FEBANTEL, FENBENDAZOLE AND OXFENDAZOLE

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ADDENDUM
to the fenbendazole, febantel and oxfendazole residue monographs prepared by the 38th and 45th meetings of the Committee and published in FAO Food and Nutrition Paper 41/4, Rome 1991 and FAO Food and Nutrition Paper 41/8, Rome 1996, respectively.

INTRODUCTION

The Committee has previously considered the three anthelmintic agents febantel, fenbendazole and oxfendazole at the thirty-eighth and forty-fifth meetings. At the thirty-eighth meeting the Committee recommended common MRLs for each of the three drugs using oxfendazole sulfone as the marker residue. Utilizing a temporary ADI of 0 - 4 μg per kg of body weight, the following temporary MRLs, expressed as the sum of the three principle metabolites (fenbendazole, oxfendazole and oxfendazole sulfone) calculated as oxfendazole sulfone equivalents, were recommended for cattle, sheep, and pigs: muscle, fat, and kidney, 100 μg/kg; liver, 500 μg/kg; milk (cow), 100 μg/L.

The Committee requested that the following additional residue information be submitted:

- Studies on the total residues of the three metabolites (fenbendazole, oxfendazole, and oxfendazole sulfone), measured as oxfendazole sulfone, in the edible tissues of cattle and sheep and in the milk of cattle over a 28-day withdrawal period after treatment of animals with fenbendazole or oxfendazole. In particular, information was requested on the use of the pelleted form of fenbendazole in cattle and sheep.

- Studies on the total residues of the above three metabolites, measured as oxfendazole sulfone, in the edible tissues of pigs given fenbendazole and observed over a 7 - 14 day withdrawal period.

- Information on the bioavailability of bound residues in liver after administration of febantel to one of the following species: cattle, pigs, or sheep.

- Development of a suitable method for the determination of total residues of the three metabolites (fenbendazole, oxfendazole, and oxfendazole sulfone, measured as oxfendazole sulfone) in milk.

At the forty-fifth meeting several residue studies following administration of fenbendazole in cattle, sheep and pigs were reviewed. However, the residue-depletion studies on total residues of fenbendazole, oxfendazole and oxfendazole sulfone in cattle and sheep following the administration of febantel and oxfendazole were ongoing. In addition to the results from these studies using febantel and oxfendazole, the Committee noted that, with the increasing production of goats in developing countries, residue data would be required for establishing MRLs in this species.

The results of the depletion studies for febantel and oxfendazole in cattle and sheep as well as three new studies with fenbendazole, one study in the horse and two in pigs, are summarized in this report. Also, information on the pharmacokinetics and residue depletion of fenbendazole and oxfendazole in goats, sheep and cattle are compared. In addition a single method for all three drugs in milk and tissues is evaluated. The method measures the sum of the three principle metabolites (fenbendazole, oxfendazole and oxfendazole sulfone) in both edible tissues and milk as equivalents of oxfendazole sulfone. The limit of quantification (LOQ) of this method in all tissues and milk is claimed by the sponsor to be 5 μg/kg and 5 μg/L, respectively.

METABOLISM AND PHARMACOKINETIC STUDIES

Goats

The *in vitro* oxidative metabolism of fenbendazole (FBZ) has been studied using liver preparations in a number of species including cattle, sheep and goats. All species investigated produced the sulfoxide metabolite (oxfendazole, FBZ-SO) and upon further oxidation, the sulfone (oxfendazole sulfone, FBZ-SO_2) but at varying rates. The rates of metabolite formation in cattle, sheep and goats are given below in Table 1. Although some degree of species specific preference in the rate of formation of known metabolites was seen, the differences were not considered substantial (Short *et al.*, 1988).

Table 1. The rates of metabolite formation, in picomoles/g liver/min, from in vitro studies using liver preparations of cattle, sheep and goats

Species	Total metabolites	FBZ-SO_2	FBZ-SO	FBZ-OH
cattle	454.79	7.26	427.37	20.16
sheep	560.63	18.90	541.74	N.D.
goat	563.87	72.39	387.61	103.33

N.D. = Not detected

The disposition of fenbendazole has been studied in the plasma, urine and feces of goats after oral and IV administration. Fenbendazole, oxfendazole and oxfendazole sulfone were the major drug-related constituents in plasma. Minor amounts of FBZ-OH and FBZ-NH_2 were observed in plasma. The authors concluded that the metabolism of FBZ in the goat is similar to that in other species including cattle and sheep (Short *et al.*, 1987).

