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Expert Opinion

Determination of Withdrawal Periods of Deltamethrin after treatment of cattle and sheep with Butox[®] 50

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1. Introduction / Product Rationale

Deltamethrin (98% cis-isomer) is a synthetic type II pyrethroid insecticide and acaricide. It is approved as Butox[®] 50, which is a concentrate containing 50 g deltamethrin (DTM) / L. Butox 50 is used topically for prevention and treatment of ticks, flies, lice and mange on cattle and sheep. For curative treatment a spraywash application at a concentration of 1 mL / L water is recommended. If necessary the treatment can be repeated after 10 days.

This expert opinion will estimate the withdrawal periods for edible bovine and ovine tissues and milk of dairy cows on the basis of relevant residue depletion studies and the maximum residue limits (MRL) as set up by the Committee for Veterinary Medicinal Products (CVMP) (EMEA/MRL/530/98-Rev.5: Deltamethrin Summary Report of the CVMP, 14.04.1999):

Marker residue	Animal species	Target tissues	MRL
Cis-Deltamethrin	Bovine	Muscle	10 µg / kg
		Fat	50 µg / kg
		Liver	10 µg / kg
		Kidney	10 µg / kg
		Milk	20 µg / kg
	Ovine	Muscle	10 µg / kg
		Fat	50 µg / kg
		Liver	10 µg / kg
Kidney		10 µg / kg	

2. Residue Depletion Studies

2.1 Deltamethrin (DTM) Residues in Bovine Tissues

Study V-0193-0007: Residues of DTM in bovine tissues following spraywash-administration of Butox[®] 50

24 German Black Pied heifers of 169 - 231 kg bodyweight were spraywashed twice at a 10 days interval with Butox[®] 50 at a concentration of 1 mL / L water. At each administration about 4 L of the spray-wash solution were sprayed onto the entire body of the animals using a spraying equipment (pressure about 5 bar) to achieve complete saturation of the fur.

Groups of 4 animals were slaughtered 12, 24 and 48 hours and 4, 7 and 14 days following 2nd administration.

Residues of DTM were determined (chromatography mass spectrometry) in samples of muscle, liver and kidney taken 12, 24 and 48 hours following 2nd administration and in samples of subcutaneous fat taken at all slaughter time points.

No DTM concentrations above LOQ were measured in muscle, subcutaneous fat, liver and kidney of all animals at all slaughter time points investigated.

2.2 Deltamethrin (DTM) Residues in Bovine Milk

Study V-0193-0012: Residues of DTM in the milk of dairy cattle following spraywash-administration of Butox[®] 50

Four low yielding and four high yielding German Black Pied dairy cows of 462 - 690 kg bodyweight were spraywashed twice at a 10 days interval with Butox[®] 50 at a concentration of 1 mL / L water. At each administration 4 L of the spray-wash solution were sprayed onto the entire body of the animals using a spraying equipment (pressure about 5 bar) to achieve complete saturation of the fur.

Residues of DTM were determined (chromatography mass spectrometry) in milk samples taken on 4 successive milkings after 2nd administration of Butox[®] 50.

No DTM concentrations above LOQ were measured in the milk samples investigated.

2.3 Deltamethrin (DTM) Residues in Ovine Tissues

Study V-0193-0056: Residues of DTM in ovine tissues following spraywash-administration of Butox[®] 50

In this study 24 female Merino x Mountain Sheep of 23 - 30 kg bodyweight were spray-washed twice at a 10 days interval with Butox[®] 50 at a concentration of 1 mL / L water. At each administration 3 L of the spray-wash solution were sprayed onto the entire body of the animals using a spraying equipment (pressure about 5 bar). A surplus of spray-wash solution was applied to make sure, that the fleece was thoroughly wet.

Groups of 4 animals were slaughtered 12, 24 and 48 hours and 4, 7 and 14 days following 2nd administration.

Residues of DTM were determined in samples of muscle, liver and kidney taken 12, 24 and 48 hours following 2nd administration and in samples of subcutaneous fat taken at all slaughter time points.

No DTM concentrations above LOQ were measured in muscle, liver and kidney of all animals at all slaughter time points investigated.

In subcutaneous fat samples concentrations above LOQ but below MRL were measured sporadically in a few animals and values slightly above MRL only in one sheep slaughtered 24 hours and in another animal slaughtered 48 hours after 2nd administration of Butox[®] 50:

Time	DTM concentration [$\mu\text{g} / \text{kg}$] in subcutaneous fat of sheep			
12 h	< LOQ	< LOQ	34.00	< LOQ
24 h	61.94*	< LOQ	< LOQ	< LOQ
48 h	< LOQ	32.12	< LOQ	68.85*
4 d	29.95	< LOQ	< LOQ	31.37
7 d	< LOQ	< LOQ	< LOQ	40.63
14 d	< LOQ	< LOQ	< LOQ	48.17

* above the MRL of 50 $\mu\text{g} / \text{kg}$

2.4 Quality of the Deltamethrin (DTM) Residue Depletion Studies V-0193-0007, V-0193-0012 and V-0193-0056

The studies were conducted to investigate the residues of cis-deltamethrin (DTM) in edible tissues of cattle (V-0193-0007) and sheep (V-0193-0056) and in the milk of dairy cows (V-0193-0012) after administration of Butox[®] 50 at the highest dosing regimen, which is spraywash-administration of 1 mL Butox 50 / L water twice at a 10 days interval as recommended for curative treatment of ticks, flies, lice and mange on cattle and sheep. Using this dosing regimen of double treatment DTM residues studies were conducted under worst case conditions in terms of exposure of the animals to DTM.

