CONCURRENT USE OF REGISTERED VETERINARY MEDICINES IN LACTATING DAIRY COWS IN NEW ZEALAND

Introduction

A recent change to the Ministry for Primary Industries (MPI) NZCP1 milk supply regulations, and consequently dairy companys' milk supply agreements, stipulates that where multiple medicines are prescribed to treat the same condition at the same time, written advice must be obtained from the prescribing veterinarian for the milk withholding time to be observed. In the absence of written advice, a 35 day milk withholding time applies.

A veterinarian is legally allowed to prescribe the use of one or more Restricted Veterinary Medicines (RVMs) for concurrent treatment of dairy cows. It is the vet's responsibility to advise the appropriate withholding periods (WHP) to be observed following veterinary medicine treatment(s). The veterinarian must apply their knowledge to set the WHP, which may include further research if this is not stated on the product labels.

This situation includes animals treated on the farm by the veterinarian, and for products prescribed for the farmer's ongoing use, such as antibiotics and anti-inflammatory vet medicines used to treat mastitis.

Veterinarians generally seek to avoid liability where an inhibitory substance may be identified in milk from a herd, for instance where concurrent treatment to animal/s has been prescribed. Many veterinarians have been reluctant to apply a milk WHP in these situations, due to the scarcity of technical data available.

Objective

To establish the effect of concurrent administration of injectable or intramammary veterinary medicine product pairs on milk residues in lactating dairy cows.

Group	Product 1	Number of treatments	Route of administration	Product 2	Number of treatments	Route of administration
1	TyloVet 25mL	3	Intramuscular	KetoMax 10mL	2	Intramuscular
2	TyloVet 25mL	3	Intramuscular	MeloxiVet 12.5mL	1	Subcutaneous
3	Orbenin LA	5*	Intramammary	KetoMax 10mL	2	Intramuscular
4	Orbenin LA	5*	Intramammary	MeloxiVet 12.5mL	1	Subcutaneous
5	Orbenin LA	5*	Intramammary	TyloVet 25mL	5	Intramuscular
6	Penclox	3*	Intramammary	KetoMax 10mL	2	Intramuscular
7	Penclox	3*	Intramammary	MeloxiVet 12.5mL	1	Subcutaneous
8	Penclox	3*	Intramammary	TyloVet 25mL	3	Intramuscular
9	Intracillin Inj 20mL	3	Intramuscular	KetoMax 10mL	2	Intramuscular
10	Intracillin Inj 20mL	3	Intramuscular	MeloxiVet 12.5mL	1	Subcutaneous
11	Lincocin Forte	3*	Intramammary	TyloVet 25mL	3	Intramuscular
12	Lincocin Forte	3*	Intramammary	KetoMax 10mL	2	Intramuscular
13	Lincocin Forte	3*	Intramammary	MeloxiVet 12.5mL	1	Subcutaneous
14	Lincocin Forte	3*	Intramammary	Engemycin 20mL	3	Intramuscular
15	Engemycin 20mL	3	Intramuscular	KetoMax 10mL	2	Intramuscular
16	Engemycin 20mL	3	Intramuscular	MeloxiVet 12.5mL	1	Subcutaneous
17	Mastalone	3*	Intramammary	KetoMax 10mL	2	Intramuscular
18	Mastalone	3*	Intramammary	MeloxiVet 12.5mL	1	Subcutaneous
19	Mastalone	3*	Intramammary	TyloVet 25mL	3	Intramuscular

Table 1. Treatment groups **All four quarters treated*

Study design

A randomised field study was undertaken on two commercial New Zealand dairy farms. Lactating, healthy dairy cows being milked twice daily that had not been treated with an antibiotic or anti-inflammatory product during the 30 days prior were enrolled. There were five cows in each of 19 study groups (refer Table 1).

All intramammary products were administered to all four quarters of the cow being treated.

Treatments were administered at the recommended label frequency for each product.