The pharmacokinetics of oxfendazole in goats was compared to that in sheep. After intravenous administration of 7.5 mg/kg BW to sheep and goats, the AUCs of oxfendazole were not significantly different. Similarly, the total AUCs for the three metabolites were not significantly different. However, the bioavailability of oxfendazole in goats after oral administration was only about 42% of that in sheep (Bogan *et al.*, 1987).

Pigs

The pharmacokinetics of a 4% powder fenbendazole formulation versus a 1.5% pellet formulation (dose rate 5 mg/kg BW) was determined in pigs (two period crossover bioequivalence study). Comparing the mean pharmacokinetic parameters of all 12 pigs after administration either of the pellets or powder, the maximum concentrations (C_{max}), the times of maximum concentrations (T_{max}) and the AUCs of fenbendazole and oxfendazole were similar (Schmid, 1997).

RESIDUE DEPLETION STUDIES

All values for residue concentrations in tissues in this section, except the study in goats with fenbendazole, were obtained by a method that determines the sum of the three principle metabolites calculated as the oxfendazole sulfone equivalents. The plasma values were determined by a method that measures the three metabolites individually.

Cattle

A single dose of febantel 10% suspension was administered orally to 16 cattle at 7.5 mg/kg BW. At day 7, 14, 21 and 28 days post dose 4 treated animals were sacrificed each time. Two untreated control animals were slaughtered on the day of administration and two more 28 days after dosing. Tissue samples of muscle, fat, liver and kidney were taken from all animals. The results of this study are summarized in Table 2 (Schmidt, 1994a).

Table 2. **Mean tissue concentrations (μg/kg) of oxfendazole sulfone in cattle after a single oral administration of 7.5 mg febantel/kg BW (n=4).**

Days after administration	Muscle	Liver	Kidney	Fat
7	<LOQ	115	LOQ - 6	19
14	<LOQ	7*	<LOQ	LOQ - 8
21	<LOQ	<LOQ	<LOQ	<LOQ
28	<LOQ	<LOQ	<LOQ	<LOQ

*n=3; LOQ = 5 μg/kg

Thirty two animals, sixteen steers and sixteen heifers, were orally administered oxfendazole suspension at a single dose of 4.5 mg/kg BW. Four animals were used as controls. Samples of plasma were collected from treated and control animals at day 1. Samples of fat, kidney, liver and muscle were collected from treated animals slaughtered on days 10, 12, 14, 16, 18, 20, 22 and 24 of the study. Residues of oxfendazole and its metabolites were undetectable in kidney and muscle between 10 and 24 days post treatment. Mean levels of metabolites present in liver had fallen to <20 μg/kg by day 14 declining to <10 μg/kg by day 18. Levels in fat were <10 μg/kg on day 10 declining to undetectable levels by day 14 (Hunt, 1996).

Cattle (milk)

A single dose of febantel 10% suspension was administered orally to 8 lactating cows at 7.5 mg/kg BW. Milk samples were taken from 12 animals (4 of them were untreated) 3 days before and 5 days after administration. Two samples were collected at each day, one in the morning and one in the evening. The results of this study are summarized in Table 3 (Schmidt, 1994b).

Table 3. **Mean concentrations (μg/L) of oxfendazole in milk of 8 lactating cows administered a single oral dose of febantel 10% suspension at 7.5 mg/kg BW.**

Hours after administration	Day of Admin.	Oxfendazole sulfone in the milk(μg/L)	Hours after administration	Day of Admin.	Oxfendazole sulfone in the milk(μg/L)
10	0, Afternoon	172*	82	3, Afternoon	19**
24	1, Morning	256	96	4, Morning	LOQ - 20
34	1, Afternoon	268	106	4, Afternoon	LOQ - 10
58	2, Afternoon	107	120	5, Morning	<LOQ
72	3, Morning	44**	130	5, Afternoon	<LOQ

*n = 6; **n = 7; LOQ = 5 μg/L

Eight lactating cows were given a single oral dose of 9% oxfendazole suspension at a dose of 4.5 mg/kg BW. Individual milk samples were collected from each cow immediately prior to treatment and every 12 hours thereafter up to 120 hours post treatment. Plasma samples were collected at 24 hours post treatment. The mean concentration of residues in plasma were: oxfendazole (268 μg/L); fenbendazole (101 μg/L) and oxfendazole sulfone (268 μg/L). The residue concentration of oxfendazole sulfone in milk are summarized in Table 4 (de Montigny, 1996a).

