Australian Government

Australian Pesticides and Veterinary Medicines Authority

TRADE ADVICE NOTICE

Virbac Nitromec Injection Endectocide **and** Flukicide for Cattle

APVMA Product No. 59844

August 2008

This Trade Advice Notice for Virbac Nitromec Injection Endectocide and Flukicide for Cattle (APVMA Product Number 59844) is published by the Australian Pesticides & Veterinary Medicines Authority.

The APVMA invites comments on this Trade Advice Notice until 2 September 2008. Submissions should be sent to:

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1. INTRODUCTION

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has before it an application from Virbac (Australia) Pty Limited for the registration of a new combination product, *Virbac Nitromec Injection Endectocide and Flukicide for Cattle*, which contains the currently approved actives clorsulon (67 mg/mL), ivermectin (6.7 mg/mL) and nitroxynil (340 mg/mL). The new product is to be administered by subcutaneous injection to beef cattle and non-lactating (dry) dairy cattle, for the treatment and control of sensitive strains of internal and external parasites, including early immature, immature and adult liver fluke.

The application involves the establishment of an Australian Maximum Residue Limit (MRL) for nitroxynil in cattle milk. Additionally, the application requires the setting of meat and milk withholding periods (WHPs), establishment of an export slaughter interval (ESI), and approval of the proposed product label.

2. WITHHOLDING PERIODS AND MAXIMUM RESIDUE LIMITS

In support of the application, Virbac (Australia) Pty Limited provided details of two (2) confirmatory tissue residues trials, and two (2) confirmatory milk residues trials. All trials were conducted with *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* in Australia.

2.1. Meat

In the first tissue residues trial, beef cattle (n=15) were administered a single subcutaneous injection of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* at the 1× nominal dose rate of 1.5 mL product/50 kg bw (equivalent to 0.67 × the maximum proposed label rate). Groups of animals (n=5) were sacrificed at 21, 28 and 42 days after treatment, and samples of liver, kidney, muscle, perirenal fat and injection site tissues were collected and stored frozen until analysed for their concentrations of nitroxynil, clorsulon and ivermectin residues.

In the second tissue residues trial, beef cattle (n=18) were administered a single subcutaneous injection of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* at the maximum 1× proposed label rate of 2.2 mL product/50 kg. Groups of animals (n=6) were sacrificed at 56, 70 and 110 days after treatment, and samples of liver, kidney, muscle, perirenal fat and injection site tissues were collected and stored frozen until analysed for their concentrations of nitroxynil residues.

Of the three active constituents present in *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* (nitroxynil, ivermectin and clorsulon), nitroxynil is the "rate-limiting" residue, with the highest concentration of residues in edible bovine tissues, and the longest decline profile. It was determined that nitroxynil residues will govern the length of the WHP and ESI that is to be assigned to the new product.

Kidney was identified as the "target tissue" for nitroxynil residues in treated cattle. When the data from the two confirmatory residues trials were combined, and corrected to reflect the 1× the maximum proposed label rate, it was found that the highest nitroxynil residue in kidney of 2.25 mg/kg occurred at 21 days after treatment. Statistical analysis of the combined (corrected) data (ie determination of the upper 95 % confidence limit of the 95th percentile residue concentration) showed that nitroxynil residues in kidney are likely to be below the existing Australian MRL of 1 mg/kg for edible offal at 49.2 days after treatment. Given that there is no overlap in the sampling times of the two residues trials, and the observed variance of the results at the 42 and 56 day sampling times, it was concluded that a 56 day meat WHP should be assigned to the new product.

When the recommended 56 day meat WHP is observed, the concentrations of nitroxynil residues in other edible bovine tissues (liver, muscle, peri-renal fat and injection site tissues) comply with the relevant Australian nitroxynil MRLs. Similarly, when the recommended 56 day meat WHP is observed, residues of ivermectin and clorsulon in all edible tissues from treated cattle are expected to comply with the relevant Australian MRLs.

In the absence of residues data for calves that have been exposed to the product *in utero* (after treatment of pregnant dairy cows), it is recommended that a meat WHP of "*56 days after treatment of the dam*" be applied to calves.