Following the longest milk WHP of the two products, a composite milk sample was collected at each milking for the next four milkings, using proportionate herd test meters. Each milk meter was used once only per milking to collect one sample per milking, and was hot-washed after each milking.

Milk samples were sent to MilkTest NZ for analysis using Liquid Chromatography-Mass spectrometry (LC-MS), to determine the presence and concentration of inhibitory substances (antibiotics) in the milk. The concentration of each antibiotic active in each milk sample was compared to the maximum residue limit (MRL) permitted in milk according to the NZ Ministry of Primary Industries 'Food Notice: Maximum Residue Levels for agricultural compounds'.

The results presented for this study include the group mean and upper 99% confidence interval for the residue concentration in milk and compared to the MRL threshold. This is the same statistical analysis and method followed for regulatory residue studies to determine the milk WHP for single product registration.

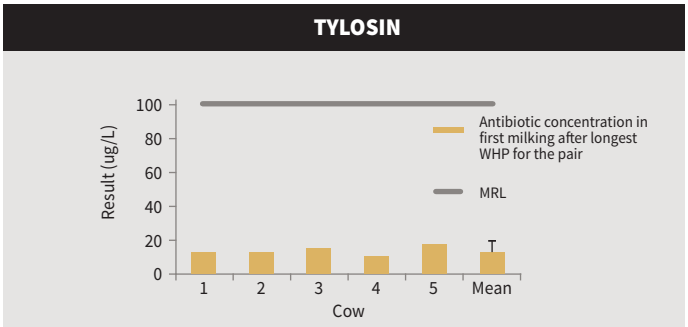
Results

There were no abnormal observations detected at any of the injection sites, or in any of the animals during the study period.

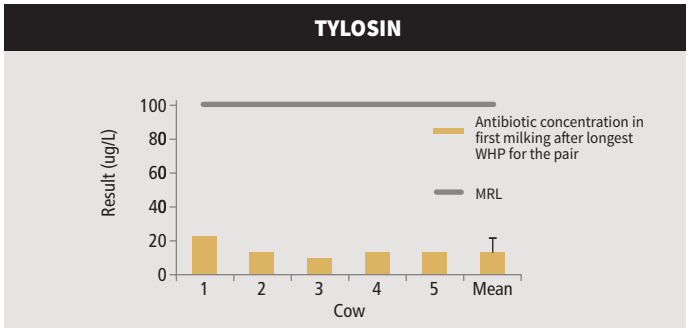
For each of the product pairs, the quantitative test results for the antibiotic level in milk at the first milking after the longest milk withholding period of the product pair are presented in the following figures. Results are presented by cow and group mean (with 99% confidence level).

The NZ MRL threshold for the antibiotic measured is indicated with a horizontal line.

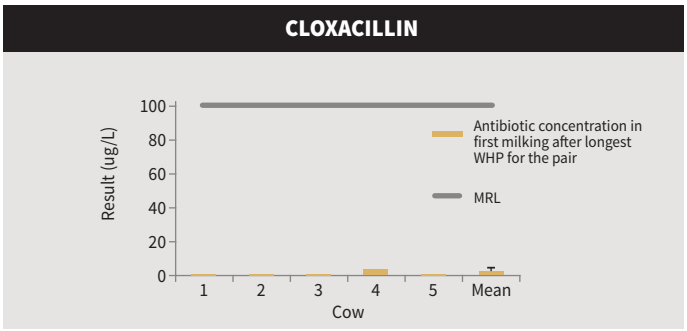
Group 1: TyloVet 25mL IM, 3 x 24 hourly, and KetoMax 10mL IM, 2 x 24 hourly



