MOXIDECTIN

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ADDENDUM
to the Moxicectin residue monographs prepared by the 45th and 47th meetings of the Committee and published in the FAO Food and Nutrition Paper 41/8, Rome 1996, and Food and Nutrition Paper 41/9, Rome 1997, respectively

Introduction

Moxidectin was evaluated for the first time at the 45th meeting in cattle, sheep and red deer, and further evaluated at the 47th meeting for residues in sheep based on a study subsequent to the original submission by the sponsor. Recommended MRL's for cattle, sheep and deer at the 45th meeting were 500 μg/kg in fat, 100 μg/kg in liver, 20 μg/kg in muscle and 50 μg/kg in kidney, expressed as parent drug. The MRL's for deer were temporary.

The sponsors provided new data at the 47th meeting on a large sheep study indicating that the residues in sheep muscle could exceed the recommended MRL in muscle if the recommended dosing schedule for sarcoptic mange was used. The new study indicated that residues persisted for at least 50 days. In the submission for the 45th meeting of the Committee, residues of moxicectin were not measurable (< 10 μg/kg) in sheep muscle at 28 days. The new study measured the residues of moxicectin in muscle, liver, kidney and at the injection sites (data on fat was submitted to the 45th meeting of the Committee) at various times following two treatments of moxicectin 1.0% injectable solution, ten days apart, at the recommended rate of 0.2 mg moxidectin/kg body weight.

Based on the new data submitted to the 47th meeting, three pertinent conclusions emerged from the sheep study:

- the residues in muscle exceeded the MRL recommended at the 45th meeting (the maximum value was 63 μg/kg at 10 days post dosing but at 20-40 days no value exceeded 40 μg/kg even when two doses were administered);

- the residue concentrations in liver, kidney and fat did not exceed the recommended MRL's; and

- there were very high concentrations of residues at the injection sites.

The residues in ovine muscle compared with non-detectable concentrations in bovine and deer muscle is probably due to the higher fat content in sheep muscle and the lipophilic nature of moxidectin. Based on the new, larger sheep study the Committee recommended an MRL of 50 μg/kg for sheep muscle.

The tenth Session of the Codex Committee on Residues of Veterinary Drugs in Foods requested that the 48th Session of the Expert Committee reassesses the MRL for cattle muscle to determine whether the MRL's for sheep and cattle muscle tissue might be harmonized and further, to consider the approved use of multiple dosing either by injection or by pour-on applications. New cattle studies using approved multiple dosing had been submitted by the sponsor for consideration at the 48th meeting of the Committee.

SUMMARY OF RADIOLABEL AND RESIDUE STUDIES FROM THE 45TH AND 47TH MEETINGS

Radiolabel Studies

In a small study, three Hereford steers received a single subcutaneous injection of ^{14}C-moxidectin at 0.2 mg/kg of body weight. One control steer was sacrificed at 6 days post dosing and the treated steers were sacrificed at 7, 14, and 28 days post dosing. Total ^{14}C-residues were determined in all samples. The total radioactivity recovered in the samples collected accounted for approximately 73, 71 and 77% of the administered dose at 7, 14, and 28 days, respectively. Residues were distributed as follows for the three post dosing periods: 0.8, 1.8 and 3.0% in urine; 32.2, 41.3 and 58.1% in feces; 29.8, 17.6, and 11.6% in the carcass; and 9.9, 10.0 and 4.2% in all other components sampled. These data demonstrate that the major route of excretion of the radiolabelled material is in the feces. The highest concentration of moxicectin equivalents were found in fat. Half-lives for clearance of total

residues from tissues were estimated for back and abdominal fat, kidney, liver and loin muscle. The percentage of extractable residues in abdominal and back fat and at injection site was greater than 95%; in liver, kidney and muscle more than 90% of the total radiolabel was extractable. These results identify fat as the target tissue, and that there is no bioaccumulation of residues in tissues. Results are summarized in Table 1 (FAO 41/8).