Table 4. **Concentration of oxfendazole sulfone (μg/L) in milk from 8 lactating cows administered a single oral dose of 4.5 mg oxfendazole/kg BW.**

Hours after administration	Mean	Range	Hours after administration	Mean	Range
Pre-treatment*	<5	<5	72	19	8 - 32
12	<5 - 87	<5 - 127	84	<5 - 15	<5 - 15
24	222	163 - 261	96	<5 - 7	<5 - 7
36	186	116 - 226	108	<5	<5
48	106	52 - 161	120	<5	<5
60	55	20 - 82			

* immediately prior to drug administration

Sheep

A single dose of febantel 2.5% suspension was administered orally to 16 sheep at 5.0 mg/kg BW. At day 3, 7, 14 and 21 days post dose 4 treated animals were sacrificed each time. The untreated control animals were slaughtered on day of administration and 21 days after dosing, two animals each. The results of this study are summarized in Table 5 (Schmidt, 1995a).

Table 5. **Mean tissue concentrations (μg/kg) of oxfendazole sulfone in sheep after a single oral administration of 5.0 febantel/kg BW (n = 4 animals)**

Days after administration	Muscle	Liver	Kidney	Fat
3	40	4617	199	133
7	<LOQ	942	11	9
14	<LOQ	123	<LOQ	<LOQ
21	<LOQ	<LOQ-10	<LOQ	<LOQ

LOQ = 5 μg/kg

Thirty six sheep (18 males and 18 females) were administered a single oral dose of 2.265% oxfendazole suspension at a dose of 5.9 mg/kg BW. Two treated males and two treated females were slaughtered on days 10, 12, 14, 16, 18, 20, 22 and 24 post treatment. The residue concentrations of oxfendazole sulfone were below the limit of quantification in muscle, kidney and fat at all days post treatment. Liver contained 476, 292 and 127 μg/kg of oxfendazole sulfone at days 10, 12 and 14, respectively. At all other times, the concentration was near or below the limit of quantification (de Montigny, 1996b).

Sheep (milk)

A single dose of febantel 2.5% suspension was administered orally to 8 lactating sheep at 5.0 mg/kg BW. Milk samples were taken from the animals 3 days before and 5 days after administration. Two samples were collected at each day, one in the morning and one in the afternoon. The results of this study are summarized in Table 6 (Schmidt, 1995b).

Table 6. **Mean concentrations (μg/L) of oxfendazole sulfone in milk of sheep receiving 5.0 mg febantel/kg BW (n= 8 animals)**

Hours after administration	Milk	Hours after administration	Milk
0	<LOQ	72	20
10	357	82	15*
24	260	96	9**
34	158	106	<LOQ-11
48	73	120	<LOQ-7
58	42	130	<LOQ

*n = 7; **n = 6; LOQ = μg/L

Goats (milk)

Two groups of four goats each were dosed orally with fenbendazole as a paste suspension at 5 (1x the recommended dose) and 25 mg/kg BW. The concentration of fenbendazole was determined in milk at 2 hours and then at 12-hour intervals for 120 hours post-treatment. The detection limit of the method was 10 μg/L. Although the metabolites of fenbendazole were observed in the chromatograms, they were not quantified. The highest levels for both doses were observed at 12-hours post-dose. In these samples, fenbendazole concentrations were 98 ± 21 μg/L and 443 ± 213 μg/L for the 5 and 25 mg/kg doses, respectively. Fenbendazole levels were below the detection limit after 48 hours and 72 hours for the 5 and 25 mg/kg doses, respectively. The fenbendazole depleted from the milk with a 9.65 hour half-life (Waldhalm et al., 1989).

