in soybean as specified in the DIRECTIONS FOR USE.

Net Contents:	1 - 5 L

Restraints:	This section contains file attachment. File Name: eLabel - GF-4898 Fungicide - RESTRAINTS 20221025.pdf File Size: 105780 bytes

Directions for Use:	This section contains file attachment. File Name: eLabel - GF-4898 Fungicide - DFU 20221025.pdf File Size: 120483 bytes

Other Limitations:	

Withholding Periods:	Soybean HARVEST: DO NOT HARVEST FOR 21 DAYS AFTER APPLICATION. GRAZING: DO NOT GRAZE OR CUT TREATED AREAS FOR STOCK FEED FOR 21 DAYS AFTER APPLICATION.

Trade Advice:	

General Instructions:	GENERAL INSTRUCTIONS GF-4898 is an emulsifiable concentrate for the control of fungal diseases in soybean, as specified in Table 2, and is to be diluted with water. MIXING Agitate or shake the container immediately prior to use. Half-fill the spray tank with water, add the appropriate amount of accurately measured GF-4898, then near the end of the filling process, add the required amount of Hasten adjuvant. Ensure thorough agitation by mechanical or hydraulic action at all times during mixing and application. Only use clean water within the pH range of 5 - 9 to dilute GF-4898. STORAGE OF DILUTED SPRAY MIX Whenever possible the spray mix should be used immediately after it is prepared. However, if weather conditions or mechanical breakdown prevent immediate use, the spray mix may be stored for up to 24 hours without loss of activity. The spray mix should be agitated thoroughly by mechanical or hydraulic action at regular intervals during storage to prevent sedimentation. Ensure that the stored spray mix is thoroughly agitated at least once every 8 hours. The spray mix must be stored out of direct sunlight. APPLICATION Thorough coverage of the crop is essential. Do not apply when conditions are unsuitable for water-based spray applications. Avoid high temperature, strong winds, inversion conditions, imminent rain or any conditions that may reduce the quality of spray coverage or result in drift from the target area. Techniques to minimise drift should be employed at all times when applying sprays to, or near, sensitive areas. Boom sprayers: Apply GF-4898 using a total spray volume of at least 150 L/ha and preferably 200 L/ha where canopies are closed and growth stage is advanced. Use a MEDIUM spray quality as defined by the ASABE S572 Standard. CLEANING SPRAY EQUIPMENT After using GF-4898 empty the tank and completely drain the system. Rinse the tank, pumps, lines, hoses, filters and nozzles by circulating clean water through the system. Drain and repeat the rinsing procedure twice. MANDATORY TANK MIX GF-4898 is to be mixed with Hasten Spray Adjuvant as recommended in the directions for use table.

Resistance Warning:	For fungicide resistance management GF-4898 Fungicide is a group 21 fungicide. Some naturally occurring individual fungi resistant to GF-4898 and other group 21 fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungal population if these fungicides are used repeatedly. These resistant fungi will not be controlled by GF-4898 and other group 21 fungicides, thus resulting in a reduction in efficacy and possible yield loss. Since the occurrence of resistant fungi is difficult to detect prior to use, Corteva Agriscience Australia Pty Ltd accepts no liability for any losses that may result from the failure of GF-4898 to control resistant fungi. GF-4898 is not currently subject to a CropLife Australia resistance management strategy. For the most up-to-date information, refer to http://www.croplife.org.au/industry-stewardship/resistance-management/ before use. A disease management program that includes rotation and/or tank mixing with fungicides with a different mode of action is essential to reduce the risk of fungicide resistance development. For guidance on a particular crop and disease control situation, contact your

	farm chemical supplier, consultant, local Department of Agriculture or Primary Industries, local Corteva Agriscience representative or CropLife Australia.

Precautions:	RE-ENTRY PERIOD DO NOT enter treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

Protections:	INTEGRATED PEST MANAGEMENT Toxic to parasitic arthropods. Not compatible with integrated pest management (IPM) programs utilising beneficial arthropods such as parasitic wasps. Minimise spray drift to reduce harmful effects on beneficial arthropods in non-crop areas. 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 to an approved waste management facility. If an approved waste management facility is not available, dispose of empty container or unused product in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product. Do not burn empty containers or product.