2.1.1. Meat WHP

Thus, the following meat WHP is recommended for the use of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* in cattle:

> DO NOT USE less than 56 days before slaughter for human consumption. Calves born to cows that have been treated with *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* during pregnancy must not be slaughtered for human consumption for 56 days after treatment of the dam.

2.1.2. MRLs

No changes to the existing Australian MRLs for clorsulon, ivermectin and nitroxynil in edible tissues from treated cattle are required to cover the use of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle*.

2.1.3. Re-treatment interval

In the absence of empirical data, the minimum re-treatment interval is estimated as the time required for tissue residues arising from the first treatment to decline to below the method LOQ, thereby minimising the likelihood of residues accumulation.

The tissue residues decline data show that nitroxynil residues in all edible tissues have declined to below the method LOQ (<0.01 mg/kg) at 120 days (4 months) after treatment. Therefore, a minimum re-treatment interval of 120 days (4 months) is recommended for *Virbac Nitromec Injection Endectocide and Flukicide for Cattle*.

2.2. Milk

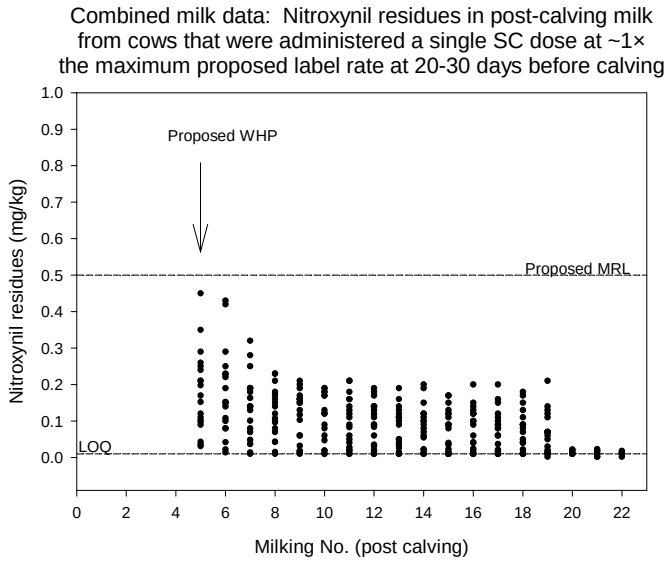
In the first milk residues trial, pregnant Friesian cows (n=10) were administered a single subcutaneous injection of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* at the 1× maximum proposed label rate at 20-34 days prior to calving. After each cow calved, the calves were allowed to suckle over a period of four (4) milkings (2 milkings/24 hours), and then were removed from their mothers. Milk samples were collected twice daily (am and pm), from the 5th to the 21st milking post-calving ie 48 to 252 hours post-calving. Milk samples collected for residues analysis were stored frozen until analysed for their content of nitroxynil, clorsulon and ivermectin residues.

In the second milk residues trial, pregnant dairy cows (n=20; sufficient to get 12 animals to calve at the appropriate time) were administered a single subcutaneous injection of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* at the 1× maximum proposed label rate at 20-28 days prior to calving. Cows were introduced into the milking herd within approximately 12 hours after calving. Milk from the first four (4) milkings (colostrum) was discarded, in accordance with standard industry practices. Milk samples were collected daily (am and pm), from the 5th milking post-calving to the 19th milking (total of 14 milkings, corresponding to 7 days). Milk samples collected for residues analysis were stored frozen until analysed for their content of nitroxynil residues. Additional milk samples were analysed for their fat content.

Once again, nitroxynil was identified as the "rate-limiting" residue component, with the highest concentration of residues in post-calving milk from treated dairy cows. It was determined that nitroxynil residues will govern the length of the milk WHP that is to be assigned to the new product.

Twenty (20) dairy cows calved between 20 and 30 days after treatment (8 from the first milk trial, and 12 from the second), and meet the requirements for consideration of the proposed 30 day treatment-to-calving interval. One animal from the first milk trial was excluded from the assessment because of abnormally low milk production volumes (<1 L) at a number of sampling times post-calving. Therefore, the concentrations of nitroxynil residues in milk from 19 cows have been considered in the combined milk residues data set.

The results for nitroxynil residues from both milk trials are presented below graphically.