Pigs

Pigs (5 per groups) were treated orally with fenbendazole 1.5% pellets at a dose rate of 5 mg/kg BW. Using HPLC, the plasma levels of fenbendazole (FBZ) and its metabolites oxfendazole (FBZ-SO) and oxfendazole sulphone (FBZ-SO_2) were determined 4, 6, 8, 10, 12, 24, 72, 120 and 168 hours after oral administration. Combined residues, expressed as FBZ-SO_2, were determined in liver, kidney, muscle, fat and skin at 12, 24, 72, 120 and 168 hours after oral administration of the pellets. FBZ was rapidly absorbed reaching it highest concentrations in plasma (C_{max}) four hours after dosing and was also rapidly eliminated from the blood ($t_{1/2}$ = 5.5 hours). The two metabolites FBZ-SO and FBZ-SO_2 reached their C_{max} at 8 and 24 hours after administration, respectively. Measurable concentrations of FBZ and its metabolites (determined as FBZ-SO_2) were detected up to 24 hours after dosing in muscle, kidney, skin and fat and up to 72 hours in liver. The results of this study are summarized in Tables 7 and 8 (Schmid and Schmidt, 1996).

Table 7. **Mean plasma concentration (μg/L) of FBZ and its metabolites in pigs receiving 5 mg fenbendazole/kg BW**

Hours after treatment	FBZ	FBZ-SO	FBZ-SO_2	Hours after treatment	FBZ	FBZ-SO	FBZ-SO_2
4	145	622	33	24	28	959	370
6	128	948	76	72	0	14	0
8	106	1154	120	120	0	0	0
10	46	841	157	168	0	0	0
12	51	521	171				

Table 8. **Mean tissue concentrations (μg/kg) and range (in parentheses) of oxfendazole sulfone in pigs receiving 5 mg fenbendazole/kg BW**

Hours after treatment	Liver	Kidney	Muscle	Skin*	Fat**
12	3160(2665-3790)	785(430-986)	809(660-1019)	975(753-1312)	1291(939-1808)
24	6317(2939-9990)	1086(809-1483)	918(657-1292)	923(634-1405)	910(753-1285)
72	18(5-63)	<LOQ	<LOQ	<LOQ	<LOQ
120	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
168	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ

* skin plus subcutaneous fat **perirenal fat

Horses

Fenbendazole as a 10% suspension was orally administered to 16 horses at a dose rate of approximately 10 mg/kg bw daily for 5 consecutive days. Two untreated control animals were also included in the study. Two treated males and females were slaughtered on each of days 5, 10, 15, and 20 following the first treatment and tissue samples were taken for analyses. In addition, blood samples from each animal were taken before dosing and at intervals during and after dosing period as follows: 0, 4, 6, 8, 16, 24, 32, 48, 56, 72, 80, 96, 100, 102, 104, 112, 120, 128, 144 hours and on day 9, 10, 11*, 12*, 15*, 20* and 25* (* if not slaughtered earlier).

The plasma analysis show, that during the multiple dosing of fenbendazole over a period of five consecutive days, all treated animals exhibit measurable concentration of parent administration on day 5, all three compounds were eliminated from blood very rapidly, within two or three days. The terminal half-lives of fenbendazole and of oxfendazole sulfone amount to approximately 9.5 hours and that of oxfendazole amounts to approximately 18.5 hours. The results of this study are summarized in Table 9.

The determinations of fenbendazole and its metabolites in horse tissue show that by 5 days after the last dosing (equivalent to 10 days after the first dosing) neither fenbendazole nor its metabolites could be measured in any of the tissues investigated in concentrations higher than the limit of quantification. All three compounds were very rapidly eliminated from the body of horses (Schmidt , 1997a).

Table 9. **Mean plasma concentrations (μg/L) of 16 treated horses**

Time (hours)	Study day	FBZ	FBZ-SO	FBZ-SO_2	Time (hours)	Study day	FBZ	FBZ-SO	FBZ-SO_2
0	1*	<LOQ	<LOQ	<LOQ	96	5*	57	97	89
4		42	35	55	100		251	82	93
6		40	43	61	102		186	117	111
8		43	60	69	104		262	83	111
16		31	58	45	112		148	59	82
24	2*	20	53	26	120	6	78	53	51
32		106	84	100	128		49	46	27
48	3*	47	57	56	144	7	14	23	<LOQ
56		136	94	98	192	9	<LOQ	<LOQ	<LOQ
72	4*	31	82	53	216	10	<LOQ	<LOQ	<LOQ
80		166	104	104					

*days of administration

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

The separate analytical methods for the quantitative determination of residues of fenbendazole and its metabolites (oxfendazole and oxfendazole sulfone) in edible tissues (cattle, sheep, pigs and horses) and milk (cattle and sheep) have been combined in a single report (Schmidt, 1997b). The method can also be applied to the determination of fenbendazole and its metabolites in skin of pigs.