Safety Directions:	Harmful if swallowed. Will damage eyes and skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If clothing becomes contaminated with product, remove clothing immediately. If product on skin, flush with water for at least 20 minutes. Take care to avoid hypothermia. If product sprayed in mouth, rinse mouth with water. When using together with other products, consult their label safety directions. When opening the container and preparing spray (closed system), wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), elbow-length chemical-resistant gloves, face shield and chemical resistant footwear. When using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing). Wash hands after use. After each day's use, wash gloves, face shield and contaminated clothing. Do not re-use footwear until thoroughly aired.

First Aid Instructions:	If poisoning occurs, contact a doctor or Poisons Information Centre. Phone: Australia 13 11 26. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.

First Aid Warnings:	

RESTRAINTS

DO NOT apply by aircraft.

DO NOT use open mixing and loading.

DO NOT apply more than three (3) applications per season.

DO NOT apply before BBCH 60 growth stage of the crop (start of flowering).

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. The buffer zones in the relevant buffer zone tables below provide guidance but may not be sufficient in all situations. 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 (3) and twenty (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 aircraft.

Boom sprayers

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

- Spray droplets are not smaller than a MEDIUM spray droplet size category.
- Minimum distances between the application site and downwind sensitive areas are observed (see 'Mandatory buffer zones' section of the following table titled 'Buffer zones for boom sprayers').

Table 1. Buffer zones for boom sprayers

Application rate	Boom height above the target canopy	Mandatory downwind buffer zones				
		Bystander areas	Natural aquatic areas	Pollinator areas	Vegetation areas	Livestock areas
Up to 400 mL/ ha	0.5 m or lower	0 m	0 m	0 m	0 m	0 m
	1.0 m or lower	0m	5 m	0 m	0 m	0 m

DIRECTIONS FOR USE

Table 1. Diseases controlled in soybean			
Apply GF-4898 as a preventative treatment from the start of flowering and maintain a regular protectant spray program.			
CROP	**DISEASE**	**RATE**	**CRITICAL COMMENTS**
Soybean	Soybean rust (*Phakopsora pachyrhizi*)	0.4 L/ha + Hasten™1 0.25% v/v	Apply two consecutive sprays of GF-4898 14 days apart. A third application may be necessary if conditions favour disease development or where disease is established in the canopy. The third application can be made 14 or more days after the second application but before BBCH 80 (first pod ripe). **DO NOT** apply more than 3 applications of GF-4898 in one season. See RESISTANCE MANAGEMENT in GENERAL INSTRUCTIONS.

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

Acronyms and abbreviations

Shortened term	Full term
ac	Active constituent
ADI	Acceptable daily intake (for humans)
ai	Active ingredient
ARfD	Acute reference dose
bw	Bodyweight
d	Day
DAF	Derman absorption factor
DAT	Days after treatment
DFU	Direction for use
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	Concentration at which the biomass of 50% of the test population is impacted
EC_{50}	Concentration at which 50% of the test population are immobilised
E_rC_{50}	Concentration at which the rate of growth of 50% of the test population is impacted
g	Gram
GAP	Good Agricultural Practice
GLP	Good Laboratory Practice
h	Hour
ha	Hectare
HPLC	High pressure liquid chromatography *or* high performance liquid chromatography
IPM	Integrated pest management
in vitro	Outside the living body and in an artificial environment
in vivo	Inside the living body of a plant or animal
kg	Kilogram

Shortened term	Full term
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
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
mg	Milligram
MOE	Margin of exposure
mL	Millilitre
MRL	Maximum Residue Limit
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short-Term Intake
ng	Nanogram
NOEC/NOEL	No observable effect concentration level
NOAEL	No observed adverse effect level
OC	Organic carbon
OPHEC	US EPA Occupational Pesticide Re-entry Calculator
OPREC	US EPA Occupational Pesticide Re-entry Calculator
PPE	Personal protective equipment
ppm	Parts per million
Q-value	Quotient-value
RAL	Regulatory Acceptable Level
REI	Re-entry interval
s	Second
SC	Suspension concentrate
SDMT	Spray Drift Management Tool

Shortened term	Full term
SDRAT	Spray Drift Risk Assessment Tool
SDS	Safety Data Sheet
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
µg	Microgram
WG	Water dispersible granule
WHP	Withholding period

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
CAS registry number	Unique numerical identifier assigned by the Chemical Abstracts Service (CAS) to every chemical substance
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	Repels water
Leaching	Removal of a compound by use of a solvent
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
Toxicology	The study of the nature and effects of poisons

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