Australian Government

Australian Pesticides and Veterinary Medicines Authority

TRADE ADVICE NOTICE

on triclabendazole (and ivermectin) in the Product
Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle

APVMA Product Number 58611

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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.

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Aging, Office of Chemical Safety and Environmental Health (OCSEH), Department of the Environment, Water, Heritage and the Arts (DEWHA), and State Departments of Primary Industry.

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 the APVMA's publication *Vet MORAG: Manual of Requirements and Guidelines*.

About this document

This is a Trade Advice Notice.

It indicates that the Australian Pesticides and Veterinary Medicines Authority (APVMA) is considering an application to vary the use of an existing registered agricultural or veterinary 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.

Any advice the APVMA receives through this consultation which it relies on to grant this application will be noted in a subsequent Advice Summary.

Advice Summaries can be found on the APVMA website: http://www.apvma.gov.au

Making a submission

The APVMA invites any person to submit a relevant written submission as to whether the application to vary the registration of **Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle** 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 grounds relate to the **trade implications** of the extended 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 **27 August 2010** 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 to grant the application. A summary of relevant comments and the APVMA's response will be published on the APVMA website.

When making a submission please include:

- Contact name
- Company or Group name (if relevant)
- Postal Address
- Email Address (if available)
- The date you made the submission.

All personal and ***confidential commercial information (CCI)***[1] material contained in submissions will be treated confidentially.

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

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Further information

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

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

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

1 INTRODUCTION

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has before it an application from Intervet Australia Pty Limited, to vary the registration of currently registered product, *Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle,* by extending the use-pattern to include use on non-lactating (dry) dairy cattle.

Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle contains ivermectin (15 mg/mL) and triclabendazole (240 mg/mL), and is currently registered for the treatment and control of ivermectin-sensitive gastro-intestinal roundworms, lungworm, adult liver fluke and lice in beef cattle, dairy calves, and replacement heifers (up until 70 days (10 weeks) prior to their first calving only).

The application involves the establishment of a permanent Australian Maximum Residue Limit (MRL) for triclabendazole residues in cattle milk. Additionally, the application requires the setting of a treatment-to-calving interval (TCI), a milk withholding period (WHP), establishment of an export slaughter interval (ESI) for calves from treated dairy cows, and approval of the proposed product label.

2 RESIDUES IN LIVESTOCK

2.1 Proposed Australian use pattern

The proposed Australian use-pattern for *Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle*, incorporating the existing use-pattern in beef cattle and the proposed extension to non-lactating (dry) dairy cattle, is provided in Table 1.

Table 1: Proposed use pattern - Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle

HOST	PURPOSE	DOSE RATE	CRITICAL COMMENTS
Cattle [beef and non-lactating (dry) dairy cattle]	For the treatment and control of ivermectin-sensitive gastro-intestinal roundworms, lungworms, adult liver fluke and lice.	**Nominal** 1 mL product per 10 kg bw (equivalent to1.5 mg ivermectin/kg bw and 24 mg triclabendazole /kg bw) **Maximum (beef cattle)** 15 mL product applied to an animal weighing 101 kg (equivalent to 2.23 mg ivermectin/kg bw and 35.6 mg triclabendazole/kg bw) **Maximum (dairy cattle)** 40 mL product applied to an animal weighing 351 kg (equivalent to 1.71 mg ivermectin/kg bw and 27.4 mg triclabendazole/kg bw)	Apply along the topline in a band extending from the middle of the back to the tailhead. Product should be applied using a recommended applicator fitted with a fan-spray nozzle.

Re-treatment interval: DO NOT re-treat animals for 70 days after last treatment.

Restraints:

DO NOT USE on lactating cows or within 56 days of calving, where milk or milk products from treated cattle may be used for human consumption.

Withholding periods

MEAT: DO NOT USE less than 28 days before slaughter for human consumption.

MILK: DO NOT USE on lactating dairy cows, where milk collected may be used for human consumption or processing.

