TRICLABENDAZOLE

IDENTITY

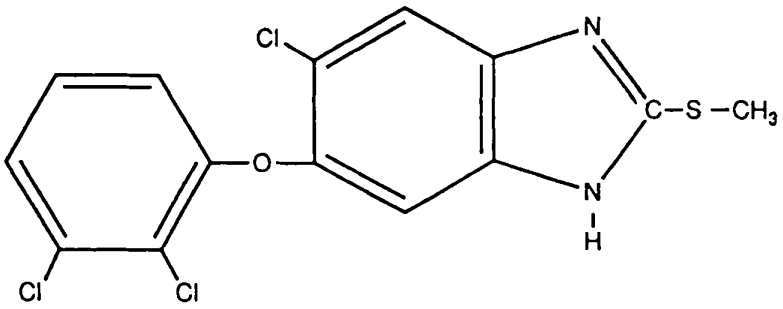
Chemical name: Triclabendazole

CAS Number: 68786-66-3

CAS Nomenclature: 5-Chloro-6-(2,3-dichlorophenoxy)-2-methylthio-1H-benzimidazole
6-Chloro-5-(2,3-dichlorophenoxy)-2-methylthio-benzimidazole

Synonyms: FASINEX®, FASCINEX®, FANEX®, SOFOREN®, with levamisole: ENDEX®, COMBINEX®, PARSIFAL®

Structural formula:



Molecular formula: $C_{14}H_9Cl_3N_2OS$

Molecular weight: 359.66

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure Active Ingredient

Appearance: White, fine crystalline powder, odorless to at most a very slight odor.

Melting point: 175°C (α-modification), 162°C (β-modification)

Solubility: Readily soluble in tetrahydrofuran, cyclohexanone (45.0%), acetone (16.0%), isopropanol (12.5%), n-octanol (17.5%)

Soluble in methanol (5.5%)
Less soluble in dichloromethane
Sparingly soluble in chloroform, toluene (0.9%), xylene (0.8%), ethyl acetate
Virtually insoluble in water, hexane

Octanol/water partition coefficient: 1.75×10^6 cal

RESIDUES IN FOOD AND THEIR EVALUATION

CONDITIONS OF USE

General

Triclabendazole is a member of a well-known and widely used chemical class of compounds known as the benzimidazoles. It is related in chemical structure and pharmacological properties to other compounds such as thiabendazole, fenbendazole, oxibendazole, mebendazole and febantel.

Triclabendazole is an anthelmintic for the treatment and control of early immature and immature parenchymal stages and the adult bile duct stage of liver fluke infections in cattle, buffalo, sheep and goats. Triclabendazole has a narrow spectrum of activity concentrated against *Fasciola hepatica* and *F. gigantea*. Efficacy has also been described and confirmed against *Fascioloides magna* and *Paragonimus*. Triclabendazole is not active against nematodes. The recommended therapeutic dose for cattle and buffalo is 12 mg triclabendazole/kg body weight. The recommended therapeutic dose of sheep and goats is 10 mg triclabendazole/kg body weight. Treatments are repeated at 8 - 10 week intervals throughout the fluke season. Treatment in the spring serves to lessen the pasture infestation in the following autumn. For acute/subacute outbreaks, animals should be treated immediately following diagnosis. Flocks of sheep and goats should then receive repeated treatments at intervals of 5 weeks. Cattle and buffalo should receive a second treatment 6 weeks after initial diagnosis and treatment. All newly arrived animals should be treated before joining the flock/herd.

Dosages

Several formulations of triclabendazole have been developed for the treatment of food producing animals. These formulations include suspensions (5% for sheep and goats; 10% and 12%[Australia] for cattle and buffalo) and tablets (250 mg triclabendazole for sheep and goats; 900 mg triclabendazole for cattle and buffalo). Additionally, triclabendazole is available as a suspension in combination with levamisole (5% triclabendazole with 3.75% levamisole for sheep [8.75%]; 12% triclabendazole with 7.5% levamisole for cattle [19.5%]).

METABOLISM

General

The absorption, distribution, metabolism and excretion of triclabendazole have been extensively studied and are qualitatively similar in both cattle and sheep. Following oral administration, a portion of triclabendazole is absorbed from the gastrointestinal tract. Following absorption, circulating levels of triclabendazole and its metabolites are higher than those produced by the same dose of fenbendazole or albendazole. This is attributed principally to strong protein binding and, to a lesser extent, to reduced absorption of fenbendazole and albendazole (Mohammed-Ali et al. 1986). The nonabsorbed triclabendazole is excreted in the feces as unchanged drug or as unidentified metabolites.