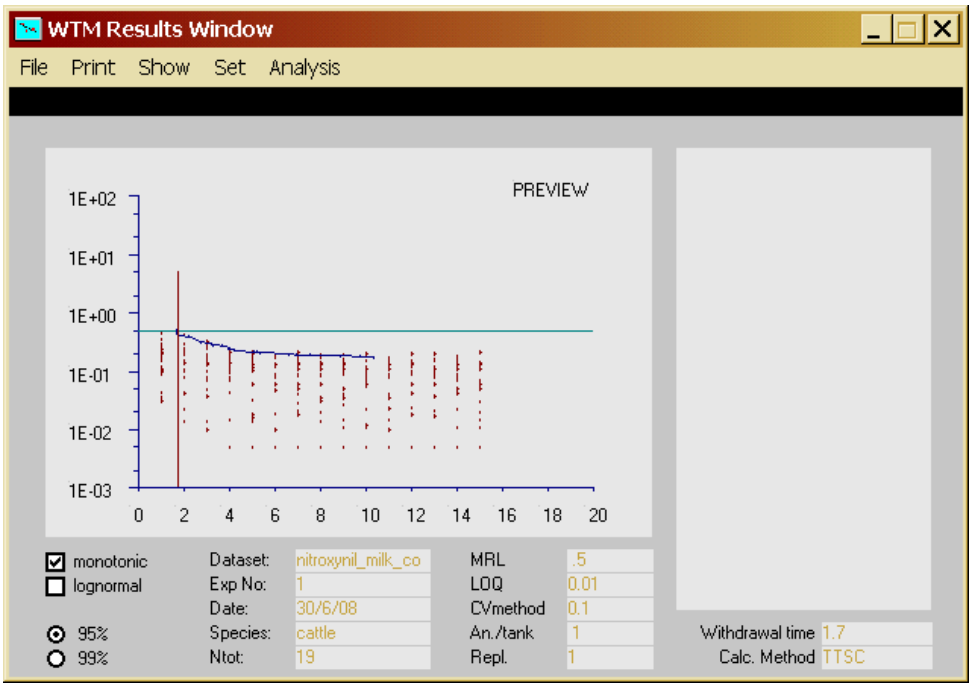


In the first milk residues trial, it was noted that the concentrations of nitroxynil residues in milk declined to <LOQ (<0.01 mg/kg) in 4 of the 7 animals, but stayed above the LOQ for the remaining 3 animals. This is in contrast to the results of the second milk residues trial, where the concentrations of nitroxynil residues in milk appear to decline between the 5th to 8th milkings, then remain relatively constant (above the LOQ) between the 9th and 19th milkings.

Statistical analysis of the combined milk residues data (using the EMEA's "MILK" program) showed that the proposed MRL of 0.5 mg/kg for nitroxynil in milk ***would not*** adequately cover the occurrence of residues in milk from the 5th milking post-calving onwards (see Figure (i) below). The plot shows milk residues concentrations (y-axis) at successive milkings (x-axis), with the first milking equating to milk collected at 60 hours after calving. The withdrawal time of 1.7 indicates that milk from the first two time points (ie the 5th and 6th milkings post-calving) would not comply with the proposed MRL of 0.5 mg/kg for nitroxynil in milk (with 95 % confidence).

After consideration of the observed decline of nitroxynil residues in milk between the 5th and 8th milkings post-calving, and statistical analysis of the results, it is concluded that a milk WHP of 84 hours (7 milkings) is appropriate.

Figure (i): Nitroxynil residues in bovine milk (MRL set at 0.5 mg/kg)



When the product is used in accordance with the 30 day treatment-to-calving interval, and the milk WHP of 84 hours (7 milkings) is observed:

- Clorsulon residues in milk are expected to be non-detectable (<0.02 mg/kg).
- Ivermectin residues in milk are expected to be below 0.005 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.
- Nitroxynil residues in milk are expected to be below the recommended Australian MRL of 0.5 mg/kg.

Owing to the occurrence of significant nitroxynil residues in post-calving milk from cows treated during the dry period, milk and colostrum from the first 7 milkings post-calving must not be fed to calves.