DO NOT USE on pregnant (dry) dairy cows within 56 days of calving. For 60 hours (5 milkings) after calving, colostrum or milk collected from treated cows MUST NOT BE USED for human consumption or supplied for processing.

Where *Coopers Sovereign* is accidentally given within this period, or should any cows calve earlier than 56 days after treatment, milk may contain residues. For at least 56 days plus 60 hours (including at least 5 milkings) following treatment, milk collected from treated cows MUST NOT BE USED for human consumption or supplied for processing.

CALVES: Calves born to cows at 28 days after treatment of the dam (or later), and not suckled/fed milk containing residues, may be slaughtered for human consumption at any time after birth.

Calves born to cows at 28 days after treatment of the dam (or later), and suckled/fed milk containing residues, MUST NOT BE slaughtered for human consumption for 14 days after last feeding of milk.

Trade advice

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 70 days before slaughter for export. Calves born to cows that were treated with Coopers Sovereign during pregnancy, and not suckled/fed milk, must not be slaughtered for export for 70 days after treatment of the dam. Calves born to cows that were treated with Coopers Sovereign during pregnancy, and suckled/fed milk, must not be slaughtered for export for 70 days after treatment of the dam plus an additional 14 days, commencing at the last feeding of milk. The ESI on this label was correct at the time of label approval. Before using this product, confirm the current ESI from Intervet on 1 800 226 511 or the APVMA website (www.apvma.gov.au/residues/ESI.shtml).

2.2 Withholding periods and maximum residue limits

In support of the application, Intervet provided details of two (2) Australian milk residues trials conducted with *Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle*.

Milk

One milk residues trial was conducted with dairy cows (n=23) in Maffra, Victoria, during the winter months. A second milk residues trial was conducted with dairy cows (n=24) in Dayboro, Queensland, during the summer months. In both trials, pregnant Friesian dairy cows were topically treated with Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle at a rate of 1 mL product/8 kg bw at 42-49 days prior to the estimated calving date (equivalent to 1.88 mg ivermectin/kg bw and 30 mg triclabendazole/kg bw; 1.1× the maximum label rate for dairy cows). Milk from the first four (4) milkings (colostrum) was discarded, in accordance with standard industry practices. Milk samples were collected twice daily (am and pm), from the 5th milking post-calving to the 13th milking (total of 9 milkings, corresponding to 4.5 days). Samples were stored frozen until analysed for their content of ivermectin and triclabendazole residues. Additional milk samples were analysed for their fat content.

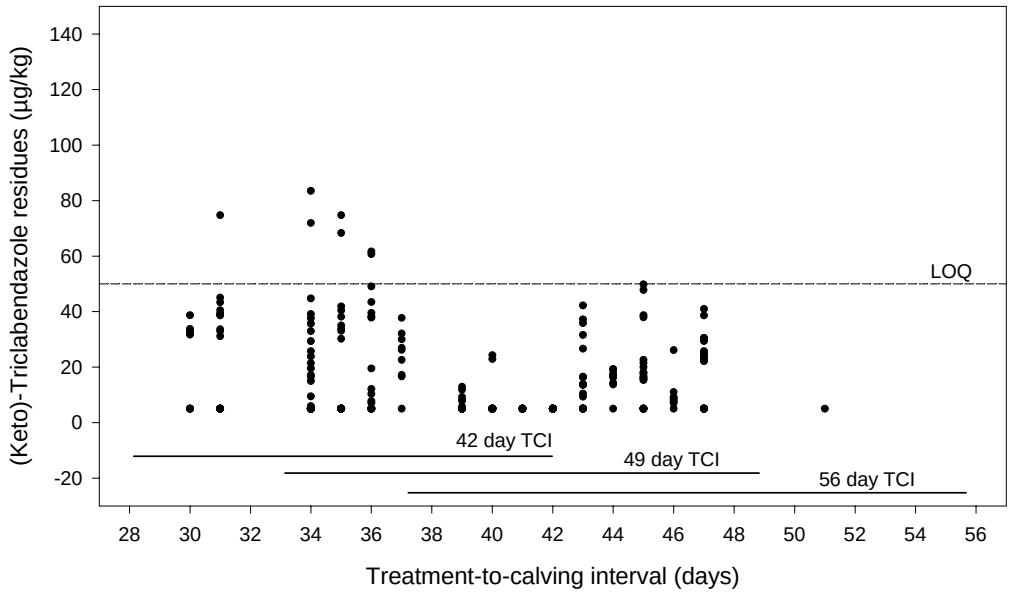
When the results from the two milk trials were combined, a total of 38 cows calved between 30 and 51 days after treatment. The 23 cows that calved between 28 and 42 days after treatment were eligible for consideration of a 42 day treatment-to-calving interval (TCI). Thirty two (32) cows calved between 33 and 49 days after treatment, and were eligible for consideration of a 49 day TCI. Twenty five (25) cows calved between 37 and 56 days after treatment, and were eligible for a 56 day TCI.