Absorbed triclabendazole which enters the circulation is rapidly metabolized by the liver (Strong et al. 1982a). Parent material is generally not detected in the blood following oral administration (Bull et Shume 1984). Metabolism proceeds via two routes: rapid oxidation of the methyl thiol group to the sulfoxide followed by a relatively slow oxidation of the sulfoxide to the sulfone and 4-hydroxylation of the dichlorophenoxy ring with direct secretion into the bile. Disappearance of parent triclabendazole is much more rapid than the appearance of the sulfoxide metabolite. This suggests temporary binding of the triclabendazole to tissues during conversion to the sulfoxide with subsequent release of the sulfoxide metabolite into the systemic circulation (Hennessy et al. 1987). Circulating sulfoxide and sulfone metabolites are bound to plasma albumin with some excretion in bile. Five identified metabolites account for approximately 40-60% of the administered dose. The same metabolites are identified in the feces of rats, sheep and goats. There are, however, quantitative differences in the relative proportions of metabolites between the three species (Hamböck 1983).

Elimination of the compound is virtually complete by 10 days after administration (Bull et Shume 1981). Excretion of the absorbed material is principally via the bile. Urinary excretion accounts for only a small portion of the dose.

Rat

Following oral administration of ^{14}C-triclabendazole (0.52 mg/kg and 25.3 mg/kg) in the rat, 6% of the radioactivity is recovered in the urine and 90% is excreted in the feces. By 49 hours after treatment of a rat with ^{14}C-triclabendazole at a dose of 4.6 mg/kg, 34% of the dose was excreted into the bile (Hamböck 1983). Altogether, more than 96% of the administered dose could be recovered from the excreta and expired air of the rats.

In balance studies in the rat, the vast majority of the orally administered dose has been excreted by 6-10 days postdosing (Mücke 1981, Reports 1991). Approximately 1% of administered dose remained in the bodies of the rats at the time of slaughter 6 days after treatment. The radioactivity was fairly evenly distributed except in fat, where none was detected. Neither dose nor sex influenced the distribution pattern.

Rabbit

Absorption and disposition of ^{14}C-triclabendazole was investigated in female rabbits following intravenous administration of 3 mg/kg and oral administration of 3 and 26 mg/kg (Reports DM 12/91 and CRBR 22/1991).

Triclabendazole was absorbed to a large extent from the gastrointestinal tract, irrespective of dose. Metabolism was rapid with little parent drug detectable in the blood. Formation of the sulfone was slower than formation of the sulfoxide.

Radioactive substances in the blood showed a biphasic decline following both intravenous and oral administration. Most of the radioactivity was cleared from the circulation within 72 hours via the bile. Excretion of radioactivity within 7 days accounted for 80-93% of the administered dose. Most of the dose was excreted in feces. Renally excreted metabolites were mainly conjugates.

Systemic exposure to the metabolites increased overproportionally to the oral dose between the 3 and 26 mg/kg doses. This phenomenon combined with high bioavailability could explain the high acute toxicity of triclabendazole in rabbits.

Dog

Concentrations of unchanged triclabendazole, sulfoxide and sulfone metabolites were measured in the plasma and urine of dogs following intravenous and oral administration of ^{14}C-triclabendazole (Report CRBR 25/91). Parent drug was rapidly cleared from the blood and converted to its sulfoxide and sulfone metabolites. The sulfoxide accounted for approximately 16% of the circulating radioactivity following both intravenous and oral administration. After oral administration of 0.5 mg/kg, systemic exposure to the sulfoxide represented 46% of that after intravenous dosing. The sulfone was slowly formed and eliminated. The proportion of sulfone in dogs was higher than in rabbits. Relative bioavailability at 5 and 40 mg/kg was similar to that after the 0.5 mg/kg dose. Renal elimination of triclabendazole and its metabolites was negligible.

Sheep and Goats

A sheep and a lactating goat were treated with labeled triclabendazole at a dose of 10 mg/kg in gelatin capsules. Approximately 2% and 3.5% of the administered dose was recovered in the urine of the treated goat and sheep, respectively. Feces of treated animals contained 97 - 101% of the administered dose (goat and sheep, respectively). Milk contained 0.5% of the administered dose. By 10 days postdosing, recovery was virtually complete (Hamböck and Strittmatter 1981 and 1982).

Pharmacokinetic parameters for total radioactivity in the blood of sheep and goat treated with ^{14}C-triclabendazole at 10 mg/kg were compared with kinetic parameters for sulfoxide and sulfone following treatment of sheep with 10 mg/kg of nonlabeled material (Hamböck 1982, Strong et al. 1983, and Bull 1985) or goats at 12 mg/kg (Kinabo and Bogan 1988). Differences between the values for

the summation curve of arithmetic mean concentrations for each metabolite at each time point and total radioactivity are within the range of values found in a population of sheep.

In sheep and goats, three phases of absorption and distribution can be identified. The initial phase lasted from 0 to 48 hours after dosing. In phase 2, from 48 to 168 hours, elimination followed first order kinetics with an apparent biological half-life of 22 hours in the goat and 26 hours in the sheep. The third phase, from 168 hours on, elimination still followed first order kinetics but with an apparent biological half life of 45 hours in the sheep and 60 hours in the goat. The total ^{14}C-triclabendazole level in milk was consistently about one tenth the residue in plasma.