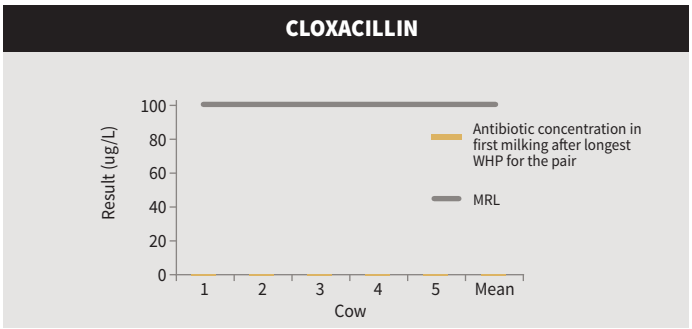
Group 2: TyloVet 25mL IM, 3 x 24 hourly, and MeloxiVet 12.5mL, 1 x SQ



Group 3: Orbenin LA 5 x all four quarters 24 hourly, and KetoMax 10mL IM, 2 x 24 hourly

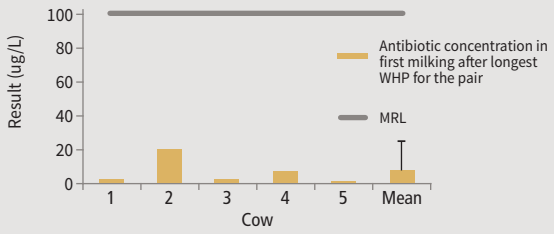


Group 4: Orbenin LA 5 x all four quarters 24 hourly, and MeloxiVet 12.5mL, 1 x SQ

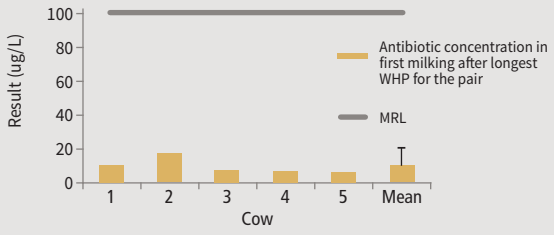


Group 5: Orbenin LA 5 x all four quarters 24 hourly, and Tylovet 25mL IM, 5 x 24 hourly

CLOXACILLIN

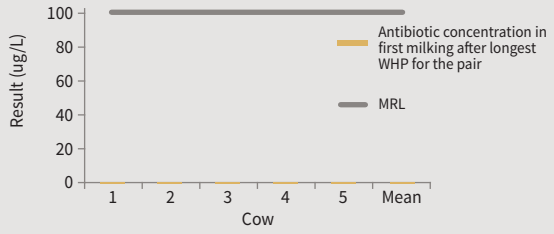


TYLOSIN

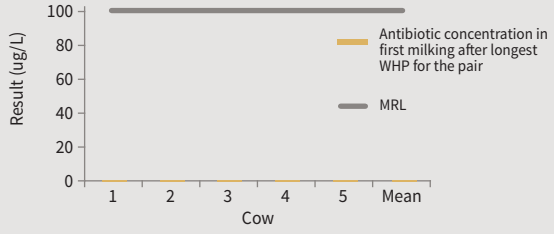


Group 6: Penclox 3 x all four quarters 24 hourly, and KetoMax 10mL IM, 2 x 24 hourly

