Australian Government

Australian Pesticides and Veterinary Medicines Authority

Trade Advice Notice

on indaziflam in the product Esplanade Herbicide
for use on areas that may be grazed

APVMA product number 86235

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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 an independent statutory authority with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking stakeholder involvement in decision making. Part of that process is the publication of Trade Advice Notices for all proposed extensions of use for existing products where there may be trade implications.

The information and technical data required by the APVMA to assess the safety of new chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in regulatory guidance published on the APVMA website.

About this document

This Trade Advice Notice indicates that the APVMA is considering an application to vary the use of an existing registered agricultural chemical.

It provides a summary of the APVMA's residue and trade assessment.

Comment is sought from industry groups and stakeholders on the information contained within this document.

Making a submission

The APVMA invites any person to submit a relevant written submission as to whether the application to vary the registration of Esplanade Herbicide should be granted. Submissions should relate only to matters that the APVMA is required by legislation to consider in deciding whether to grant the application. These grounds relate to the trade implications of the extension of use of the product. Submissions should state the grounds on which they are based. Comments received outside these grounds cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on Monday 19 December 2022 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 considered by the APVMA in deciding whether to grant the application and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

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

Please note: submissions will be published on the APVMA's 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:

Executive Director, Risk Assessment Capability

Australian Pesticides and Veterinary Medicines Authority

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Sydney NSW 2001

Phone: +61 2 6770 2300

Email: enquiries@apvma.gov.au

Further information

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

Further information on Trade Advice Notices can be found on the APVMA website.

Introduction

The APVMA has before it an application from 2022 Environmental Science AU Pty Ltd to vary the registration of Esplanade Herbicide (containing the active constituent indaziflam, SC formulation) to allow grazing of treated areas including in agricultural non-crop situations. Esplanade Herbicide is currently registered in the same situations as proposed (except for agricultural non-crop situations) with the following grazing restraint:

“DO NOT graze treated areas or feed grass clippings from any treated area to poultry or livestock”

With this application 2022 Environmental Science AU Pty Ltd have provided metabolism and residue trial data to allow consideration of replacement of the above grazing restraint with a 7-day grazing withholding period. This will be the first use of indaziflam in food producing situations in Australia and currently no Maximum Residue Limits (MRLs) or residue definitions are established for indaziflam in the APVMA MRL Standard or in the Food Standards Code.

Trade considerations

Commodities exported

Commodities of animal origin, such as meat, offal and dairy products, which may be derived from livestock fed feeds produced from treated areas are major export commodities.[1] Residues in these commodities resulting from the use of Esplanade Herbicide may have the potential to unduly prejudice trade.

Destination and value of exports

The significant export markets for Australian beef, sheep, pig meat and offal are listed in the APVMA Regulatory Guidelines – Data Guidelines: Agricultural – Overseas trade (Part 5B).[1]

Proposed Australian use pattern

Esplanade Herbicide (500 g/L indaziflam)[2]

Table 1: Proposed use pattern

Crop	Weeds controlled	Rate	Critical comments
Non-crop areas around buildings, commercial and industrial areas for maintenance of bare ground, e.g. public service areas, rights of way, rail tracks, roadsides, guideposts, powerlines, substations, airports, public utilities and fence lines. Agricultural non-crop situations including along fence lines and boundary areas, around farm buildings and grazed areas in and around these sites.	Various broadleaf weeds and grasses. Refer to *Weeds* table in the *General instructions*	150 mL/ha or 30 mL/100 L (75 g ai/ha or 15 g ai/100 L)	Apply this product prior to weed seed germination. Do not exceed 300 mL/ha (150 g a.i./ha) in a 12-month period after the previous application. Do not re-apply within 6 months of the first application. For control of emerged weeds, use this product in combination with a contact herbicide. Refer to the *General instructions*. Application to hard surfaces such as paved parking lots and walkways should be made by spot application only.
Grassed areas on roadsides, airports, utility rights of way, median and centre strips	Various broadleaf weeds and grasses. Refer to *Weeds* table in the *General instructions*	150 mL/ha or 30 mL/100 L (75 g ai/ha or 15 g ai/100 L)	Apply this product to promote the growth of warm-season grasses. See *Tolerant species* table in the *General instructions*. Grass should be in robust and healthy condition at the time of treatment. Apply this product prior to germination of the weeds. Ensure adequate coverage for optimum weed control.