Moxidectin was the only significant component in both omental and back fat, and accounted for >75% of the residue. No single metabolite contributed more than 5% of the total residue in fat. Moxidectin accounted for 39, 55 and 39% of the residues, respectively, in liver, kidney and muscle. Total ^{14}C-moxidectin residues in excreta indicated feces was the primary route of excretion and moxidectin accounted for 51% of the residue.

Table 1. Total Residues as Moxidectin Equivalents in Steer Tissues (µg/kg) Following Subcutaneous Treatment With 0.2 mg ^{14}C-Moxidectin/kg of Body Weight

Tissue	Day 7	Day 14	Day 28	$t_{½}$ (days)
Abdominal fat	898	636	275	14.3
Back fat	495	424	186	12.2
Liver	109	77	31	11.4
Kidney	42	38	13	11.8
Loin Muscle	21	10	4	9.0

In a larger study, four groups of three beef type steers were administered a single subcutaneous injection of ^{3}H-moxidectin at a dose of approximately 0.4 mg/kg b.w. (two times recommended dose). Total residues were determined at 7, 14, 28 and 49 days post treatment. Mean values as moxidectin equivalents are shown in Table 2 (FAO 41/8).

Table 2. Total Residues of ^{3}H-Moxidectin (µg-eq/kg) in Steers Administered a Single Subcutaneous Injection at Approximately 0.4 mg/kg of Body Weight

Tissue	Day 7	Day 14	Day 28	Day 49
Omental Fat	974	778	350	181
Back Fat	920	685	359	182
Liver	148	97	47	17
Kidney	92	46	21	<10
Muscle	29	39	<10	<4
Injection Site	6220	570	667	35

In another small study where six steers were administered a single topical dose of ^{14}C-moxidectin at 0.5 mg/kg b.w. groups of three animals each were sacrificed at 2 and 14 days post treatment. Total residues as mean µg/kg moxidectin equivalents at day 2 and 14, respectively, were 8 and 113 in omental fat; 4 and 55 in back fat; 3 and 12 in liver; <2 and 8 in kidney; and <2 and <3 in muscle. The radioactive residue profiles were qualitatively similar for all tissues. The study concluded that the results of this metabolism study demonstrated that the metabolic fate of moxidectin administered to steers topically as a pour-on solution was qualitatively similar to that administered subcutaneously, although the residues are lower following pour-on treatment. In both cases, fat is the target tissue, with declining residues in liver, kidney and muscle, respectively.

Elimination half-lives for each tissue using simple semi-logarithmic linear regression analysis of data for residues at day 7 and later are shown in Table 3 for cattle and sheep for various formulations.

Table 3. Half-lives (days) and Regression Coefficients of Total Residues in Cattle and Sheep TreatedWith Various Formulations of Moxidectin

Tissue / Dose	Cattle (s.c.) 0.2 mg/kg bw		Cattle (s.c.) 0.4 mg/kg bw		Sheep (s.c.) 0.4 mg/kg bw		Sheep (drench) 0.4 mg/kg bw	
	$t_{½}$ (days)	r	$t_{½}$ (days)	r	$t_{½}$ (days)	r	$t_{½}$ (days)	r
Omental fat	12.2	-0.999	17.0	-0.963	7.3	-0.912	15.8 7.8[1]	-0.717 -0.968
Back fat	14.3	-0.983	18.4	-0.943	7.4	-0.909	17.5 8.1[1]	-0.677 -0.974
Liver	11.4	-1.000	13.7	-0.978	8.1	-0.984	nd	
Kidney	11.8	-0.967	10.5	-0.917	nd		nd	
Muscle	9.0	-0.992	nd		nd		nd	
Injection site			6.4	-0.854				
Ref. (FNP 41/8)	MR19		MR9		MR14		MR15	

[1] Values calculated after omitting residue data from day 36; nd indicates that the concentrations of residues could not be quantified at a sufficient number of time points.