Ivermectin residues in milk: Residues of ivermectin (H_2B_{1a}) in milk from the 5th - 15th milkings post-calving were below the method LOQ (<0.39 µg/kg) for all 38 trial animals. Residues ranged from <0.006 µg/kg (<LOD) to 0.39 µg/kg (<LOQ). Statistical analysis[℘] of the data revealed that the upper confidence limits for all milkings post-calving were below the method LOQ (<0.39 µg/kg). Thus, ivermectin residues in all milk samples are likely to comply with the existing Australian MRL of 0.05 mg/kg (50 µg/kg) for ivermectin in cattle milk.

[℘] Determination of the mean + 2.6 × standard deviation, to approximate the upper 95 % confidence limit for the 95th percentile (ie 95/95).

Triclabendazole residues in milk: A plot of the concentration of keto-triclabendazole residues in post-calving milk (5th-15th milkings) from dairy cows treated at 1.1× the maximum label rate for Sovereign is provided below.

(Keto)-Triclabendazole residues in post-calving milk (5th - 15th milkings) from dairy cows treated at 1.1× the maximum label rate for *Sovereign*.



Residues of keto-triclabendazole in milk from the 5th - 15th milkings post-calving were below the method LOQ (<50 µg/kg) for 13 of the 15 animals in the winter milk trial (Maffra), and for 20 of the 22 animals in the summer milk trial (Dayboro). A total of four (4) of the 37 trial animals produced milk with keto-triclabendazole residues above the method LOQ: in each case, the cows calved between 31 and 36 days after treatment, with highest residues (61-84 µg/kg) occurring at the 12th-13th milkings post-calving. The occurrence of keto-triclabendazole residues above the method LOQ in the afore-mentioned milk samples could not be attributed to abnormalities in milk production volumes or the % fat content of the samples.

Statistical analysis[℘] of the residues data for (keto)-triclabendazole in milk revealed that:

- When the proposed 42 day TCI and 96 hour (8 milkings) WHP was considered, the upper confidence limits for the 9th, 10th, 12th and 13th milkings post-calving exceed the proposed MRL of *0.05 mg/kg for triclabendazole residues in milk.
- Similarly, when a 49 day TCI with a 96 hour (8 milkings) WHP was considered, the upper confidence limits for the 12th and 13th milkings post-calving still exceed the proposed milk MRL of *0.05 mg/kg.
- However, when a 56 day TCI was considered, the upper confidence limits for all of the post-calving milkings were below the proposed milk MRL of *0.05 mg/kg.

[℘] Determination of the mean + 2.6 × standard deviation, to approximate the upper 95 % confidence limit for the 95th percentile (ie 95/95).

These data support:

(i) the assignment of a 56 day TCI and a 60 hour (5 milkings) WHP to the use of Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle in non-lactating (dry) dairy cows; and

(ii) the establishment of an MRL of *0.05 mg/kg for triclabendazole in cattle milk.