[1] Australian Pesticides and Veterinary Medicines Authority, *Regulatory Guidelines – Data Guidelines, Pesticides: Overseas trade (Part 5B)*, APVMA website, accessed October 2022

[2] Infopest, *Currently approved label for Esplanade Herbicide, which contains the weeds table*, accessed 11 November 2022.

Crop	Weeds controlled	Rate	Critical comments
Rehabilitation and restoration of desirable vegetation in natural and non-crop areas, e.g. those impacted by fire, mining, erosion, logging or infrastructure projects.	Various broadleaf weeds and grasses. Refer to *Weeds* table in the *General instructions*	150 mL/ha or 30 mL/100 L (75 g ai/ha or 15 g ai/100 L)	Apply this product prior to weed seed germination. Do not exceed 300 mL/ha (150 g a.i./ha) in a 12-month period after the previous application. Do not re-apply within 6 months of the first application. For control of emerged weeds, use this product in combination with a contact herbicide. Refer to the *General instructions*. Ensure adequate coverage for optimum weed control. See *Tolerant species* table in the *General instructions*.
Forestry – Pre-plant application: Radiata pine *(Pinus radiata)*, Tasmanian bluegum *(Eucalyptus globulus)*, Shining gum *(Eucalyptus nitens)*, Hoop pine *(Araucaria cunninghamii)*, African mahogany *(Khaya senegalensis)*	Various broadleaf weeds and grasses. Refer to *Weeds* table in the *General instructions*.	150 mL/ha (75 g ai/ha)	Apply this product once pre-planting. DO NOT apply to Eucalyptus plantations post-planting. Apply to bare ground prior to weed seed germination. If weeds are present, add a knockdown or other partner herbicide as a tank mix. Refer to the *General instructions*.
Forestry – Post-plant application Radiata pine *(Pinus radiata)*	Various broadleaf weeds and grasses. Refer to *Weeds* table in the *General instructions*	150 mL/ha (75 g ai/ha)	Apply this product once from 2 weeks to 2 months post-planting. Apply to bare ground prior to weed seed germination. If weeds are present, add a knockdown or other partner herbicide as a tank mix. Refer to the *General instructions*.

Application

Ensure spraying equipment is properly calibrated before use. Uniform application is essential for satisfactory weed control. Ensure that complete and even spray coverage is achieved. DO NOT overlap sprayed areas. Use spray volumes of 150 to 400 L/ha, spray boom height and spray pressures as low as practical, use coarse droplet-producing nozzle tips, use drift-control additives and spray when wind speed is low.

Withholding periods

Grazing: DO NOT graze or cut for stockfood for 7 days after application

Restraints: DO NOT apply by aircraft.

Trade advice

Export trade advice for livestock: Consumption by livestock of any materials previously treated with this product may produce residues in the animal that might not be acceptable in some export markets. Before you use this product you are advised to contact 2022 Environmental Science AU Pty Ltd and/or the relevant

livestock industry body about any potential trade issues and their management. You should also be prepared to inform other livestock producers, who intend using the material as stockfeed, of its chemical exposure history.

Livestock destined for export markets

The grazing withholding period only applies to stock slaughtered for the domestic market. Some export markets apply different standards. To meet these standards, ensure that in addition to complying with the grazing withholding period, the export slaughter interval is observed before stock are sold or slaughtered.

Export slaughter interval (ESI): 3 days.

Livestock that has grazed on treated areas should be placed on clean feed for 3 days prior to slaughter.

Results from residues trials presented to the APVMA

Residue definition

Metabolism studies have been provided to allow the consideration of a residue definition for indaziflam. The studies were conducted in apples, grapes, sugarcane, confined rotational crops (turnip, Swiss chard and wheat) and in target animals (lactating goats) with compound labelled in the triazine and indane rings.

Plant commodities

Metabolism in plants was limited with indaziflam-triazinediamine (6-[(1R)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine) the only metabolite identified. In the apple, grape and sugarcane metabolism studies, parent formed 8 to 24% of total radioactive residues (TRR) (<0.001 to 0.005 mg/kg). Indaziflam-triazinediamine formed 30 to 72% TRR (0.006 to 0.03 mg eq/kg).

In the confined rotational crop study, parent was identified only in wheat straw (2nd rotation) in the indane label confined rotational crop study at 24% TRR, 0.003 mg/kg. For the triazine label experiment, the only identified metabolite in rotational crops was indaziflam-triazinediamine (75 to 98% TRR when identified).