Fenbendazole and its two metabolites are extracted from milk and tissue homogenates using ethyl acetate. Fenbendazole and oxfendazole are oxidized to oxfendazole sulfone with peracetic acid. The total amount of oxfendazole sulfone is quantitatively analyzed after extensive purification using HPLC with fluorescence detection at 295 nm (Ex.) and 410 nm (Em.). Methyl-(5-cyclopentylsulfinyl-1H-benzimidazole-2yl)-carbamate is used as an internal standard. Non-interference from albendazole, mebendazole, ivermectin, levamisole, streptomycin and tetracycline was demonstrated. The method is linear in the range from 5 to 1000 µg/kg in liver and from 5 to 200 µg/kg in kidney, fat and muscle of all species investigated, as well as in skin from pigs. The linear range in milk from cattle and sheep ranges from 5 to 1000 µg/L.

The mean absolute recovery for fenbendazole and its metabolites (measured as oxfendazole sulfone) ranged from:

- 70.8% (muscle) to 87.8% (liver) in cattle;
- 48.8% (fat) to 93.9% (liver) in sheep;
- 54.1% (fat) to 102.9% (kidney) in pigs;
- 58.9% (fat) to 75.0% (liver) in horse;
- and from 94.8% (milk of cattle) to 95.6% (milk of sheep).

APPRAISAL

The Committee has previously considered the three anthelmintic agents febantel, fenbendazole and oxfendazole at the thirty-eighth and forty-fifth meetings. A group temporary ADI of 0 - 4 µg per kg of body weight was established for all three anthelmintics based on a NOEL of 0.7 mg per kg of body weight per day for oxfendazole identified at the thirty-eighth meeting and a safety factor of 200.

At the thirty-eighth meeting the Committee recommended group MRLs for each of the three anthelmintics using oxfendazole sulfone as the marker residue. Temporary MRLs, expressed as the sum of the three principle metabolites (fenbendazole, oxfendazole and oxfendazole sulfone) calculated as oxfendazole sulfone equivalents, were recommended for cattle, sheep, and pigs: muscle, fat, and kidney, 100 µg/kg; liver, 500 µg/kg; milk (cow), 100 µg/L.

At the forty-fifth meeting several residue studies in cattle, sheep and pigs were reviewed. However, the residue-depletion studies on total residues of fenbendazole, oxfendazole and oxfendazole sulfone in cattle and sheep following the administration of febantel and oxfendazole were ongoing. In addition to the results from these studies, the Committee noted that, with the increasing production of goats in developing countries, residue data would be required for establishing MRLs in this species.

At the present meeting, the Committee reviewed the results of the residue depletion studies for febantel and oxfendazole in cattle and sheep as well as three new studies with fenbendazole, one study in the horse and two in pigs. Also, information on the metabolism, pharmacokinetics and residue depletion of fenbendazole and oxfendazole in goats, sheep and cattle were compared. In addition, a single method for all three drugs in milk and tissues was evaluated. The method measures the sum of the three principle metabolites (fenbendazole, oxfendazole and oxfendazole sulfone) in both edible tissues and milk as equivalents of oxfendazole sulfone. The sponsor claimed that the limit of quantification (LOQ) of this method in all tissues and milk is 5 µg/kg.

Metabolism data

The *in vitro* oxidative metabolism of fenbendazole was studied using liver preparations in a number of species including cattle, sheep and goats. All species investigated produced the sulfoxide metabolite (oxfendazole) and upon further oxidation, the sulfone (oxfendazole sulfone) but at varying rates. Although some degree of species specific preference in the rates of formation of the two principle metabolites was seen, the differences were not of practical significance.

The disposition of fenbendazole was studied in the plasma, urine and feces of goats after oral and intravenous administration. As fenbendazole, oxfendazole and oxfendazole sulfone were the major drug-related constituents in plasma, the metabolism of fenbendazole in the goat was demonstrated to be similar to other species including cattle and sheep.