PENICILLIN

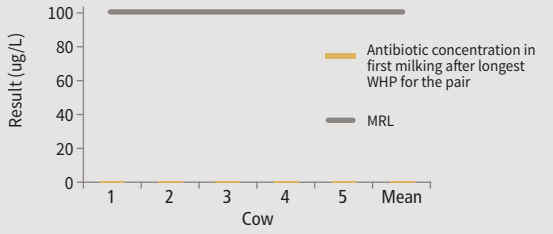


CLOXACILLIN

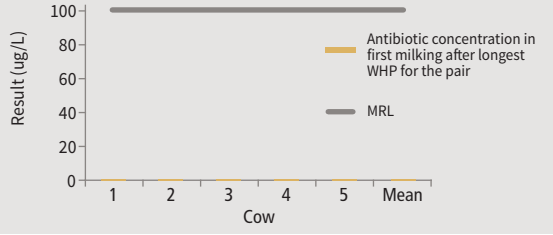


Group 7: Penclox 3 x all four quarters 24 hourly, and MeloxiVet 12.5mL, 1 x SQ

PENICILLIN

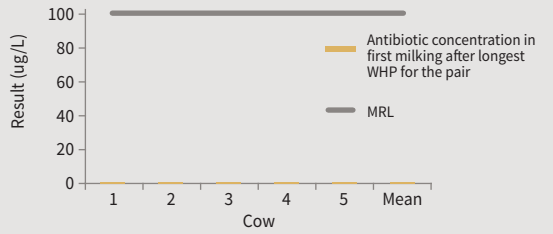


CLOXACILLIN

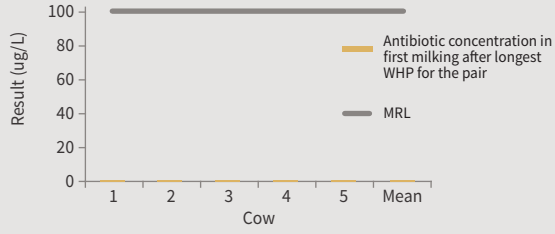


Group 8: Penclox 3 x all four quarters 24 hourly, and TyloVet 25mL IM, 3 x 24 hourly

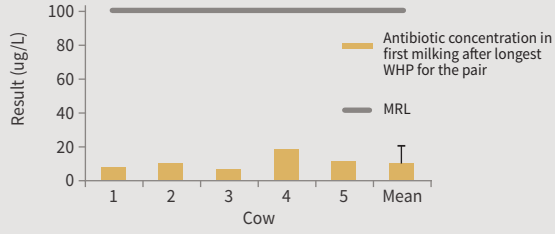
PENICILLIN



CLOXACILLIN

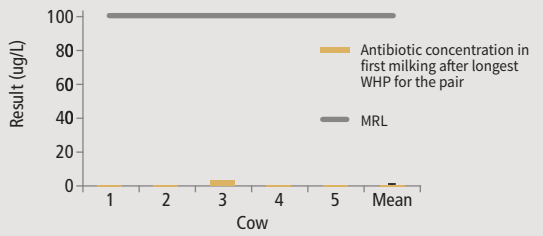


TYLOSIN



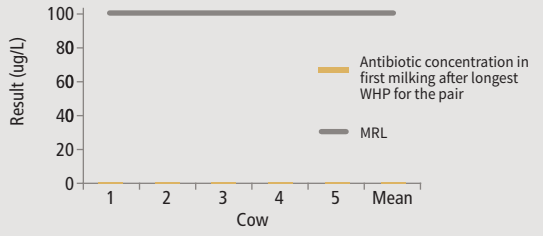
Group 9: Intracillin 20mL IM, 3 x 24 hourly, and KetoMax 10mL, IM 2 x 24 hourly

PENICILLIN



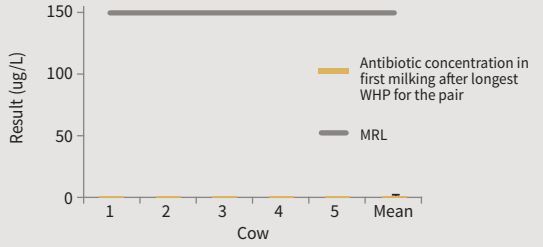
Group 10: Intracillin 20mL IM, 3 x 24 hourly, and MeloxiVet 12.5mL, 1 x SQ

PENICILLIN



Group 11: Lincocin Forte 3 x all four quarters 12 hourly, and TyloVet 25mL IM, 3 x 24 hourly

LINCOMYCIN



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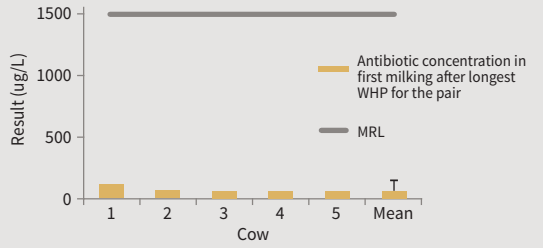
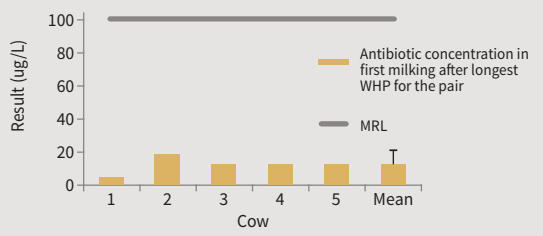