In the pasture residue trials submitted with this application samples were analysed for parent indaziflam and indaziflam-triazinediamine with appropriately validated analytical methods involving the same extraction method for each analyte.

The recommended residue definition for plant commodities is the sum of indaziflam and *6-[(1R)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine (=indaziflam-triazinediamine)*, expressed as indaziflam and is suitable for both dietary risk assessment and enforcement. This definition is the same as that established for plant commodities in the United States by the US Environmental Protection Agency (EPA).

Animal commodities

Indaziflam underwent extensive metabolism in goats. The highest TRR was observed in liver, while a low TRR was observed in muscle (therefore characterisation and identification did not occur in muscle for the

indane label). Parent compound accounted for 1 to 9 % TRR (0.004 to 0.02 mg/kg) in tissues and milk for the triazine label and 2 to 20% TRR (0.003 to 0.01 mg/kg) for the indane label.

For the triazine label the major residues found above 10% TRR in the milk and tissues were indaziflam-triazinediamine (2% to 15% of the TRR; 0.001 to 0.05 mg eq/kg), AE 1170437-4-hydroxy-hydroxymethyl (4% to 18% of the TRR; 0.003 to 0.07 mg eq/kg), AE 1170437-dihydroxy (2% to 18% of the TRR; 0.002 to 0.07 mg eq/kg), AE 1170437-4-hydroxy acid (5% to 14% of the TRR; 0.005 to 0.06 mg eq/kg), AE 1170437-3-ketohydroxymethyl (2% to 28% of the TRR; 0.001 to 0.09 mg eq/kg), AE 1170437-3-hydroxyindane GA (9% to 24% of the TRR; 0.004 to 0.20 mg eq/kg), 3-hydroxyindane (3% to 14% of the TRR; 0.003 to 0.02 mg eq/kg), and AE 1170437-carboxylic acid (2% to 20% of the TRR; 0.001 to 0.13 mg eq/kg).

For the indane label the major residues found above 10% TRR in the milk and tissues (apart from parent) were AE 1170437-4-hydroxy-hydroxymethyl (2% to 16% of the TRR; <0.001 to 0.02 mg eq/kg), AE 1170437-dihydroxy (11% to 14% of the TRR; 0.02 mg eq/kg), AE 1170437-3-ketohydroxymethyl (2% to 13% of the TRR; <0.001 to 0.02 mg eq/kg), AE 1170437-3-ketohydroxymethyl GA (2% to 28% of the TRR; 0.002 to 0.11 mg eq/kg), AE 1170437-3-hydroxyindane GA (12% to 19% of the TRR; 0.002 to 0.02 mg eq/kg), 3-hydroxyindane (12% to 18% of the TRR; 0.02 mg eq/kg), and AE 1170437-carboxylic acid (6% to 26% of the TRR; 0.008 to 0.09 mg eq/kg).

In a dairy cattle transfer study, parent was the major component of the residue in liver (the tissue with the highest residues) and in fat. Parent was the second most significant residue in milk.

The US EPA has established a residue definition of parent compound only for compliance with its animal commodity MRLs for indaziflam. Given that many metabolites were observed in the goat study and that parent was found in milk, liver and fat, parent is a suitable marker for the enforcement definition for animal commodities (for compliance with MRLs). For dietary risk assessment, the definition will also include the additional metabolites analysed for in the dairy cattle feeding study which will cover a major part of the residues observed in the goat metabolism study: indaziflam-acid (AE 2158969), BCS-CA59465 (AE1170437-3-hydroxyindane), BCS-DF21263 (AE 1170437-3-ketohydroxymethyl) and indaziflam-triazinediamine.

A poultry metabolism study has not been submitted as indaziflam residues are not expected to occur in any poultry feeds as a result of the proposed use but may be required in the future if significant residues are expected in feed for poultry from any new uses.

Residue trials

The proposed application rate on the label is 75 g ai/ha or 15 g ai/100 L with a 6-month re-treatment interval and no more than 150 g ai/ha to be applied in a 12-month period. The 15 g ai/100 L rate is for spot spraying to treat individual weed plants or areas that only have small clumps of weed infestations and the proposed general instructions indicate that spray volumes of 150 to 400 L/ha should be used for Esplanade. MRLs will therefore be based on the per ha rate as it is the critical Good Agricultural Practice (GAP). The proposed grazing withholding period is 7 days.