Balance studies in sheep and goats show that by 6 - 10 days after dosing the majority of orally administered doses have been excreted, predominantly via the feces (Hamböck and Strittmatter 1981 and 1982, Mücke 1981, Reports 1991). The five identified metabolites account for approximately 43% and 45% of the administered dose in sheep and goats, respectively. The biliary metabolites in sheep are predominantly sulfate or glucuronide conjugates of 4-OH-triclabendazole, 4-OH-triclabendazole-sulfoxide and 4-OH-triclabendazole-sulfone (Hennessy et al. 1987).

Cattle

Triclabendazole is rapidly metabolized following intravenous administration in cattle. The sulfoxide metabolite forms rapidly and reaches a maximum blood concentration 4 hours after treatment. The terminal half-life for the sulfoxide is approximately 13 hours. The sulfone is formed more slowly. Peak plasma concentrations are measured 32 hours after dosing. The terminal elimination half-life for the sulfone is calculated to be 40 hours (Bull et al. 1986).

Pig

Following oral administration of 10 mg/kg and 30 mg/kg, plasma concentrations of triclabendazole and its sulfoxide and sulfone metabolites were determined in pigs. Only at the higher dose were plasma concentrations of the parent drug detectable. The sulfoxide metabolite formed rapidly and reached maximum plasma concentrations 8 hours after drug administration. The sulfone metabolite was produced more slowly with maximum plasma concentrations occurring 12-24 hours after dosing. The sulfone also displayed a longer elimination half-life. Overall metabolism in the pig was approximately 3 times faster than in ruminants (Galtier and Alvinerie, undated).

Horse, Pony, Donkey

Horses, ponies (*Equus caballus*)and donkeys (*E. assinus*) were treated orally with 12 mg triclabendazole/kg body weight. Triclabendazole was not detected in any plasma sample (Formica 1987, Kinabo and Bogan 1987, Tournayre 1986). Sulfoxide plasma concentrations and area under the plasma concentration curve

(AUC) in the two species were similar. The sulfoxide concentration is approximately 33% of the levels achieved in goats, sheep and cattle at the same dose. The concentration and AUC for the sulfone were much lower in the donkey than in the other species (Kinabo and Bogan 1987).

TISSUE RESIDUE DEPLETION STUDIES

Radiolabeled Residue Depletion Studies

Rat

Six days following oral administration of ^{14}C-triclabendazole, rats were slaughtered and the residual radioactivity assayed. Residues in rats treated with 0.5 mg/kg were uniformly low. Residues in rats treated with 25 mg/kg were accordingly higher. There was no organ-specific retention of radiolabel and approximately 1% of the administered dose remained in the animals six days after dosing (Mücke 1981).

Sheep and Goats

A sheep and a goat were treated once orally with ^{14}C-triclabendazole at 10.12 mg/kg and 10.49 mg/kg, respectively (Giannone and Formica 1981b, Giannone and Formica 1983a). Animals were slaughtered 10 days after dosing. Residues were extracted after thorough alkaline solubilization of the tissues and partitioning into methylene chloride. Total radioactivity data are given in Table 1.

A lactating goat was treated orally with a single dose of 10.1 mg ^{14}C-triclabendazole/kg body weight. Radioactivity was determined in the blood and milk over a 240 hour period. Radioactivity in selected tissues was determined at slaughter 10 days following drug administration. Residues in the plasma and milk are shown in Table 2 (Hamböck and Strittmatter 1981). Tissue residues were comparable to those seen in Table 1.

Table 1. **^{14}C-Triclabendazole residues in the tissues of sheep and goats dosed orally at 10.49 mg/kg and 10.12 mg/kg, respectively**

Animal	Sample	Total Radioactivity	Extracted Radioactivity		Nonextracted Radioactivity	
		mg/kg	mg/kg	%total	mg/kg	%total
Sheep	Muscle	0.58	0.011 0.020	1.9 3.6	0.53 0.56 0.56	91 96 96
	Liver	1.84	0.13	7.2	1.66 1.72	90 93
	Kidney	1.11	0.14	12.9		
	Fat	0.09	0.012	13.0		
Goat	Muscle	0.44	0.009	2.0		
	Liver	1.00	0.075 0.069	7.5 6.9		
	Kidney	0.69	0.05	7.2		
	Fat	0.08	0.005	6.0		

Table 2. **Concentration of radioactivity (in ppm triclabendazole equivalents) in the plasma and milk of a lactating goat treated with 10.1 mg ^{14}C-triclabendazole/kg body weight**

Collection (h)	Triclabendazole eq (ppm)	
	Plasma	Milk
8	15.75	0.529
24	22.78	1.788
48	15.30	1.375
72	7.28	0.771
96	3.17	0.372
120	1.28	0.158
144	0.52	0.072
168	0.26	0.039
176	NA	0.027
192	0.15	0.020
200	NA	0.020
216	0.11	0.016
224	NA	0.014
239	0.09	0.012

A sheep was treated with 10.5 mg ^{14}C-triclabendazole/kg as a single oral dose. Radioactivity was determined in the blood for 240 hours. First order elimination resulted in half-lifes of 26 hours for the period from 48-200 hours postdosing and 45 hours for the period from 200 hours to the end of the sampling period at 240 hours postdosing. The sheep was sacrificed 10 days after dosing and the residues in selected tissues were determined. The concentration of radioactivity in the plasma is shown in Table 3 (Hamböck and Strittmatter 1982). Tissue residues were comparable to those seen in Table 1 above.