The studies were conducted in compliance with the Council Directive 81/852/EEC, the Volume VI of the Rules Governing Medicinal Products in the European Community and the OECD Principles of Good Laboratory Practice (Directive 87/18/EEC, Directive 88/320/EEC).

The analytical method (chromatography mass spectrometry) was previously validated (A. Renoux and P. Blain-Violeau, 2000) in terms of linearity, recovery, repeatability, reproducibility, limit of quantification (LOQ), specificity and long term stability. LOQs were set at 5 µg / kg for muscle, liver and kidney; 25 mg / kg for fat and 10 µg / L for milk, which is half of the respective MRLs and therefore sufficiently sensitive to detect DTM concentrations below the respective MRLs.

3 Determination of Withdrawal Periods for Butox[®] 50

3.1 Edible Bovine Tissues (Study V-0193-0007)

Deltamethrin (DTM) concentrations determined in Study V-0193-0007 were below the LOQ in all tissues of all animals at all slaughter time points investigated.

According to the EMEA note for guidance "Approach towards Harmonisation of Withdrawal Periods" (EMEA/CVMP/036/95) the use of the statistical model is not possible if all values are below the LOQ; therefore an alternative approach in order to estimate the withdrawal period was considered:

Since DTM concentrations in edible tissues were below the respective MRLs and even below the respective LOQs throughout the entire study at all time points investigated (fat: 12, 24, 48 hours and 4, 7 and 14 days after 2nd administration; muscle, liver and kidney: 12, 24 and 48 hours after 2nd administration), it can be concluded, that with a high probability the treatment of cattle with Butox[®] 50 at the recommended dosing regimen does not lead to measurable DTM residues in edible tissues.

Therefore a zero withdrawal period is recommended for edible tissues after treating cattle with Butox[®] 50.

3.2 Bovine Milk (Study V-0193-0012)

DTM concentrations determined in Study V-0193-0012 were below the LOQ (10 µg / L) in all milk samples taken at 4 consecutive milkings following 2nd administration of Butox[®] 50.

According to EMEA note for guidance "Approach towards Harmonisation of Withdrawal Periods" (EMEA/CVMP/036/95) the use of the statistical model is not possible if all values are below the LOQ; therefore an alternative approach in order to estimate the withdrawal period has to be considered:

Since DTM concentrations in the milk were below the MRL and even below the LOQ throughout the entire study at all time points investigated (milkings at about 12, 24, 36 and 48 hours following 2nd administration), it can be concluded, that with a high probability the treatment of dairy cows with Butox[®] 50 at the recommended dosing regimen does not cause measurable DTM residues in the milk.

Therefore a zero withdrawal period is recommended for milk after treating dairy cows with Butox[®] 50.

3.3 Edible Ovine Tissues (Study V-0193-0056)

DTM concentrations determined in study V-0193-0056 in muscle, liver and kidney were below the LOQ (5 mg / kg) at all slaughter time points investigated (12, 24, and 48 hours following 2nd administration of Butox[®] 50).

In subcutaneous fat concentrations above LOQ (25 µg / kg) but below MRL (50 µg / kg) were measured 12 hours (1 animal: 34 µg / kg), 48 hours (1 animal: 32 µg / kg), 4 days (2 animals: 30 and 31 µg / kg), 7 days (1 animal: 41 µg / kg) and 14 days following treatment (1 animal: 48 µg / kg). Values above the MRL were determined at two occasions: 24 hours (1 animal: 62 µg / kg) and 48 hours following treatment (1 animal: 69 µg / kg).

The use of the statistical model as recommended in the EMEA note for guidance "Approach towards Harmonisation of Withdrawal Periods" (EMEA/CVMP/036/95) is not possible, because most values are below the LOQ and therefore the linear regression assumption of normally distributed errors and linearity of the log e- transformed data versus time are unlikely to be fulfilled.

Therefore establishing the withdrawal period at the time where the concentrations of residues in all tissues for all animals are below the respective MRLs, which is at 4 days after treatment in study V-0193-0056, is considered as an alternative approach.