TYLOSIN



Group 12: Lincocin Forte 3 x all four quarters 12 hourly, and KetoMax 10mL IM, 2 x 24 hourly

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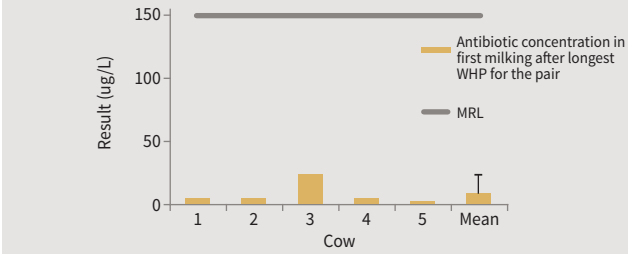

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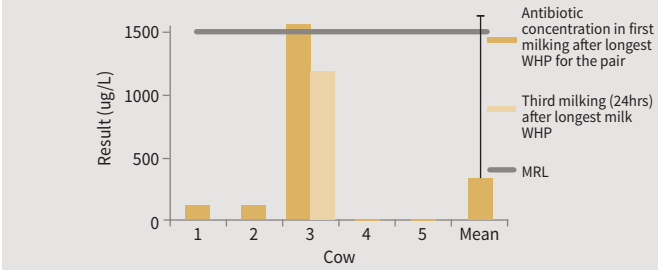
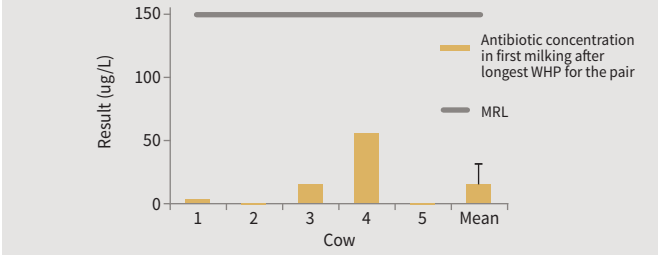


Group 13: Lincocin Forte 3 x all four quarters 12 hourly, and MeloxiVet 12.5mL, 1 x SQ

LINCOMYCIN



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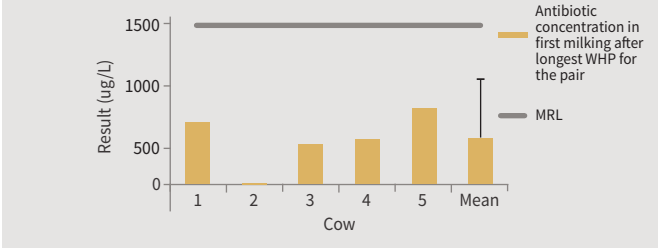
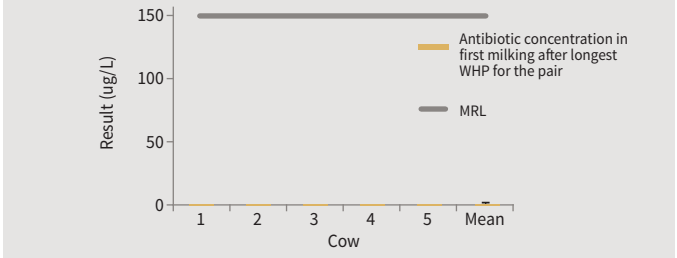


Group 14: Lincocin Forte 3 x all four quarters 12 hourly, and Engemycin 20mL IM, 3 x 24 hourly