Table 3. Concentration of radioactivity (in ppm triclabendazole equivalents) in the plasma of a sheep treated with 10.5 mg ^{14}C-triclabendazole/kg body weight

Collection (h)	Triclabendazole eq (ppm)
1	0.05
4	5.16
8	13.62
24	27.04
48	22.08
72	12.14
96	6.08
120	3.00
144	1.62
168	0.71
192	0.37
216	0.22
239	0.11

Cattle

Two ruminating heifers were treated with a single oral dose of ^{14}C-triclabendazole at the rate of 12 mg/kg body weight. The animals were slaughtered at 28 and 42 days after dosing (Downs et al. 1991). Total residues are shown in Table 4.

Table 4. Concentration of radioactivity (in ppm triclabendazole equivalents) in the tissues of cattle treated with a single oral dose of ^{14}C-triclabendazole at 12 mg/kg body weight

Withdrawal (days)	Liver	Kidney	Muscle	Fat
28	0.241 ± 0.013	0.106 ± 0.016	0.131 ± 0.017	0.013 ± 0.003
42	0.093 ± 0.009	0.069 ± 0.011	0.097 ± 0.007	< 0.008 ± 0.001

OTHER RESIDUE DEPLETION STUDIES

Sheep and Goats

In a lactating goat, triclabendazole and its sulfoxide and sulfone metabolites are present in the milk following oral administration of 10.12 mg triclabendazole/kg body weight. Unchanged triclabendazole is detectable in milk samples for 96 hours following dosing. Both the sulfoxide and sulfone metabolites reach their maximum concentrations in milk 24 hours after treatment and decrease thereafter (Giannone and Formica 1981a).

Sixteen sheep were treated with triclabendazole as a single oral administration at either 10 mg/kg or 15 mg/kg. "Total" residues were determined by a method that measures residues of triclabendazole and its metabolites that are oxidizable to 5-chloro-6-(2',3'-dichlorophenoxy)-benzimidazole-2-one (MR). The "total" residues are converted to triclabendazole equivalents using a conversion factor of 1.0913. Residues were determined at 2, 7, 14, 21 or 28 days for the sheep receiving the 10 mg/kg dose and at 7 and 14 days for sheep treated with 15 mg/kg (Giannone and Formica 1983a). Results of the study are shown in Table 5.

Table 5. Total residues of triclabendazole in the tissues of sheep after a single oral treatment of 10 or 15 mg/kg body weight

Treatment mg/kg	Days After Treatment	Residues (mg Triclabendazole eq/kg)			
		Muscle	Liver	Kidney	Fat
Control		<0.029	<0.047	<0.029	<0.029
10	2	1.1	3.0	2.8	1.6
		1.5	4.0	3.4	1.1
10	7	0.16	0.54	0.34	0.043
		0.19	0.66	0.42	0.050
10	14	0.17	0.46	0.35	<0.029
		0.13	0.20	0.15	<0.029
10	21	0.092	0.18	0.15	<0.029
		0.085	0.17	0.15	<0.029
10	28	0.083	0.074	0.11	<0.029
		0.14	0.18	0.12	<0.029
15	7	0.43	1.2	0.79	0.11
		0.31	1.3	0.82	0.14
15	14	0.15	0.33	0.19	0.029
		0.13	0.44	0.22	<0.029

In a second study, 18 sheep were treated with 10 mg triclabendazole/kg body weight as a single oral dose. The animals were slaughtered 2, 7, 14, 21, 28, 42 or 56 days following administration. Total residues were determined as 5-chloro-6-(2',3'-dichloropenoxy)-benzimidazole-2-one and converted to triclabendazole equivalents using a conversion factor of 1.0913 (Giannone and Formica 1983e). The residues in the tissue of sheep are shown in Table 6.