Unchanged moxidectin was the major residue in all edible tissues. The ratios of moxidectin to total residues are tabulated in Table 4 from some of the radiolabel studies.

Table 4. Percentage of Parent Drug in Total Residues in Cattle and Sheep Tissues

Species Dose (mg/kg bw)	Withdrawal time (days)	Omental fat	Back fat	Liver	Kidney	Muscle
Cattle (s.c.) 0.2 mg/kg	7 14 28	95 88 91	83 76 86	48 40 36	74 71 77	62 50 50
Cattle (pour-on) 0.5 mg/kg	14	81	76	39	55	39
Sheep (oral) 0.2 mg/kg	7		91	51	52	92
Mean		87	82	43	66	59[1]

[1] The mean value for muscle tissue in cattle is 50 percent.

Unlabeled Residue Depletion Studies

In the original submission by the sponsor one study was reported for residues of unlabeled moxidectin in cattle following a 0.2 mg/kg subcutaneous treatment and two studies following a 0.5 mg/kg pour-on treatment (FNP 41/8). Residues were reported for edible tissues and the injection site. The upper 99% confidence limit (CL) for residues in fat were calculated. Data in muscle tissue were not reported because most results were below the limit of quantification of 10 µg/kg. Results are summarized in Tables 5 and 6.

The main points of these residue studies in cattle were:

1. The residues were always highest in fat with little difference between omental and back fat. Residues in liver tissue are higher than in muscle tissue.
2. Fat was the recommended target tissue and parent drug the marker residue.
3. Residues were higher when moxidectin was administered subcutaneously.
4. Moxidectin was always the major residue constituent, representing about 40-70% of the total residues in liver, kidney and muscle tissue, and about 75-95% in fat.
5. The percentage of moxidectin in the total residues did not change significantly with time.

Table 5. Residues of Moxidectin (µg/kg) in Cattle Following a 0.2 mg/kg b.w. Subcutaneous Dose

Withdrawal Time (days)	Injection Site	Back Fat	99% upper CL for fat	Liver	Kidney
14	3269	275	438	14	27
21	3848	243	402	15	29
28	4019	225	367	<10	22
35	2332	153	332	<10	19
42	1326	77	296	<10	<10
49	1178	141	261	<10	11

Table 6. Residues of Moxidectin (µg/kg) in Cattle Fat Following a 0.5 mg/kg b.w. Pour-on Treatment

Withdrawal time (days)	Australian Study (MR5)		United States Study (MR8)	
	Mean	Upper 99% CL	Mean	Upper 99% CL
7	21	70	nd	nd
14	36	67	92	201
21	31	63	106	192
28	10	59	77	183
38	<10		65	174
42			67	165

Supplemental New Studies on Multiple Dose Treatments

Two multiple dose treatment studies in cattle were submitted by the sponsor. In the subcutaneous multiple injection study, 45 Angus crossbred feeder steers were allocated to seven groups. Three animals were assigned to the non-medicated control group (Group 1) and seven animals each were assigned to the six medicated groups (Groups 2-7). Cattle in Groups 2 through 5 received subcutaneous injections of moxidectin at 0.2 mg/kg b.w. on days 0, 28, 56, and 84. Withdrawal periods for Groups 2-5 were 14, 21, 28 and 35 days, respectively. Cattle in Groups 6 and 7 received a single subcutaneous injection at 0.2 mg/kg b.w. on day 84 of the experiment followed by 14- and 35-day withdrawals, respectively. Loin muscle and back fat samples from six animals in each group were analyzed for residues of moxidectin. For the non-medicated control animals, loin muscle and back fat were collected from two animals when the Group 2 (14-day withdrawal) animals were sacrificed and the remaining animal in Group 1 was sacrificed when Group 5 (35-day withdrawal) animals were sacrificed. Only one muscle sample in Group 2 (13 µg/kg) of the study had residues above the 10 µg/kg limit of quantification. Control animals had no detectable moxidectin residues. Residues were not recovery corrected. Results are summarized in Table 7.