The daily intake of DTM was calculated on the basis of the residues measured in study V-0193-0056 (values below LOQ were set = LOQ) and on the basis of an assumed daily consumption of 300 g muscle, 100 g liver, 50 g kidney, and 50 g fat (standard food basket). The results clearly demonstrate that at each slaughter time point the daily intake of DTM is far below the Acceptable Daily Intake of 240 µg, which underlines the safety of edible tissues of Butox[®] 50 treated sheep for human consumption (for details see Annex 1):

Time	Calculated daily intake of DTM [µg] *	% of Acceptable Daily Intake **
12 h	3.61	1.50
24 h	3.96	1.65
48 h	3.76	1.57
4 d	3.64	1.52
7 d	3.69	1.54
14 d	3.79	1.58

* Total of DTM [µg] intake via fat, muscle, liver and kidney

** ADI = 240 µg according to EMEA/MRL/530/98-Rev.5: Deltamethrin Summary Report of the CVMP, 14.04.1999

Taking into account, that in study V-0193-0056 DTM concentrations in the fat samples of all animals were below the MRL at 4 days and that the calculated daily DTM intake was far below the ADI (acceptable daily intake) at any time of the study, a withdrawal period of 4 days is recommended for edible ovine tissues after treating sheep with Butox[®] 50.

4 Conclusion

Residue depletion studies of Butox[®] 50 (50 mg DTM / L spraywash solution) in bovine and ovine tissues and in bovine milk, which have been conducted in compliance with the relevant guidelines and the principles of Good Laboratory Practice, provide an appropriate basis for the recommendation of the following withdrawal periods for Butox[®] 50:

Cattle	Edible tissues (muscle, liver, kidney, fat)	0 days
	Milk	0 days
Sheep	Edible tissues (muscle, liver, kidney, fat)	4 days

5 Annex 1

Calculation of the daily intake of deltamethrin on the basis of the residue data of study V-0193-0056 and a daily consumption of 300 g muscle, 100 g liver, 50 g kidney and 50 g fat (for calculation values below LOQ were set = LOQ, i.e. 5 µg / kg for muscle, liver and kidney and 25 µg / kg for fat)

Time	Tissues	DTM concentrations [µg / kg]					Daily intake [µg]	Total daily intake [µg]	% of Acceptable Daily Intake *
		Individual values				Mean			
12 h	fat	25.00	25.00	34.00	25.00	27.25	1.36	3.61	1.50
	muscle	5.00	5.00	5.00	5.00	5.00	1.5		
	liver	5.00	5.00	5.00	5.00	5.00	0.5		
	kidney	5.00	5.00	5.00	5.00	5.00	0.25		
24 h	fat	61.94	25.00	25.00	25.00	34.23	1.71	3.96	1.65
	muscle	5.00	5.00	5.00	5.00	5.00	1.5		
	liver	5.00	5.00	5.00	5.00	5.00	0.5		
	kidney	5.00	5.00	5.00	5.00	5.00	0.25		
48 h	fat	25.00	32.12	25	68.85	30.19	1.51	3.76	1.57
	muscle	5.00	5.00	5.00	5.00	5.00	1.5		
	liver	5.00	5.00	5.00	5.00	5.00	0.5		
	kidney	5.00	5.00	5.00	5.00	5.00	0.25		
4 d	fat	29.95	25.00	25.00	31.37	27.83	1.39	3.64	1.52
	muscle	5.00	5.00	5.00	5.00	5.00	1.5		
	liver	5.00	5.00	5.00	5.00	5.00	0.5		
	kidney	5.00	5.00	5.00	5.00	5.00	0.25		
7 d	fat	25.00	25.00	25.00	40.63	28.91	1.44	3.69	1.54
	muscle	5.00	5.00	5.00	5.00	5.00	1.5		
	liver	5.00	5.00	5.00	5.00	5.00	0.5		
	kidney	5.00	5.00	5.00	5.00	5.00	0.25		
14 d	fat	25.00	25.00	25.00	48.17	30.79	1.54	3.79	1.58
	muscle	5.00	5.00	5.00	5.00	5.00	1.5		
	liver	5.00	5.00	5.00	5.00	5.00	0.5		
	kidney	5.00	5.00	5.00	5.00	5.00	0.25		

* ADI = 240 µg according to EMEA/MRL/530/98-Rev.5: Deltamethrin Summary Report of the CVMP, 14.04.1999:

6. Intervet International Reports

V-0193-0007:

K. Schmid: Investigation of residues of Deltamethrin in edible tissues of cattle following spraywash-administration of Butox[®] 50 (5 g Deltamethrin / 100 mL) at the recommended concentration of 1 mL Butox[®] 50 / L water (November 07, 2000)

V-0193-0012

K. Schmid: Investigation of residues of Deltamethrin in the milk of dairy cattle following spraywash-administration of Butox[®] 50 (5 g Deltamethrin / 100 mL) at the recommended concentration of 1 mL Butox[®] 50 / L water (November 14, 2000)

V-0193-0056:

K. Schmid: Investigation of residues of Deltamethrin in edible tissues of sheep following spraywash-administration of Butox[®] 50 (5 g Deltamethrin / 100 mL) at the recommended concentration of 1 mL Butox[®] 50 / L water (November 21, 2000)

A. Renoux and P. Blain-Violeau:

Validation of a GC/KS Assay for the Determination of Cis-Deltamethrin in Bovine and Ovine (November 17, 2000)

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Curriculum Vitae

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