Table 6. Total residues of triclabendazole in the tissues of sheep after a single oral treatment of 10 mg/kg body weight

Days After Treatment	Residues (mg Triclabendazole eq/kg)			
	Muscle	Liver	Kidney	Fat
7	0.30	0.62	0.28	0.071
	0.19	0.49	0.40	0.061
	0.20	0.52	0.20	0.088
14	0.25	NA	0.14	<0.03
	0.15	0.24	0.14	<0.03
	0.16	0.21	0.11	<0.03
21	0.16/0.14	0.16	0.097	<0.03
	0.15	0.11	0.11	<0.03
	0.12	0.12	0.07	<0.03
28	0.13	0.070	0.052	<0.03
	<0.095	0.098	0.048	<0.03
	0.082	0.061	0.048	<0.03
42	0.036	<0.03	0.044	<0.03
	0.043	0.033	<0.03	<0.03
	0.061/0.058	<0.03	<0.03	<0.03
56	0.092	NA	<0.03	<0.03
	0.070	<0.03	<0.03	<0.03
	0.070/0.066	<0.03	<0.03	<0.03

In a study involving a single sheep dosed orally with triclabendazole at a rate of 10 mg/kg, triclabendazole and its sulfoxide and sulfone metabolites were quantified individually in the plasma. Parent drug was not detected at any time during the study. The sulfoxide metabolite peaked at 24 hours postadministration and the sulfone peaked at 48 hours after dosing. An elimination half-life of approximately 30 hours was calculated from the combined terminal elimination phase of sulfoxide plus sulfone (Alvinerie and Galtier 1986).

Twelve sheep were treated a single oral dose of a 8.75% ENDEX® suspension (10 mg triclabendazole and 7.5 mg levamisole hydrochloride) at a rate of 17.5 mg/kg body weight. Two additional heifers served as controls. Animals were slaughtered at 1, 21 and 28 days after dosing. Results are are shown in Table 7. Total residues were determined as 5-chloro-6-(2',3'-dichlorophenoxy)-benzimidazole-2-one and converted to triclabendazole equivalents using a conversion factor of 1.0913 (Lanter 1989a).

Table 7. Total residues of triclabendazole (as triclabendazole equivalents/kg) in the tissues of sheep treated with 8.75% ENDEX

Days After Treatment	Residues (mg Triclabendazole eq/kg)			
	Muscle	Liver	Kidney	Fat
Control	<0.04	<0.05	<0.04	<0.05
1	2.2	5.4	6.2	13.4
	2.1	8.9	6.2	10.7
	2.3	7.6	8.7	8.8
	1.7	7.8	6.0	7.6
21	0.16	0.25	0.17	<0.05
	0.15	0.15	0.13	<0.05
	0.15	0.24	0.12	<0.05
	0.09	0.16	0.07	<0.05
28	0.10	0.11	0.07	<0.05
	0.19	0.10	0.06	<0.05
	0.14	0.11	0.07	<0.05
	0.17	0.18	0.06	<0.05

Cattle

Twelve cattle were treated with a single oral dose of triclabendazole at a rate of 12 mg/kg body weight. The animals were slaughtered 2, 7, 14, 21 or 28 days following administration. Total residues were determined as 5-chloro-6-(2',3'-dichlorophenoxy)-benzimidazole-2-one and converted to triclabendazole equivalents using a conversion factor of 1.0913 (Giannone and Formica 1983c). The residues in the tissue of cattle are shown in Table 8.

Table 8. Total residues of triclabendazole in the tissues of cattle after a single oral treatment of 12 mg/kg body weight

Days After Treatment	Residues (mg Triclabendazole eq/kg)			
	Muscle	Liver	Kidney	Fat
Control	<0.03	<0.03	<0.046	<0.03
2	1.01	2.9	2.8	1.7
	0.74	3.6	3.3	1.9
7	0.14	0.43	0.41	0.088
	0.16	0.44	0.52	0.079
14	0.080	0.096	0.14	<0.03
	0.064	0.17	0.16	<0.03
21	0.056	0.089	0.068	<0.03
	0.065	0.12	0.092	<0.03
28	0.044	0.055	0.049	<0.03
	<0.03	0.048	0.046	<0.03

In a later study (Formica 1984), ten cattle were treated once orally with 12 mg triclabendazole/kg body weight. The animals were slaughtered 2, 7, 14, 28 or 42 days following administration. Total residues were determined as 5-chloro-6-(2',3'-dichlorophenoxy)-benzimidazole-2-one and converted to triclabendazole equivalents using a conversion factor of 1.0913. Results are shown in Table 9.

Table 9. Total residues of triclabendazole in the tissues of cattle after a single oral treatment of 12 mg/kg body weight

Days After Treatment	Residues (mg Triclabendazole eq/kg)			
	Muscle	Liver	Kidney	Fat
Control	<0.04	<0.04	<0.03	<0.06
2	1.42	7.46	4.33	2.55
	1.42	4.28	4.26	2.39
7	0.34	1.0	0.70	0.11
	0.24	0.58	0.68	0.15
14	0.20	0.61	0.29	0.07
	0.19	0.35	0.28	<0.05
28	0.09	0.17	0.09	<0.06
	0.10	0.15	0.11	<0.05
42	0.11	0.07	0.08	<0.06
	0.09	0.09	0.07	<0.05

Twelve Friesian heifers were treated with a single oral dose of a 19.5% ENDEX® suspension (12 mg triclabendazole and 7.5 mg levamisole hydrochloride). Two additional heifers served as controls. Animals were slaughtered at 1, 21 and 28 days after dosing. Results are are shown in Table 10. Total residues were determined as 5-chloro-6(2',3'-dichlorophenoxy)-benzimidazole-2-one and converted to triclabendazole equivalents using a conversion factor of 1.0913 (Lanter 1989b).