Consideration of the calf meat WHP

In utero exposure of calves to residues: Residues data were not provided for calves that have been exposed *in utero* to the product, as a result of treating the pregnant dairy cows. However, the levels of residues in unborn calves are likely to mirror those of the treated dams. Given that the recommended TCI (56 days) is longer than the existing meat WHP (28 days), residues in calves born to cows at 28 days after treatment of the dam (or later) are expected to comply with the relevant MRLs at any time after birth.

Exposure of calves to residues via milk consumption: Milk from treated dairy cows that is not suitable for human consumption (because it may contain residues) could be fed to calves. No residues data were provided to address this scenario.

Provided calving occurs not less than 56 days after treatment, calves suckling milk from their dams for the first five (5) milkings post-calving are not expected to contain tissue residues above the relevant MRLs.

However, when calving occurs less than 56 days after treatment, milk from treated cows will contain triclabendazole residues. Ingestion of this milk by calves may lead to an increase in the overall levels of triclabendazole residues in calf tissues. Therefore, when calves have been fed/suckled milk containing residues, they must not be slaughtered for human consumption for 14 days after last feeding of milk.

Minimum re-treatment interval

The currently approved label for *Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle* is “silent” with regard to the minimum re-treatment interval. Given that residues of triclabendazole in edible tissues of treated animals are well above the method LOQ after the recommended WHPs have been observed, there is the potential for accumulation of residues to occur (and violation of the recommended MRLs) if the re-treatment interval is too short.

In the absence of empirical data (ie residues data generated after animals have been treated twice at the maximum label rate and minimum re-treatment interval), the minimum re-treatment interval is estimated as the time required for triclabendazole residues in tissues arising from the first pour-on application to decline to levels below the method LOQ (<0.1 mg/kg).

The residues data submitted with the original application for registration showed that triclabendazole residues in edible tissues of treated cattle declined to below the method LOQ within 70 days of treatment. Therefore, a minimum re-treatment interval of 70 days (10 weeks) is recommended for the product.

3 RESIDUES-RELATED ASPECTS OF TRADE

3.1 Commodities exported

Exports of beef/veal and live cattle were considered at the time of original registration for *Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle*. Extension of use of the product to non-lactating (dry) dairy cattle has the potential to impact on Australian exports of dairy produce. The export trade aspects of calves from treated dairy cows also requires further consideration.

3.2 Destination and value of exports

Dairy produce exports

In 2008/2009, Australia exported $AUS 2.675 billion of dairy products, including cheese, butter and butterfat, skim and whole milk powder. Details of the export destinations are provided in the following table.

Table 2: Dairy Product Exports in 2008-2009

RANK (BY $ VALUE)	IMPORTING COUNTRY	QUANTITY (KTONNE)	VALUE ($AUS MILLION)
CHEESE			
1	Japan	74.4	398.9
2	USA	10.6	59.7
3	Saudi Arabia	5.4	30.6
Total		**146.4**	**796.1**
BUTTER AND BUTTERFAT			
1	Egypt	8.5	22.0
2	Singapore	5.1	20.2
3	Malaysia	3.7	14.0
Total		**70.4**	**232.1**
SKIM MILK POWDER			
1	Philippines	25.4	99.7
2	Singapore	17.1	54.0
3	Malaysia	14.9	49.0
Total		**162.3**	**552.9**
CASEIN			
1	Japan	2.3	43.6

RANK (BY $ VALUE)	IMPORTING COUNTRY	QUANTITY (KTONNE)	VALUE ($AUS MILLION)
2	USA	2.4	29.5
Total		**7.6**	**107.5**
WHOLE MILK POWDER			
1	Singapore	17.0	77.0
2	Malaysia	3.2	14.9
3	Thailand	3.4	14.6
Total		**116.3**	**475.3**
OTHER PRODUCTS			
Fresh milk		69.2 ML	102.1
Other fresh products		0.2 ML	0.4
Condensed milk		81.4	158.9
Other powders		51.4	249.7
Total			**511.1**

3.3 Comparison of the (proposed) Australian MRLs with Codex and overseas MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides. Codex CXLs are primarily intended to facilitate international trade, and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods. Ivermectin and triclabendazole have been considered by Codex. The following relevant Codex CXLs and overseas tolerances have been established for ivermectin and triclabendazole.