LINCOMYCIN



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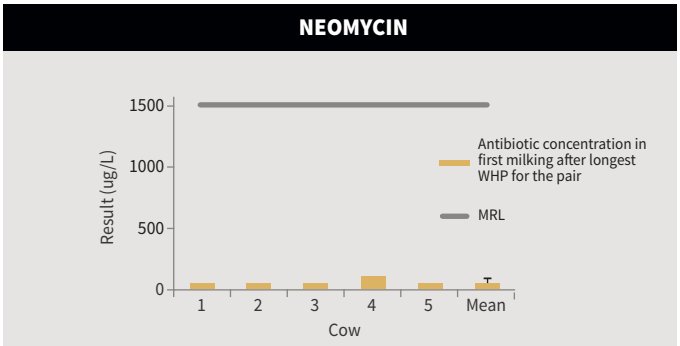

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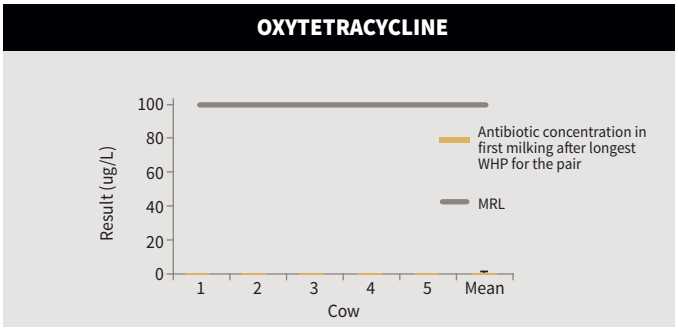
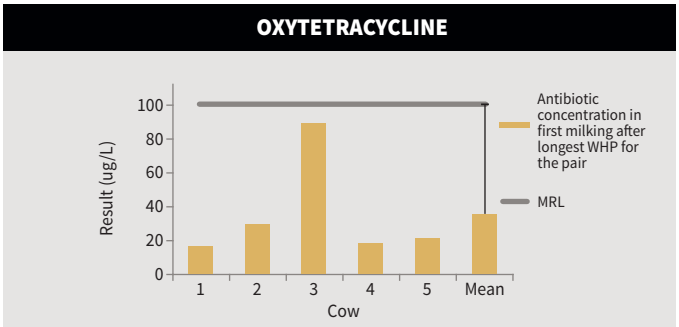


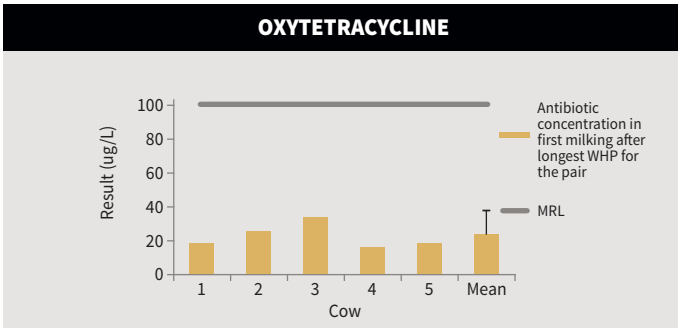
Group 15: Engemycin 20mL IM, 3 x 24 hourly and KetoMax 20mL IM, 2 x 24 hourly

OXYTETRACYCLINE



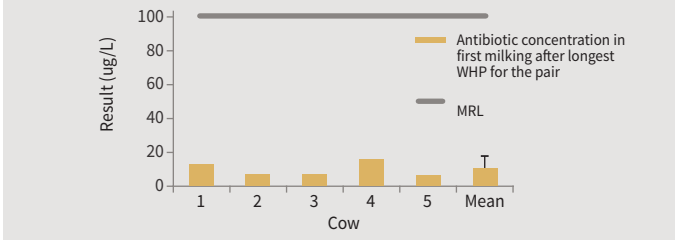
Group 16: Engemycin 20mL IM, 3 x 24 hourly and MeloxiVet 12.5mL, 1 x SQ