Table 10. Total residues of triclabendazole (as triclabendazole equivalents/kg) in the tissues of cattle treated with 19.5% ENDEX

Days After Treatment	Residues (mg Triclabendazole eq/kg)			
	Muscle	Liver	Kidney	Fat
Control	<0.04	<0.04	<0.04	<0.04
1	1.3	6.4	5.8	3.7
	1.9	9.5	6.9	7.6
	1.3	6.3	5.4	4.6
	1.1	6.0	5.0	4.1
21	0.19	0.32	0.18	<0.04
	0.11	0.19	0.14	<0.04
	0.15	0.26	0.17	<0.04
	0.16	0.29	0.22	<0.04
28	0.11	0.15	0.11	<0.04
	0.14	0.14	0.10	<0.04
	0.13	0.12	0.08	<0.04
	0.19	0.16	0.12	<0.04

BIOAVAILABILITY

Sheep and Goats

To estimate the bioavailability of triclabendazole in sheep after oral administration, the AUC of the sulfoxide metabolite was compared after intravenous and oral dosing. The sulfoxide was used due to the rapid metabolism of parent drug to this primary metabolite. The assumption is made that intravenously administered drug is 100% available. The relative bioavailability of triclabendazole was calculated to be 90% (Strong et al. 1982a, Strong et al. 1983). Biliary and renal excretion data raise doubts about the bioavailability of the intravenously administered dose. In sheep, approximately 50% of the dose was excreted in the bile in 6 days and urinary excretion in 10 days accounted for only 2.1% of the administered dose.

This means that the real bioavailability is much lower than that calculated by comparing intravenous and oral dosing. This could be due to removal of a proportion of the intravenous dose by a specific tissue or tissues. While the appearance of triclabendazole metabolites in the plasma is a function of both absorption from the gastrointestinal tract and release of bound material, circulating levels do not directly correlate with the efficacy of triclabendazole in controlling flukes (Strong *et al.* 1982b).

Based on limited experimentation, there are no consistent differences in the absorption properties of suspension formulations containing triclabendazole at concentrations of 25 mg/ml, 50 mg/ml or 100 mg/ml (Strong et al. 1982a), in different 50 mg/ml suspension formulations (Strong et al 1982b) or in bolus vs. drench preparations (Bowen et al. 1984). Differences in plasma levels of triclabendazole metabolites which were observed appear to be the result of interanimal variability and not esophageal groove reflex in treated sheep (Strong et al. 1983). In general, changes in crystal form or particle size distribution do not affect the plasma kinetic profiles of the triclabendazole metabolites (Strong et al. 1986).

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

Triclabendazole residues can be measured by a high performance liquid chromatograph (HPLC) method using ultraviolet absorbance detection. The method measures residues of triclabendazole with are hydrolyzable and oxidizable to 5-chloro-6-(2',3'-dichlorophenoxy)-benzimidazole-2-one (MR). Tissue samples are hydrolyzed under alkaline conditions at 90-100°C and the entire hydrolysate is extracted with methylene chloride under acidic conditions. Following evaporation of the methylene chloride, lipid material is removed by dissolving the residue in hexane and partitioning with acetonitrile. The acetonitrile is evaporated and the residue is dissolved in a mixture of acetic acid/ethanol and oxidized overnight with hydrogen peroxide at 90°C. The mixture is acidified and MR is partitioned into methylene chloride. Further clean up is carried out on a Silica Gel column followed by a C_{18} SEP-PAK column prior to HPLC on a 10 μm LiChrosphere Si 100 column, 25 cm x 4.6 mm i.d. A mobile phase consisting of a mixture of dichloromethane/hexane/anhydrous ethanol/glacial acetic acid (700/300/50/4) at a flow rate of 1.5 cm^3/min is used to effect separation. Effluent is monitored at 295 nm (Giannone and Formica 1983b). Alternatively, the SEP-PAK clean up can be omitted by the use of column switching with two LiChrosphere Si 100 columns (Giannone and Formica 1983f). The limit of detection is 4 ng corresponding to 0.027 mg MR/kg or 0.03 mg triclabendazole/kg (conversion factor 1.0913). Recoveries from spiked samples in tissues of cattle and sheep are shown in Table 11.

Table 11. Recoveries (%) of MR in tissues of sheep and cattle

Tissue	Fortification level mg/kg	Recoveries after SEP-PAK		Recoveries after Column Switching
		Cattle	Sheep	Sheep
Muscle	0.1	109	85/69/95	97/95
	0.5	76	87/67/70/74	72/79
Kidney	0.1	80	80/73/83/74	89/98
	0.5	70	77/72/75/67/75	75/76
Liver	0.1	41	82/76/68/68	67/75
	0.5	77	58/70/60/66	76/79
Fat	0.1	69	53	71/73/68
	0.5	55	69	54/60/61

Modification of the method to use HPLC column 2 packed with 10μm Lichrosorb Diol instead of LiChrosphere Si 100 permits the determination of MR in the tissues of sheep treated with 8.75% ENDEX (Lanter 1989a) or cattle treated with 19.5% ENDEX (Lanter 1989b). The practical limit of detection is 0.04-0.05 mg/kg as CGA 89317 (triclabendazole).