2.2.1. Milk WHP

Thus, the following milk WHP is recommended for the use of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* in non-lactating (dry) dairy cattle:

> DO NOT USE in lactating cows or within 30 days of calving. For 84 hours (7 milkings) after calving, all colostrum and milk collected from treated cows MUST BE DISCARDED, and not be used or processed for human consumption or fed to calves. If cows calve earlier than 30 days after treatment, consult your veterinarian for advice on the milk discard period.

2.2.2. MRLs

The available milk residues data support the establishment of a nitroxynil MRL of 0.5 mg/kg for cattle milk.

No changes to the existing Australian MRLs for clorsulon and ivermectin in milk are required to cover the use of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* in non-lactating (dry) dairy cattle.

3. COMMODITIES EXPORTED

Australian exports of beef/veal, live cattle, and dairy produce could be affected by the use of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle*.

3.1. Destination and value of exports

3.1.1. Beef/veal exports

Australia exported ~954 ktonne of beef and veal during 2006, which was valued at $AUS 4.6 billion. Details of the top 6 export markets for Australian beef are provided below.

Beef and veal exports in 2006 (Source: ABARE 2007)

Rank (by $ value)	Importing country	Quantity (ktonne)	Value ($AUS million)	Cumulative total (%)
1	Japan	405.8	2172.1	47.2
2	USA	295.2	1180.7	72.8
3	Korea, Rep. of	149.6	734.7	88.8
4	Chinese Taipei	28.6	134.6	91.7
5	European Union†	8.5	77.2	93.4
6	CIS$^{\Psi}$	12.5	61.0	94.7
Total		**953.9**	**4604.0**	

†Regarded as 25 countries

$^{\Psi}$ Commonwealth of Independent States

3.1.2. Live cattle exports

Australia exported over 634,000 head of live cattle during 2006, which were valued at approximately $AUS 408 million. Details of the top 6 export markets for Australian live cattle are provided below.

Live cattle exports in 2006 (Source: ABARE 2007)

Rank (by $ value)	Importing country	Quantity ('000 of animals)	Value ($AUS million)	Cumulative total (%)
1	Indonesia	386.6	246.9	60.5
2	Israel	79.4	58.2	74.8
3	Malaysia	56.5	31.3	82.5
4	Saudi Arabia	27.6	19.3	87.2
5	Japan	20.2	17.3	91.4
6	Philippines	13.1	7.7	93.3
Total		**634.3**	**407.9**	

3.1.3. Dairy produce exports

In 2006/2007, Australia exported $AUS 2.43 billion of dairy products, including cheese, butter and butterfat, skin and whole milk powder. Details of the export destinations are provided in the following table.

Dairy product exports in 2006 - 2007 (Source: ABARE 2007)

Rank (by $ value)	Importing country	Quantity (ktonne)	Value ($AUS million)
CHEESE			
1	Japan	95.8	337.9
2	Saudi Arabia	18.1	86.7
3	USA	13.8	53.1
Total		***212.3***	***824.6***
BUTTER AND BUTTERFAT			
1	Singapore	6.9	14.4
2	Egypt	7.4	13.9
3	Malaysia	4.4	11.0
Total		***80.7***	***178.6***
SKIM MILK POWDER			
1	Malaysia	24.3	72.2
2	Singapore	23.0	67.1
3	Thailand	17.9	51.1
Total		***164.5***	***505.0***
CASEIN			
1	USA	3.4	32.4
2	Japan	2.5	31.8
Total		***11.7***	***113.5***
WHOLEMILK POWDER			
1	Singapore	13.7	41.4
2	Malaysia	4.6	14.5
3	Taiwan	4.6	13.5
Total		***110.3***	***333.6***
OTHER PRODUCTS			
Fresh milk		81.8 ML	96.3
Other fresh products		2.1 ML	11.8
Condensed milk		83.0	156.9
Other powders		61.7	211.0
Total			***476.0***

3.2. Proposed Australian use pattern

Virbac Nitromec Injection Endectocide and Flukicide for Cattle [Clorsulon (67 mg/mL), Ivermectin (6.7 mg/mL) and Nitroxynil (340 mg/mL)]