Table 7. Residues of Moxicectin (µg/kg) in Fat and Muscle Tissues of Cattle Following Multiple Subcutaneous Injections of Moxidectin at 0.2 mg/kg b.w.

Group	Treatments (days)	Withdrawal time (days)	Fat Mean	Fat Upper 99% CL	Muscle Mean
1	0	0	<10	na	<10
2	0, 28, 56, 84	14	247	574	<10-13[1]
3	0, 28, 56, 84	21	193	424	<10
4	0, 28, 56, 84	28	85	160	<10
5	0, 28, 56, 84	35	37[2]	97	<10
6	84	14	171	306	<10
7	84	35	20	77	<10

[1] Range reported because five values were non-detectable; [2] With non-detectable residues, a mean value of 5 µg/kg was used for the calculation.

Based on the 14- and 35-day withdrawal periods data, residue levels in fat, following the multiple dose administration, were approximately 85-90% higher than after a single dose, based on the 99% upper confidence limits. Comparable values were observed in liver tissue based on the 99% upper confidence limits.

The second study employed multiple treatment with a 0.5% solution of moxidectin as pour-on formulation. Fifty-eight Hereford mixed sex cattle were selected for the trial. In the trial, an additional eight animals were held as reserves. The control group (Group 1) consisted of three animals, while treatment Groups 2 through 7 contained five animals each. Group 8 containing three animals served as a second set of untreated controls. Groups 9 through 12 had three animals each and Groups 13 and 14 had five animals each. Groups 2 through 7 were treated with moxidectin pour-on on days 0, 21, 42, 63 and 84 using the 0.5% solution at 1 ml/10 kg bw (0.5 mg/kg b.w.).

Groups 9 through 14 were treated at days 0, 21, 42, 63 and 84 with moxidectin pour-on using a 0.5% medicated dose at twice the recommended dose (1.0 mg/kg b.w.). Withholding times for Groups 2 through 7 were 1, 7, 14, 21, 28 and 35 days, respectively. Similarly, withholding times for Groups 9 through 14 were 1, 7, 14, 21, 28 and 35 days. Samples of liver, back fat and perirenal fat were collected from each animal and kept at minus 20°C until analysis. Results for Groups 2 through 7 receiving the recommended dose are summarized in Table 8 and Groups 9 through 14 receiving twice the recommended dose are summarized in Table 9. The study (Cyanamid Websters 45970) only reported the limit of detection (0.5 µg/kg). Mean values and the 99% upper confidence limits of the mean concentration were reported for fat and liver tissues. Results were not recovery corrected.

In this study, there were no data provided to make a correlation of a single pour-on treatment with multiple pour-on treatments at any withdrawal time.

Table 8. Residues (µg/kg) in Cattle Treated With 0.5% Moxidectin Pour-on Formulation at the Recommended Dose of 0.5 mg/kg bw

Group	Number of Animals	Withdrawal time (days)	Fat		Liver	
			Mean	Upper 99% CL	Mean	Upper 99% CL
2	5	1	56	152	4	10
3	5	7	141	273	11	35
4	5	14	163	217	8	14
5	5	21	94	217	5	11
6	5	28	88	196	4	10
7	5	35	41	122	2	5

Table 9. Residues (µg/kg) in Cattle Treated With 0.5% Moxidectin Pour-on Formulation at Twice the Recommended Dose (1.0 mg/kg bw)

Group	Number of Animals	Withdrawal time (days)	Fat		Liver	
			Mean	Upper 99% CL	Mean	Upper 99% CL
9	3	1	393	858	41	68
10	3	7	386	725	39	78
11	3	14	337	685	34	64
12	3	21	164	479	11	35
13	5	28	132	411	8	23
14	5	35	92	182	7	13

APPRAISAL

Moxidectin was evaluated previously at the 45th and 47th meeting of the Committee. At the 45th meeting, MRL's were recommended for cattle, sheep and deer in muscle, liver, kidney and fat. The MRL's in deer were temporary.