The applicant has provided full details of relevant Good Laboratory Practice (GLP) residue studies conducted on pasture in Australia (2 trials) and Europe (6 trials).

The Australian trials sampled at 0, 1 and 20 to 21 days after application at 75 g ai/ha but did not sample at the proposed 7-day grazing withholding period. Estimated half-lives for the total residue in forage on a dry weight basis over 0 to 20 to 21 days were 7.2 and 9.6 days in the first and second Australian trial respectively. Based on these estimated half-lives, total residues of 18.4 and 23.1 mg/kg (dry weight) at day 0 in each trial respectively would be expected to decline to 9.4 and 13.9 mg/kg (dry weight) respectively at 7 days after application. These values are at the upper range of the European trials considered below.

In the European trials (including both Northern and Southern Europe) total residues of parent plus the triazine metabolite in grass green material at 7 days after application at 100 g ai/ha (~1.3× proposed) were 0.51, 0.58, 1.6, 1.8, 2.4 and 2.8 mg/kg (assume fresh weight basis). The Organisation for Economic Cooperation and Development (OECD) Feed Calculator indicates grass forage consists of 25% dry matter. On a dry weight basis, residues in the European trials were 2.0, 2.3, 6.4, 7.2, 9.6 and 11.2 mg/kg.

Based on the European dataset the OECD MRL calculator recommends an MRL of 30 mg/kg (unrounded 21.4 mg/kg, Supervised Trials Median Residue (STMR)= 6.8 mg/kg, n= 6) noting a high uncertainty due to the small dataset. Based on the European trials which addressed the proposed 7-day grazing withholding period with consideration also to the estimated 7-day results from the Australian trials, it is recommended that an MRL of 30 mg/kg should be established for indaziflam on primary feed commodities to cover the proposed uses in conjunction with the proposed 7-day grazing withholding period.

Animal commodity MRLs

Primary feed commodities can form 100% of the diet for mammalian livestock in Australia. The maximum livestock dietary burden is 11.2 ppm based on a HR (highest residue observed 7 days after application) in grass forage of 11.2 mg/kg dry weight.

Required animal commodity MRLs based on an enforcement residue definition of parent are estimated below based on the residues observed in the dairy cattle feeding study involving dosing at 31.2 ppm:

Table 2: Estimated residues in cattle tissues and milk and required MRLs

Feeding level (ppm)	Milk	Muscle	Liver	Kidney	Fat
				Indaziflam parent residue (mg/kg)	
31.2 (feeding study)	0.009	<0.01	0.192	0.047	0.068
11.2 to beef, estimated burden	–	<0.01	0.069	0.017	0.024
11.2 to dairy, estimated burden	0.003	–	–	–	–
Established MRLs	–	–		–	
Recommended MRLs	*0.005	0.03 (in the fat)		0.1 (offal)	–

MRLs are recommended at *0.005 mg/kg for Milks, 0.03 mg/kg for Meat (mammalian) [in the fat] and 0.1 mg/kg Edible offal (mammalian) based on estimated residues of parent indaziflam. It is noted that one metabolite (AE 1170437-3-ketohydroxymethyl) was observed in milk at up to 0.014 mg/kg after feeding at

31.2 ppm. This metabolite would be approximately at the LOQ (0.005 mg/kg) for the expected burden of 11.2 ppm.

In the feeding study an average total indaziflam residue (based on the risk assessment definition noting most markets have not yet set a residue definition) of 1.3 mg/kg in liver after dosing at 311 ppm declined to the combined LOQ of 0.05 mg/kg after 3 days depuration, giving a half-life of 0.64 days. It would take approximately 1 day for the estimated total indaziflam residue of 0.104 mg/kg in liver (from feeding at 11.2 ppm) to decline to the combined LOQ of 0.05 mg/kg. For parent indaziflam, the proposed Australian and current US residue definition for MRL enforcement in animal commodities, the high parent residue in liver of 0.833 mg/kg declined to at LOQ (0.01 mg/kg) after 3 days giving a half-life of 0.47 days. It would take 1.31 days for estimated parent residue of 0.069 mg/kg in liver to decline to 0.01 mg/kg. A 3-day ESI is recommended to ensure there are no quantifiable residues of parent indaziflam or its metabolites in animal commodities for export.