OXYTETRACYCLINE



Group 17: Mastalone 3 x all four quarters 24 hourly, and KetoMax 10mL IM, 2 x 24 hourly

OXYTETRACYCLINE



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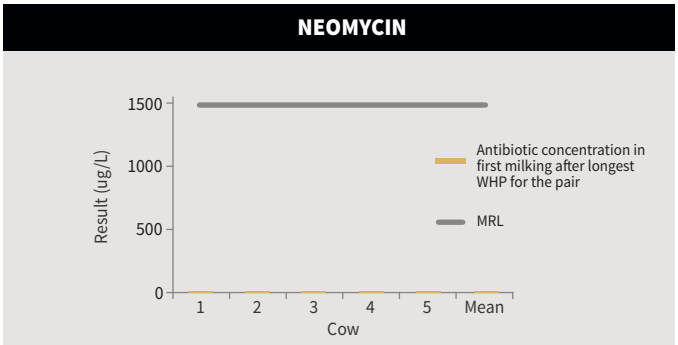
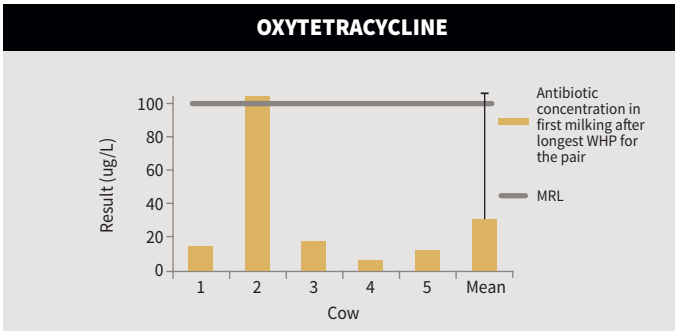


Group 18: Mastalone 3 x all four quarters 24 hourly, and MeloxiVet 12.5mL, 1 x SQ

OXYTETRACYCLINE



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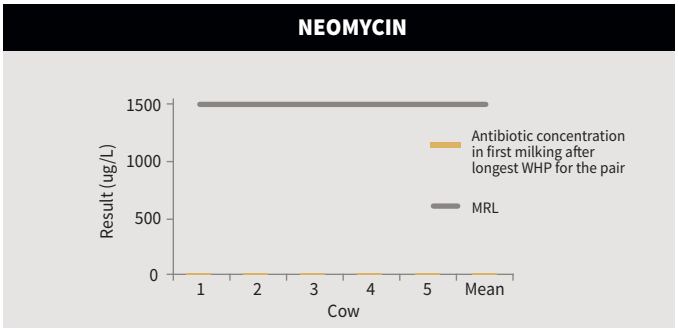
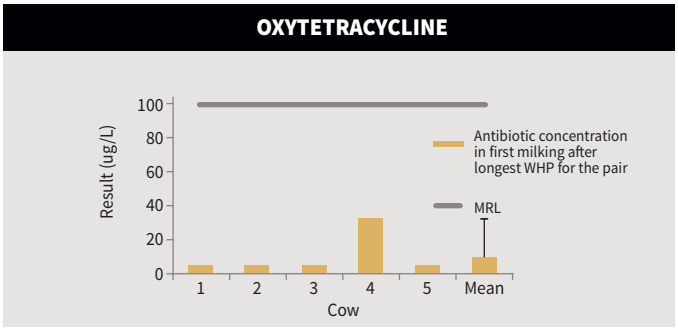
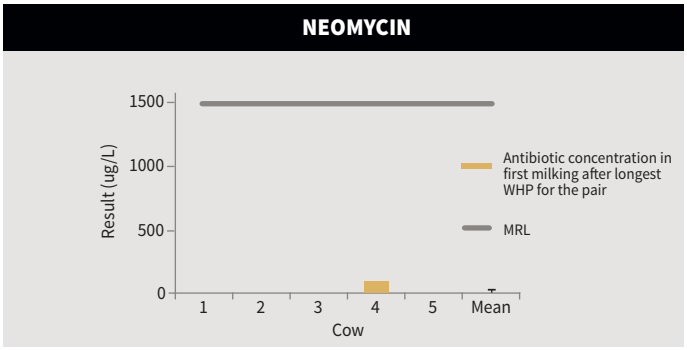
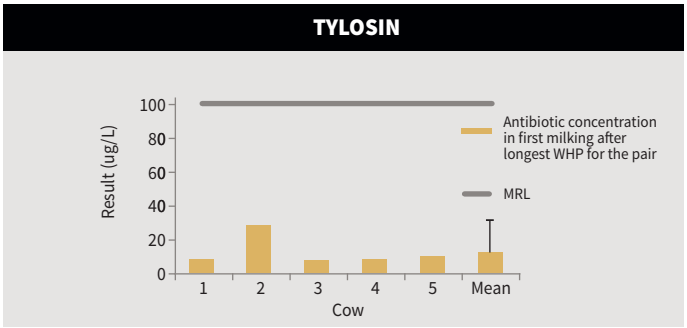