Pharmacokinetic data

The pharmacokinetics of oxfendazole in goats was compared to that in sheep. After intravenous administration of 7.5 mg oxfendazole/kg BW to sheep and goats, the areas under concentration-time curve (AUCs) of oxfendazole in the two species were not significantly different. Similarly, the total AUCs for the three metabolites were not significantly different. However, the bioavailability of oxfendazole in goats after oral administration was only about 42% of that in sheep.

The pharmacokinetics of a 4% powder fenbendazole formulation versus a 1.5% pellet formulation (dose rate 5 mg fenbendazole/kg BW) was determined in pigs (two-way crossover bioequivalence study). Comparing the mean pharmacokinetic parameters of all 12 pigs after administration either of the pellets or powder, the maximum concentrations (C_{max}), the times of maximum concentrations (T_{max}) and the AUCs of fenbendazole and oxfendazole were similar.

Residue data

All values for tissue residue concentrations in this section, except the study in goats with fenbendazole, were obtained by a method that determines the sum of the three principle metabolites calculated as the oxfendazole sulfone equivalent. The plasma values were determined by a method that measures the three metabolites individually.

Cattle A single dose of febantel 10% suspension was administered orally to 16 cattle at 7.5 mg/kg BW. At day 7, 14, 21 and 28 days post treatment 4 treated animals were sacrificed each time. The concentrations of oxfendazole sulfone in muscle and kidney were at or below the LOQ at all times. The concentrations in liver and fat were 115 and 19 μg/kg at day 7 and at or below the LOQ at all other times.

Thirty-two cattle were orally administered oxfendazole suspension at a single dose of 4.5 mg oxfendazole/kg BW. Edible tissues were collected from treated animals slaughtered on days 10, 12, 14, 16, 18, 20, 22 and 24 of the study. Residues of oxfendazole and its metabolites were undetectable in kidney and muscle after day 10. Mean levels of metabolites present in liver had fallen to less than 20 μg/kg by day 14 declining to less than 10 μg/kg by day 18. Levels in fat were less than 10 μg/kg on day 10 declining to undetectable levels by day 14.

A single dose of febantel 10% suspension was administered orally to 8 lactating cows at 7.5 mg/kg BW. Milk samples were taken from 12 animals (4 of them were untreated) beginning 3 days before to 5 days after administration. Two samples were collected at each day for each cow, one in the morning and one in the evening. Residues of febantel and its metabolites were a maximum of 268 μg/L at 34 hours after administration to near the LOQ at 96 hours.

Eight lactating cows were given a single oral dose of 9% oxfendazole suspension at 4.5 mg/kg BW. Individual milk samples were collected from each cow immediately prior to treatment and every 12 hours thereafter up to 120 hours post treatment. Residues of oxfendazole and its metabolites peaked at 222 μg/L at 24 hours and declined to near or below the LOQ at 96 hours.

Sheep A single dose of febantel 2.5% suspension was administered orally to 16 sheep at 5.0 mg/kg BW. At day 3, 7, 14 and 21 days post dose 4 treated animals were sacrificed at each time. Residue concentrations of febantel and its metabolites in muscle, liver, kidney and fat were 40, 4617, 199 and 133 μg/kg, respectively, at 3 days after administration. The residues deplete to near or below the LOQ in muscle, liver, kidney and fat by day 7, 21, 14 and 14, respectively.

Thirty-six sheep were administered a single oral dose of 2.3% oxfendazole suspension at 5.9 mg/kg BW. Two treated males and two treated females were sacrificed on days 10, 12, 14, 16, 18, 20, 22 and 24 post treatment. The residue concentrations of oxfendazole sulfone were below the LOQ in muscle, kidney and fat at all days post treatment. Liver contained 476, 292 and 127 μg/kg of oxfendazole sulfone at days 10, 12 and 14, respectively. At all other times, the concentration was at or below the LOQ.

A single dose of febantel 2.5% suspension was administered orally to 8 lactating sheep at 5.0 mg febantel/kg BW. Milk samples were taken from the animals beginning 3 days before to 5 days after administration. Two samples were collected

at each day from each sheep, one in the morning and one in the afternoon. The residue concentrations peaked at 357 μg/L at 10 hours and depleted to the LOQ by 106 hours.