The sponsors provided new data for consideration at the 47th meeting of the Committee on a large sheep study indicating that the residues in sheep muscle could exceed the recommended MRL, if the preferred dosing schedule for psoroptic mange was used. The observation that there were higher residues in ovine muscle compared to bovine muscle was likely due to the higher fat content in sheep muscle and the lipophilic nature of moxidectin. Based on this large sheep study the 47th Committee recommended an MRL of 50 µg/kg in sheep muscle. The Tenth Session of the Codex Committee on Residues of Veterinary Drugs in Foods requested the 48th meeting of the Committee to consider, if the MRL for cattle muscle could be harmonized with the higher MRL in sheep muscle, and also consider new residue studies for cattle using the approved multiple dose treatments of moxidectin by either subcutaneous or pour-on administration.

Two studies using multiple dose treatment were submitted by the sponsor. In the subcutaneous injection study, 45 Angus steers were divided into one control and six treatment groups. All treatment groups contained seven animals. Four of the treatment groups received subcutaneous injections of moxidectin of 0.2 mg/kg body weight at day 0, 28, 56 and 84. Withdrawal periods for these four groups were 14, 21, 28 and 35 days following the last treatment, respectively. The two other groups received a single subcutaneous injection on day 84 also using the 0.2 mg/kg body weight dose. Withdrawal periods for these two groups were 14 and 35 days, respectively. Loin muscle and back fat samples were collected for residue analysis. The three standard deviation upper confidence limit for mean residues in fat for the four multiple treatments declined from 574 µg/kg at 14 days to 97 µg/kg at day 35. Only one muscle sample in the 14 day post treatment group had residues above the 10 µg/kg limit of quantification at 13 µg/kg.

In the second study 58 Hereford cattle animals were treated with a 0.5% solution of moxidectin as a pour-on formulation. Two control groups were used. Six treatment groups with five animals each received the 0.5% solution at 1 ml/10 kg body weight (equivalent to 0.5 mg moxidectin/kg bw) on days 0, 21, 42, 63 and 84 days, having withholding periods of 1, 7, 14, 21, 28 and 35 days. The remaining treatment groups received the 0.5% solution at twice the recommended dose (1.0 mg/kg bw) with the same treatment and withholding periods. Samples of back fat, perirenal fat and liver were collected for residue analysis. The three standard deviation upper confidence limit for mean residues in the recommended dose treatment groups reached a maximum concentration for fat of 273 µg/kg on day 7 and declined to 122 µg/kg on day 35. Residues followed a similar pattern in liver tissue, reaching a maximum concentration of 35 µg/kg on day 7 and declining to 5 µg/kg on day 35.

Following multiple treatments at scheduled intervals, residues were higher in the subcutaneous than in the pour-on treatment groups. Residues were highest in fat with residues in liver and muscle tissues being successively lower. Using the recommended MRL for cattle fat of 500 µg/kg, and data from the subcutaneous treatment study, residues would deplete to the MRL in approximately 17 days based on the 99% upper confidence limit of the mean residue data. No direct determination of residues in liver or kidney tissue could be made for this subcutaneous treatment study. However, based on studies using a single subcutaneous treatment (see 45th report of the Committee), mean residue concentrations in liver and kidney would not be expected to exceed the respective MRL's of 100 µg/kg and 50 µg/kg when the residues in fat are at or below the MRL of 500 µg/kg. Raising the MRL for cattle muscle to 50 µg/kg was not considered warranted based on the residue data available for multiple subcutaneous administration of moxidectin in cattle which indicated only one animal had residues (13 µg/kg) above the limit of quantification of the analytical method which was 10 µg/kg. Therefore, the Committee retained the MRL for cattle muscle at 20 µg/kg.

REFERENCES

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