Group 19: Mastalone 3 x all four quarters 24 hourly, and TyloVet 25mL IM, 3 x 24 hourly

OXYTETRACYCLINE







Discussion

Milk samples from two out of 95 cows tested had one antibiotic concentration above the MRL at the first milking after the longest withholding period for the product pair. Test results for these two animals were only slightly above the MRL, but due to limited statisical power this still resulted in the group mean 99% confidence interval upper limit above the MRL. In both cases the other four cows in each group returned a low result at the same time point. The two outliers did return to antibiotic concentration levels below MRL within 24 hours.

These results show individual animal variation that occurs in biological systems. The major route of clearance for most intramammary products is via milk excretion, and subsequent milk removal.

The incidence of antibiotic concentration above the MRL threshold in this study was rare. The two cows with results above MRL could be attributed to low milk production (reducing excretion and 'flushing' of the antibiotic from the mammary gland). Scar tissue or damage inside one or more quarters as a result of prior mastitis or trauma to the mammary tissue may also change the rate of clearance of antibiotic from the body via milk.

Note, it is unusual to treat all four quarters simultaneously with lactating cow products, as occurred in this study. Thus a higher quantity of antibiotic was administered to each cow than would be customary in practice.

Individual cow (and group mean) antibiotic concentration in milk have been presented in this Technical Bulletin. On a commercial farm the milk from recently treated cows will generally be significantly diluted with milk from the remaining cows supplying the herd. In addition, cows supplying milk following compliance with WHPs will generally contribute only a small proportion of milk collected by the milk processor on any given day.

Inhibitory substance (IS) testing by milk companies uses different thresholds to those presented in this study as assessment against the MRL is not undertaken. Product label, and veterinary recommended withholding periods provide farmers with confidence that milk supplied to their milk processor will not incur an IS grade.

This study demonstrates that when two veterinary medicines were administered concurrently, there was no impact on the concentration of the active ingredients in the milk. This provides evidence that one medication does not appear to impact on the pharmacokinetics of milk clearance of the other medication.

This study did not assess the pharmacokinetics of the anti-inflammatories used in the product combinations. KetoMax (containing ketoprofen) has a nil milk withholding period and is unlikely to become more concentrated in milk as a result of being used with systemic or intramammary antibiotics. MeloxiVet (containing meloxicam) has a shorter treatment and withholding period than the antibiotics tested. Pharmacokinetic principles would suggest it is unlikely there would be any effect on the residue profile of MeloxiVet when used concurrently with systemic or intramammary antibiotics.

Conclusions

Concurrent administration of two veterinary medicines to dairy cattle following label directions does not appear to impact the residue profile of the antibiotic active ingredients for the product pairs tested in this study.

This study provides evidence for veterinarians to prescribe appropriate milk withholding periods when treating cows, or providing veterinary authorisations for farmers to treat cows with antibiotic, and anti-inflammatory combinations.

This study was conducted under animal ethics approval from Ruakura AEC, approval number 14134.