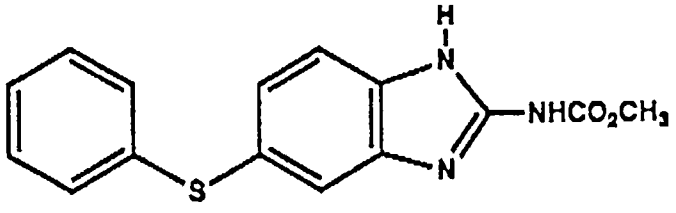
FENBENDAZOLE

IDENTITY

Chemical: Methyl 5-(phenylthio)-2-benzimidazolecarbamate,

Synonyms: HOE 881, CAS 43210-67-9

Structural formula:



Molecular formula: $C_{15}H_{13}N_3O_2S$

Molecular weight: 299.35

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient:

Contains not less than 98.0 to 101.0%, calculated with reference to the dried substance. The by-products are equal or less than 1.0% (sum) and less than or equal to 0.5% (individual) for derosal (benzimidazole-2-carbamic acid, methyl ester) , chloroderosal (5(6)-chloro-2-benzimidazole-carbamic acid, methyl ester), aminophenylmercaptoaniline, nitrophenylmercaptioaniline, and 1-amino-2,4-dithiophenylbenzole.

Appearance: Light, brownish-gray, crystalline powder.

Melting point: 233 ° (with decomposition).

Solubility: Insoluble in water (approximately 10-40 ppb); insoluble or only slightly soluble in the usual solvents; freely soluble in DMSO.

Octanol/Water Partition Coefficient: Log_{ow} 3.9

RESIDUES IN FOOD AND THEIR EVALUATION

CONDITIONS OF USE

General

Fenbendazole is an anthelmintic used for the treatment of gastrointestinal parasitism in many mammalian species (e.g. cattle, sheep, goats, horses and pigs). Fenbendazole has a broad spectrum of activity against all stages of gastrointestinal nematodes including larval stages, cestodes and lungworms. It is administered as a single therapeutic dose or over several days in divided doses depending on the species.

Dosage

Typical single therapeutic doses for cattle, sheep, goats, horses and pigs are 5-10, 5.0, 5.0, 5-10 and 5.0 mg/kg, respectively. Also, 3 mg/kg daily for 3 consecutive days or 9 mg/kg for 3-12 consecutive days.

METABOLISM

General

Fenbendazole is metabolized by oxidation of the sulfur molecule, hydroxylation of the phenyl ring and degradation of the carbamate to the amine. All radiolabelled studies in this report have been conducted with ^{14}C labelled at the 2-imido position. In all species studied, the main residues found in edible tissues are the parent drug (fenbendazole), fenbendazole sulfoxide (oxfendazole) and oxfendazole sulfone (HOE 5151). Metabolism and safety studies using ^{14}C-fenbendazole in mammals have demonstrated that blood levels and excretion half-lives are longer in ruminants than in monogastric animals. (Kellner et al, 1974)

Rat

Rats were given 10, 50 and 100 mg/kg of fenbendazole by stomach tube. Blood was taken from three rats of each dose group at the same test time and the blood was pooled to obtain serum. Fenbendazole was not detected in any of the sera at a level of 0.25 μg/ml. (Duwel and Hajdu, 1974a)

Male and female Wistar rats were dosed with 10 mg/kg ^{14}C-fenbendazole. The blood levels peaked 5-7 hours post administration at a level of 0.19 μg/ml and depleted with a half-life of 6 $\pm$ 1 hours. The amount excreted in the urine and feces was 7.8 and 90.6%, respectively. Liver was the only tissue that had measurable levels of radioactivity.

The level at 7 and 14 days post administration was 0.06 and 0.01-0.02 μg/g, respectively. (Kellner and Christ, 1973)

Cattle

The oral administration of 5.3 mg/kg ^{14}C-fenbendazole in a 2% suspension to a lactating cow resulted in slow absorption with a peak in blood levels of 0.52 μg/ml and 0.71 μg/ml in serum occurring 28-30 hours post-administration. After this time, the levels were lower in the milk than in serum. The predominant half-life in blood, serum and milk was 15 hours. Almost 77% of the applied dose was recovered with the feces, 14% with urine, and 0.3% in the milk. Excretion was as rapid as elimination from blood and serum (Kellner and Christ, 1975)

Twenty-four hours after two cows had each been given a single oral dose of 10 mg/kg fenbendazole in the form of a 2.5% aqueous suspension, the metabolites of the compound in the liver were examined. The radioactivity of the liver was distributed among the original substance (79% and 83%) and three metabolites (2% and 1%: 6% and 4%; and 8% and 7%). (Klopffer, 1977)

Metabolism studies in bovine liver tissue, seven days after dosage with ^{14}C-fenbendazole at 10 mg/kg revealed two major drug-related residues: fenbendazole and its sulfoxide metabolite (oxfendazole). Both substances were present in an unconjugated form. In addition, two minor metabolites of a more polar nature were evidenced but not identified. (Hoffman, 1980)