Table 3: Comparison of Australian and Overseas MRLs for triclabendazole and ivermectin in milk

COMPOUND	OVERSEAS MRL/TOLERANCE (mg/kg)				AUSTRALIAN MRL(mg/kg)
	CODEX	EU	USA	JAPAN	
TRICLABENDAZOLE					
Cattle milk	--	--	--	--	*0.05
IVERMECTIN					
Cattle milk	0.01	--	--	0.04	0.05

***** *MRL set at or about the limit of quantification for the analytical method*

3.4 Potential risk to trade

Export of treated produce containing finite (measurable) residues of triclabendazole and ivermectin 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.

Export trade of dairy commodities

The recommended use-pattern for *Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle* includes treatment of non-lactating (dry) dairy cattle at 56 days prior to calving, with a milk WHP of 60 hours (5 milkings) post-calving.

When the recommended milk WHP of 60 hours (5 milkings) is observed, it is concluded that:

(i) Ivermectin residues in milk are expected to be below the method LOQ of 0.4 µg/kg (<0.0004 mg/kg), which is below the Australian MRL of 0.05 mg/kg for ivermectin in milk, and the Codex CXL of 0.01 mg/kg for ivermectin in milk.

(ii) Triclabendazole residues in milk are expected to be below the method LOQ of 0.05 mg/kg ie the recommended Australian MRL of *0.05 mg/kg.

It is noted that there are no overseas MRLs/tolerances for triclabendazole residues in milk. However, given that:

- The levels of triclabendazole residues in milk are below the method LOQ; and
- The methodology used to quantify triclabendazole residues in edible commodities in Australia is similar to that used in overseas countries. Therefore, similar method LOQs would be applied overseas.

It is concluded that the risk to Australia's export trade in dairy commodities is low.

3.5 Trade advice statements

An export slaughter interval (ESI) of 70 days was assigned to *Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle* at the time of original registration, to ensure that triclabendazole and ivermectin residues in tissues from treated cattle declined to below the method LOQs (ie <0.1 mg/kg and <0.001 mg/kg, respectively).

It is concluded that the 70 day ESI remains appropriate. However, the trade advice statement on the product label needs to be amended to provide specific advice on calves born to dairy cows that were treated during pregnancy. The following trade advice statements are recommended:

TRADE ADVICE

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 70 days before slaughter for export. Calves born to cows that were treated with Coopers Sovereign during pregnancy, and not suckled/fed milk, must not be slaughtered for export for 70 days after treatment of the dam. Calves born to cows that were treated with Coopers Sovereign during pregnancy, and suckled/fed milk, must not be slaughtered for export for 70 days after treatment of the dam plus an additional 14 days, commencing at the last feeding of milk. The ESI on

this label was correct at the time of label approval. Before using this product, confirm the current ESI from Intervet on 1 800 226 511 or the APVMA website (www.apvma.gov.au/residues/ESI.shtml).

4 CONCLUSIONS

The risk to Australia's export trade in beef/veal and live cattle, arising from the use of *Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle*, was previously determined to be low when the recommended ESI of 70 days is observed, as residues in edible tissues from treated cattle are expected to be below the method LOQs for each analyte (ivermectin and triclabendazole).

Similarly, the risk to Australia's export trade in dairy commodities is considered to be low when the recommended 56 day treatment-to-calving interval and 60 hour (5 milkings) milk WHP are observed, as residues in milk from treated dairy cattle are expected to be below the method LOQs for each analyte (ivermectin and triclabendazole).

The APVMA is seeking comment from relevant industry groups and stakeholders in relation to whether the proposed use of *Coopers Sovereign Pour-on Flukicide and Anthelmintic for Cattle* on non-lactating (dry) dairy cattle poses an undue prejudice to Australia's export trade in calf meat and dairy commodities.

The APVMA also welcomes comment on any residues aspects of trade.