Overseas registration and approved label instructions

The applicant indicated that indaziflam products are registered for use in different situations in a range of countries including in Africa, Asia and North and South America.

Codex Alimentarius Commission and overseas MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides and veterinary medicines. Codex CXLs are primarily intended to facilitate international trade and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods. Indaziflam has not been considered by Codex. The following relevant international MRLs have been established for indaziflam.

Table 3: International MRLs for indaziflam

Commodity	Tolerance for residues arising from the use of Indaziflam (mg/kg)						
	Australia	EU[3]	Japan[4]	Codex[5]	Korea[6]	Taiwan[7]	USA[8]
Residue definition	Indaziflam (proposed for animal commodities for enforcement)	–	–	–	–	–	Indaziflam
Edible offal (mammalian)	0.1 (proposed)	–	–	–	–	–	0.2 (cattle and sheep meat byproducts)
Meat mammalian [in the fat]	0.03 (proposed)	–	–	–	–	–	0.07 (cattle and sheep fat) 0.01 (cattle and sheep meat)
Milk	*0.005 (proposed)	–	–	–	–	–	0.01 (milk) 0.25 (milk fat)

Current and proposed Australian MRLs for indaziflam

There are currently no MRLs established for indaziflam in Australia. The following changes are proposed to the MRL Standard.

[3] European Commission, *EU Pesticide residue(s) and maximum residue levels (mg/kg)*, European Commission website, accessed October 2022.

[4] Japanese Food Chemistry Research Foundation, *Table of MRLs for Agricultural Chemicals*, JFCRPF website, accessed October 2022.

[5] Food and Agriculture Organisation of the United Nations, *Codex Alimentarius, International Food Standards*, FAO website, accessed October 2022.

[6] Ministry of Food and Drug Safety, Korea, *MRLs in Pesticides*, accessed October 2022.

[7] Laws and Regulations Database of the Republic of China (Taiwan), *Standards for Pesticide Residue Limits in Foods*, accessed October 2022.

[8] Electronic Code of Federal Regulations, *USA Electronic Code of Federal Regulations*, eCFR website, accessed October 2022.

Table 4: Proposed MRL Standard – Table 1

Compound	Food	MRL (mg/kg)
Add:		
Indaziflam		
MO 0105	Edible offal (mammalian)	0.1
MM 0095	Meat (mammalian) [in the fat]	0.03
ML 0106	Milks	*0.005

Table 5: Proposed MRL Standard – Table 3

Compound	Residue
Add:	
Indaziflam	Commodities of plant origin for enforcement and dietary exposure assessment: sum of indaziflam and 6-[(1R)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine, expressed as indaziflam. Commodities of animal origin for enforcement: Indaziflam Commodities of animal origin for dietary exposure assessment: sum of indaziflam, (2S,3R)-3-[[4-amino-6-[(1R)-1-fluoroethyl]-1,3,5-triazin-2-yl]amino)-2,3-dihydro-2-methyl-1H-indene-5-carboxylic acid (indaziflam-acid), (2R,3R)-3-[[4-amino-6-[(1R)-1-fluoroethyl]-1,3,5-triazin-2-yl]amino]-2,5-dimethyl-indan-1-ol (3-hydroxyindane), (2S,3R)-3-[[4-amino-6-[(1R)-1-fluoroethyl]-1,3,5-triazin-2-yl]amino)-5-hydroxymethyl-2-methylindane-1-one (3-ketohydroxymethyl) and 6-[(1R)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine, expressed as indaziflam

Table 6: Proposed MRL Standard – Table 4

Compound	Animal feed commodity	MRL (mg/kg)
Add:		
Indaziflam		
	Primary feed commodities	30

Potential risk to trade

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

The proposed Australian animal commodity MRLs are lower than those established in the United States, however Codex and many export markets do not have MRLs established. The recommended 3-day Export

Slaughter Interval should ensure there are no quantifiable residues of indaziflam or its metabolites in animal commodities for export.

Conclusion

2022 Environmental Science AU Pty Ltd have applied to vary the registration of Esplanade Herbicide containing indaziflam. 2022 Environmental Science AU Pty Ltd are proposing to replace the current label grazing restraint with a 7-day grazing withholding period, including for the additional new use in agricultural non-crop situations. This will be the first food use of indaziflam in Australia and requires the establishment of animal commodity MRLs and a residue definition. Comment is sought on the potential for the proposed change to prejudice Australian trade in animal commodities.