Host	Purpose	Dose Rate
Cattle (Beef and non-lactating dairy cattle)	For the treatment and control of sensitive gastro-intestinal roundworms, liver flukes (early immature, immature and adult), lungworms, eyeworms, sucking and biting lice, mites, screw worm fly and cattle tick	Nominal: 1.5 mL product/50 kg BW (equivalent to 2 mg clorsulon/kg bw, 0.2 mg ivermectin/kg bw, and 10.2 mg nitroxynil/kg bw). ***Beef cattle*** Maximum: 2.25 mL product/50 kg animal or 4.5 mL product/101 kg animal (equivalent to 3 mg clorsulon/kg bw, 0.3 mg ivermectin/kg bw and 15.3 mg nitroxynil/kg bw). ***Non-lactating (dry) dairy cattle*** Maximum: 13.5 mL product/401 kg animal (equivalent to 2.26 mg clorsulon/kg bw, 0.23 mg ivermectin/kg bw, and 11.4 mg nitroxynil/kg bw).

3.2.1. Critical comments

Administer by subcutaneous injection only.
DO NOT USE intravenously or intramuscularly.
Inject high on the neck behind the ear.

3.2.2. Re-treatment interval

DO NOT re-treat animals for 120 days (4 months) after last treatment.

3.2.3. Withholding periods

MEAT: DO NOT USE less than 56 days before slaughter for human consumption. Calves born to cows that have been treated with *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* during pregnancy must not be slaughtered for human consumption for 56 days after treatment of the dam.

MILK: DO NOT USE in lactating cows or within 30 days of calving. For 84 hours (7 milkings) after calving, all colostrum and milk collected from treated cows MUST BE DISCARDED, and not be used or processed for human consumption or fed to calves. If cows calve earlier than 30 days after treatment, consult your veterinarian for advice on the milk discard period.

3.2.4. Trade advice

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 120 days (4 months) before slaughter for export. Calves born to cows that were treated with *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* during pregnancy must not be slaughtered for export for 120 days (4 months) after treatment of the dam. Before using

this product confirm the current ESI from either Virbac on 1800 009 847 or the APVMA website www.apvma.gov.au/residues/ESI.shtml.

3.3. Overseas registrations

Virbac Nitromec Injection Endectocide and Flukicide for Cattle is not currently registered in any overseas country.

3.4. 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 has been considered by Codex. In contrast, clorsulon and nitroxynil have not been considered by Codex. The following relevant Codex CXLs and overseas tolerances have been established for ivermectin, clorsulon and nitroxynil.

Comparison of Australian and Overseas MRLs/tolerances for clorsulon, ivermectin and nitroxynil

Commodity	Overseas MRL/tolerance (mg/kg)				Australian MRL (mg/kg)
	CODEX	EU	USA	Japan	
Clorsulon					
Cattle, Edible offal of	--	--	--	0.1†	*0.1
Cattle meat	--	0.035	0.1	0.08†	*0.1
Cattle fat	--	--	--	0.08†	--
Cattle milk	--	--	--	2†	1.5
Cattle liver	--	0.1	--	0.1†	--
Cattle kidney	--	0.2	1.0	0.4†	--
Ivermectin					
Cattle kidney	--	0.03		0.01	*0.01
Cattle liver	0.10	0.10	0.10	0.10	0.1
Cattle meat [in the fat]	--	--	--	--	0.04
Cattle milk	0.01	--	--	--	0.05
Cattle fat	0.04	0.10	--	0.04	--
Cattle muscle	--	--	0.01	0.01	--
Cattle, edible offal	--	--	--	0.01	--
Nitroxynil					
Cattle, Edible offal of	--	--	--	0.5†	1
Cattle meat	--	0.4	--	0.5†	1
Cattle fat	--	0.2	--	0.6†	--
Cattle liver	--	0.02	--	0.5†	--
Cattle kidney	--	0.4	--	0.5†	--
Cattle milk	--	--	--	--	0.5

†Provisional MRLs

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

3.5. Potential Risk to Trade

Export of treated produce containing finite (measurable) residues of clorsulon, ivermectin or nitroxynil 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.

3.5.1. Identification of the "critical" residue component

Of the three active constituents present in *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* (nitroxynil, ivermectin and clorsulon), nitroxynil is the "rate-limiting" residue, with the highest concentration of residues in edible bovine tissues and milk, and the longest decline profile. Thus, it is the decline of nitroxynil residues that governs the length of the ESI (and WHP) that is assigned to the new product.