Goat Two groups of four goats each were dosed orally with fenbendazole as a paste suspension at 5 mg/kg BW (the recommended dose) and 25 mg/kg BW. The concentration of fenbendazole was determined in milk at 2 hours and twelve-hour intervals for 120 hours post-treatment. The detection limit of the method was 10 μg/L. Although the metabolites of fenbendazole were observed in the chromatograms, they were not quantitated. The highest levels for both doses were observed at 12-hours post-dose. In these samples, fenbendazole mean concentrations were 98 μg/L and 443 μg/L for the 5 and 25 mg/kg doses, respectively. Fenbendazole levels were below the detection limit after 48 hours and 72 hours for the 5 and 25 mg/kg doses, respectively. The fenbendazole depleted from the milk with a half life of 9.65 hour.

Pig Pigs (5 per group) were treated orally with fenbendazole 1.5% pellets at a dose rate of 5 mg/kg BW. Combined residues, expressed as oxfendazole sulfone were determined in liver, kidney, muscle, fat and skin 12, 24, 72, 120 and 168 hours after oral administration of the pellets. Residue concentrations of fenbendazole and its metabolites peaked at 24 hours in liver, kidney and muscle: 6317, 1086 and 918 μg/kg, respectively. Residue concentrations in skin and fat peaked at 12 hours after treatment at 975 and 1291 μg/kg, respectively.

Horse Fenbendazole as a 10% suspension was orally administered to 16 horses at a dose rate of approximately 10 mg/kg BW daily for 5 consecutive days. Two treated males and females were slaughtered on each of days 5, 10, 15, and 20 following the last treatment and tissue samples were taken for analyses. The determinations of fenbendazole and its metabolites in horse tissue show that by 5 days after the last dosing neither fenbendazole nor its metabolites could be measured in any of the tissues investigated in concentrations higher than the limit of quantification.

Analytical Method

The separate analytical methods for the quantitative determination of residues of fenbendazole and its metabolites (oxfendazole and oxfendazole sulfone) in edible tissues (cattle, sheep, pigs and horses) and milk (cattle and sheep) have been combined in a single report. The method can also be applied to the determination of fenbendazole and its metabolites in skin of pigs.

Fenbendazole and its two metabolites are extracted from milk and tissue homogenates using ethyl acetate. Fenbendazole and oxfendazole are oxidized to oxfendazole sulfone with peracetic acid. The total amount of oxfendazole sulfone is quantitatively analyzed after extensive purification using HPLC with fluorescence detection. An internal standard is used to correct for recoveries. The method has a linear range of 5 to 1000 μg/kg in liver and from 5 to 200 μg/kg in kidney, fat and muscle of all species investigated, as well as in skin from pigs. The linear range in milk from cattle and sheep is 5 to 1000 μg/L. The range of mean absolute recovery for fenbendazole and its metabolites (measured as oxfendazole sulfone) in cattle, sheep, pigs and horse were 70.8% (muscle) to 87.8% (liver) in cattle; 48.8% (fat) to 93.9% (liver) in sheep; 54.1% (fat) to 102.9% (kidney) in pigs; 58.9% (fat) to 75.0% (liver) in horse; and 94.8% (milk of cattle) to 95.6% (milk of sheep).

Based on a statistical evaluation of the precision data of the method by the Committee for various species/tissues combinations and milk, the LOQ was found to vary from approximately 5 to 35 μg/kg.

Maximum Residue Limits

In reaching its decision on MRLs, the Committee took into account the following factors:

- An ADI of 0 - 7 μg per kg of body weight was established. This would result in a maximum ADI of 420 μg for a 60-kg human.
- Metabolism, pharmacokinetic and residue depletion information are similar between cattle, sheep, goats, pigs and horses.
- The correlation between plasma and milk residues are similar in sheep and cows.
- With the analytical performance data provided by the sponsor, the highest LOQ for any of the edible tissues or milk is well below the recommended MRLs.
- Residues are expressed as oxfendazole sulfone equivalents, tissues and milk in all species.
- The MRLs represent the sum of the three principle metabolites (fenbendazole, oxfendazole and oxfendazole sulfone) calculated as oxfendazole sulfone equivalents.

The Committee recommended MRLs for febantel, fenbendazole and oxfendazole of 100 μg/kg (muscle, fat and kidney), 500 μg/kg (liver) in cattle, sheep, goats, pigs and horses and 100 μg/L in milk for cattle and sheep. The recommended MRLs would result in a theoretical maximum daily intake of 240 μg of residues based on a daily food intake of 300 g of muscle, 100 g of liver, 50 g each of kidney and fat and 1.5 L of milk.

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