Using a mobile phase of hexane/ethanol/glacial acetic acid (500:50:0.6, v/v/v) on a 5μm Partisil silica gel column, triclabendazole and its sulfoxide and sulfone metabolites are quantified from a plasma matrix following ethyl acetate extraction. The HPLC system employs an ultraviolet detector set at 215 nm and a solvent flow rate of 1.5 ml/min. Oxfendazole is used as an internal standard. The system is linear from 0.1-4.0 μg/ml and has a detection limit of 50 ng/ml for all products (Alvinerie and Galtier 1986).

A reversed-phase HPLC method using a 10μm microBondapak column and a solvent system containing methanol/water/reagent 1(120 ml glacial acetic acid + 200 g ammonium acetate q.s. 1 l)/chloroform (750:200:25:10, v/v/v/v) also provides quantification of triclabendazole and its metabolites. Detection is ultraviolet at 300 nm with a flow rate of 1 ml/min. The limit of detection is 0.1 mg/l (Bull and Shume 1987a).

A similar method is employed for the simultaneous detection of fenbendazole, its sulfoxide and sulfone metabolites and the corresponding metabolites of triclabendazole. Using a reversed-phase column, a solvent system containing acetonitrile/0.04M diammonium hydrogen orthophosphate (41:59, v/v) adjusted to pH 7.5-7.6 effects the separation. The system is linear over a range of 5-500 ng with a 10 ng/ml limit of determination in plasma (Bull and Shume 1987b).

In an earlier method for the simultaneous determination of fenbendazole, its sulfoxide and sulfone metabolites and the corresponding metabolites of triclabendazole, a 5μm Hypersil SAS (mixed C_2-, C_4-, C_6-silica) column was used. A mobile phase containing 0.005M phosphoric acid (adjusted to pH 5.9 with tetraethylammonium hydroxide solution)/ acetonitrile (70:30) at a flow rate of 2.0 ml/min was used for the separation. The effluent was monitored at 300 nm. The system is linear over the range of 20-1000 ng/ml in plasma for fenbendazole and its metabolites and 50-1000 ng/m for the triclabendazole metabolites. The limit of determination is stated to be 10 ng/ml for the fenbendazole metabolites, 15 ng/ml for parent fenbendazole, and 20 ng/ml for the triclabendazole metabolites (Lehr and Damm 1986).

A solid phase extraction procedure is also reported for sample preparation prior to HPLC analysis with fluorescence detection. Blood samples from goats, horses, ponies and donkeys and milk samples from goats were precipitated with acetone. The resultant supernatant is mixed with water and loaded onto preconditioned SEP-PAK cartridge. A 5μm ODS-Hypersil column with a mobile phase of 0.13M ammonium acetate buffer (pH 6.7)/methanol (30:70, v/v) was used to effect separation. Excitation and emission wavelengths were 300 nm and 676 nm, respectively. Detection limits were 0.02 μg/ml for triclabendazole sulfone and 0.04 μg/ml for triclabendazole sulfoxide. Recovery of triclabendazole and its sulfoxide and sulfone metabolites from plasma and milk ranged from 76-92% (Kinabo and Bogan 1987 and 1988).

An extraction method was validated to determine the relationship of residues resulting from chemical extraction to "true" total residues determined using combustion analysis and liquid scintillation. Tissue samples were macerated with methanol and shaken for 30 minutes. An aliquot of the clear extract was taken for scintillation counting. Only 2-13% of the total radioactivity was extracted from the tissue samples. The method is considered not valid for the determination of total residues in tissue samples (Giannone and Formica 1981b).

The HPLC method was validated to determine the relationship of residues determined by HPLC-UV to "true" total residues. Tissue samples were collected from a goat treated with ^{14}C-triclabendazole ten days following treatment. Total radioactivity was determined via liquid scintillation counting after combustion. The SEP-PAK clean up was not included in the tissue sample preparation and only muscle tissue was analyzed. Approximately 32-38% of the total radioactivity in goat muscle can be determined using the HPLC-UV method (Giannone and Formica 1983d).

Blood and milk were collected from a goat treated with ^{14}C-triclabendazole. Milk and blood samples were prepared by precipitation of proteins with acetone followed by partitioning into dichloromethane. Samples were evaporated to dryness. Milk samples were dissolved in hexane and cleaned up with acetonitrile. After evaporation of the acetonitrile, samples were cleaned up and separated on a degassed alumina column prior to final HPLC-UV analysis. Blood samples were prepared similarly but the hexane/acetonitrile partition step was eliminated. Residues of triclabendazole and its metabolites account for approximately 54-79% of the radioactivity in milk and 100% of the radioactivity in blood. The limit of determination in blood and milk is 0.005 mg/kg (Giannone and Formica 1981a).