3.5.2. Identification of the most sensitive export markets for Australian cattle (*edible tissues*)

Beef and veal exports

The top three importing countries for Australian beef/veal are Japan, the USA and Korea, with exports to these countries representing ~90 % of the total market.

In relation to the importing standards for nitroxynil, it is noted that Japan has set provisional MRLs for this chemical in cattle tissues, but these MRLs are lower than the corresponding Australian MRLs. Further, there are no tolerances for nitroxynil in the USA, and there are no Codex CXLs (which are generally adopted by Korea).

Live cattle exports

Australia's main export markets for live cattle are Indonesia, Israel, Malaysia, Saudi Arabia and Japan.

As indicated above, Japan has set provisional MRLs for nitroxynil residues in cattle tissues, but these MRLs are lower than the corresponding Australian MRLs. The remaining export markets are either Asian or Middle Eastern, and typically adopt the Codex CXLs as their import standards. In the absence of any Codex CXLs for nitroxynil, it is possible these countries could default to the relevant European MRLs. However, it is noted that the EU MRLs for nitroxynil residues in cattle tissues are lower than the corresponding Australian MRLs.

Conclusion

The appropriate "endpoint" for the ESI determination is the standard applied by the most sensitive importing market. In the absence of any tolerances for nitroxynil in the

USA, the ESI "endpoint" has been identified as the decline of nitroxynil residues in cattle tissues down to the method LOQ (<0.01 mg/kg).

ESI determination

Kidney is the "target tissue" for nitroxynil residues in treated cattle, and it is the decline of nitroxynil residues in kidney that governs the length of the ESI that is to be assigned to the new product. Statistical analysis of the available data for nitroxynil residues in cattle kidney showed that a period of 118 days is required for kidney residues to decline to below the method LOQ (<0.01 mg/kg). Therefore, a 120 day (4 month) ESI is recommended for *Virbac Nitromec Injection Endectocide and Flukicide for Cattle*.

3.5.3. Trade Advice Statements

The following trade advice statement is to be included on the product label:

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 120 days (4 months) before slaughter for export. Calves born to cows that were treated with *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* during pregnancy must not be slaughtered for export for 120 days (4 months) after treatment of the dam.

3.5.4. Identification of the most sensitive export markets for Australian *dairy commodities*

The recommended use-pattern for *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* includes treatment of non-lactating (dry) dairy cattle at 30 days prior to calving, with a milk WHP of 84 hours (7 milkings) post-calving.

When the recommended milk WHP of 84 hours (7 milkings) is observed, it is concluded that:

(i) Clorsulon residues in milk are expected to be non-detectable (<0.02 mg/kg).

(ii) Ivermectin residues in milk are expected to be below 0.005 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.

(iii) Nitroxynil residues in milk are expected to be below the recommended Australian MRL of 0.5 mg/kg. ***However, there are no overseas MRLs/tolerances for nitroxynil residues in milk.***

Thus, the use of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* in accordance with the label instructions has the potential to unduly prejudice Australia's export trade in dairy commodities. Accordingly, advice is sought from stakeholder groups (including Dairy Australia) on the perceived level of risk to Australia's export trade in dairy commodities, and whether there are industry-based strategies available to manage the identified trade risks.

4. CONCLUSIONS

The APVMA has considered whether use of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle*, in accordance with the label instructions, could potentially unduly prejudice trade and commerce between Australia and places outside Australia, as per Section 14(3)(e)(iv) of the Agvet Codes.

Beef/veal and live cattle: The risk to Australia's export trade in beef/veal and live cattle, arising from the use of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle*, is considered to be low when the recommended ESI of 120 days (4 months) is observed, as residues in edible tissues from treated cattle are expected to be below the method LOQs for each analyte (clorsulon, ivermectin and nitroxynil).

Dairy commodities: In contrast, the use of *Virbac Nitromec Injection Endectocide and Flukicide for Cattle* in non-lactating (dry) dairy cows has ***the potential to unduly prejudice Australia's export trade in dairy commodities***, ***due to the presence of nitroxynil residues in milk***.

Accordingly, the APVMA is seeking comment from relevant industry groups and stakeholders in relation to the perceived level of risk to Australia's export trade in dairy commodities, and whether there are industry-based strategies available to manage the identified trade risks.

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