APPRAISAL

The absorption, distribution, metabolism and excretion of triclabendazole have been studied and are qualitatively similar in both cattle and sheep. As with several other benzimidazoles, the use of triclabendazole in food producing animals results in a large portion of the total residue being bound to endogenous tissue. The proportion of bound residue to total residue increases with increasing withdrawal periods. The marker residue for triclabendazole is 5-chloro-6-(2',3'-dichlorophenoxy)-benzimidazole-2-one (MR). MR results when common fragments of triclabendazole-related residues are hydrolyzed under alkaline conditions at 90-100°C. As the marker residue does not measure total residues, the ratio for the marker residue and the total residue needs to be determined for each species. The marker residue levels are converted to triclabendazole equivalents using a conversion factor of 1.09.

Cattle - In three separate residue depletion studies cattle were dosed with triclabendazole at 12 mg/kg body weight. The residues of MR were determined in the edible tissues at various withdrawal times. A common withdrawal time for all three studies was 28 days. The average values ($n=8$) of MR at the 28 day withdrawal time were 0.12, 0.07, 0.11 and 0.05 mg/kg in liver, kidney, muscle and fat. These values represent 50, 66, 84 and >100% of the total residue in the respective tissues at a withdrawal time of 28 days.

Sheep. - In two separate residue depletion studies sheep were dosed with triclabendazole at 10 mg/kg body weight. The residues of MR were determined in the edible tissues at various withdrawal times. Common withdrawal times for both studies were 7, 14 and 28 days. Combining the residue levels at 7 and 14 days to approximate the residue levels at 10 days in the radiolabel study, the average values ($n=10$ for kidney and muscle; $n=9$ for liver) of MR were 0.44, 0.25, 0.19 and 0.04 mg/kg in liver, kidney, muscle and fat. These values represent 24, 23, 33 and 51% of the triclabendazole-related total residues in the respective tissues. Using these percentages and residue concentrations of MR at 28 days withdrawal of 0.097, 0.076, 0.11 and <0.03 mg/kg in the respective tissue, the concentration of total triclabendazole-related residues is approximated to be 159 μg.

The following information was utilized in setting the MRLs for triclabendazole:

An ADI of 0-3 μg/kg of body weight was established. This would result in a maximum ADI of 180 μg for a 60 kg human.

Considering the vigorous extraction conditions of the method for MR, the method likely measures more residues than those usually defined as extractable residues. However, the method does not measure total residues.

Recommended MRLs for Triclabendazole in Cattle

Tissue	Concentration of MR at Day 28 Withdrawal, μg/kg 12 mg/kg oral dose	Total Residue Consumed μg(a)	Recommended MRL μg/kg MR	Theoretical Maximum Daily Intake μg(a)
Muscle	110(131)b	39	200(238)b	71
Liver	120(240)c	24	300(600)c	60
Kidney	70(106)d	5	300(454)d	23
Fat	50	2	100	5
	Total	70		159

a) Based on a daily intake of 0.3 kg muscle, 0.1 kg liver, 0.05 kg kidney and fat.
b) Adjusted observed value by 84% to estimate total residues.
c) Adjusted observed value by 50% to estimate total residues.
d) Adjusted observed value by 66% to estimate total residues.

Recommended MRLs for Triclabendazole in Sheep

Using the residue data at 28 days withdrawal for sheep and assuming the ratio of marker residue to total residue at 28 days is approximated by the ratio at 10 days withdrawal, the dietary intake for all triclabendazole related residues at 28 days withdrawal is approximately 159 μg.

Tissue	Concentration of MR at Day 28 Withdrawal, μg/kg 10 mg/kg oral dose	Total Residue Consumed μg(a)	Recommended MRL μg/kg MR	Theoretical Maximum Daily Intake μg(a)
Muscle	110(333)b	100	100(303)b	91
Liver	97(404)c	40	100(417)c	42
Kidney	76(330)d	16	100(435)d	22
Fat	<30(59)e	3	100(196)e	10
	Total	159		165

a) Based on a daily intake of 0.3 kg muscle, 0.1 kg liver, 0.05 kg kidney and fat.
b) Adjusted observed value by 33% to estimate total residues.
c) Adjusted observed value by 24% to estimate total residues.
d) Adjusted observed value by 23% to estimate total residues.
e) Adjusted observed value by 51% to estimate total residues.

Additional data are required if the MRLs for triclabendazole in sheep are to be increased. A more accurate estimate of the total residues in edible tissues of sheep is needed. Also, the ratio of total residue concentrations to the marker residue concentrations is needed. Considering that the recommended MRLs require all of the ADI at 28 days, bioavailability studies on the bound residue of triclabendazole may be needed to reduce the amount of residue of toxicological concern.

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