Sheep

Sheep were given fenbendazole at 5.0 mg/kg as a suspension. Blood levels peaked between 6 and 24 hours at levels of approximately 0.2-0.4 μg/ml. (Duwel and Hajdu, 1974a)

Two sheep were given ^{14}C-fenbendazole at 5 mg/kg in a 2% starch suspension. The highest blood levels in the two sheep were 0.32 and 0.24 μg/g and occurred 2-2.3 and 1.3 days, respectively. The half lifes from blood were 26 and 22 hours, respectively. The amount excreted in the urine and feces averaged 7 and 94.8%, respectively. (Kellner and Christ, 1973)

In sheep about 10-20% of the excretion is in the urine and the remainder is in the feces. About 50-75% of the urine extract contained a metabolite, which differs from the compound in its hydroxyl group in the phenyl ring. Mainly unchanged compound is excreted in the feces. (Klopffer, 1973)

Swine

Three pigs were given 5 mg/kg ^{14}C-fenbendazole orally as a 2.5% aqueous solution. Urinary and fecal samples were incubated with enzymes to split any conjugates. Evaluation of isotope excretion in all three animals showed that 30-35% of the administered radioactivity was recovered in the first three days in the urine and 50-60% in the feces. Six different substances were detected in the urine and five in the feces

along with the original compound in each case. Parent fenbendazole was only 1% in urine and 37-52% in feces. (Klopffer, 1975)

TISSUE RESIDUE DEPLETION DATA

Radiolabelled Residue Depletion Studies

Cattle

^{14}C-Fenbendazole was given orally to six lactating dairy cows in doses of 10 mg/kg body weight as a 2.5% suspension. Serum levels as well as the excretion in urine and milk were examined. The maximum serum levels were ca. 1.6 µg/ml, and they were reached between 23 and 32 hours after drug administration. The highest milk levels, 1.29 ± µg/ml, were found at the second and third milking; one week after administration they had dropped to <0.01 µg/ml. Excretion in milk was 0.27 to 0.48% of the dose. Renal elimination was 14 to 18% of the dose. Tissue levels in two of the cows are summarized in Table I. (Kellner et al, 1977)

Table I. Tissue levels (µg/g) 25 hours after oral administration of 10 mg/kg ^{14}C-fenbendazole in two dairy cows.

	Cow 2	Cow 3
Liver		
Homogenate	17.1 ± 0.5	18.6 ± 0.4
Biopsy 1 *	11.9 ± 2.6	19.1 ± 4.1
Biopsy 2 **	19.6 ± 1.6	23.3 ± 4.8
Kidney	3.68 ± 0.03	5.63 ± 0.06
Muscle	1.01 ± 0.02	1.33 ± 0.02
Fat		
Subcutaneous	1.36 ± 0.04	2.84 ± 0.08
Kidney	3.64 ± 0.49	4.89 ± 0.38

* Biopsy 1 = before animals were sacrificed
**Biopsy 2 = biopsy on exenterated liver of sacrificed animal

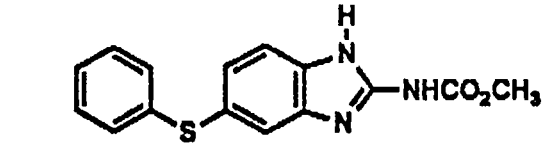
^{14}C-Fenbendazole was administered orally as an aqueous suspension to 6 cattle weighing 200-300 kg at a dose level of 10 mg/kg body weight. The residues in kidneys, liver, muscle and fat based on radioactivity were determined in two animals each after 7, 14 and 30 days. The tissue residue levels are summarized in Table II. (Kellner and Eckert, 1978)

Table II. Tissue residue levels (μg/g) in cattle administered ^{14}C-fenbendazole at 10 mg/kg.

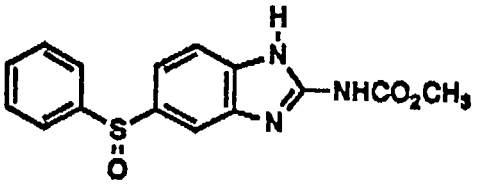
Withdrawal (Days)	Tissue Concentrations Liver	Kidney	Muscle	Fat
7	9.92	1.86	0.03	0.033
7	12.6	2.0	0.046	0.050
14	2.34	0.30	0.004	0.014
14	2.66	0.49	<0.004	0.012
30	0.97	0.078	<0.004	0.008
30	1.05	0.11	<0.004	0.014

Milk and serum levels of fenbendazole and its metabolites in cows treated orally with 7.5 mg/kg body weight fenbendazole as a 10% suspension or 1.5% pellets were determined. A HPLC method quantitated each of the compounds shown in Figure 1.

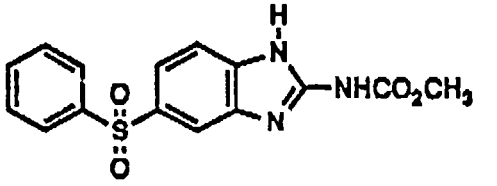
Figure 1. Fenbendazole and Metabolites



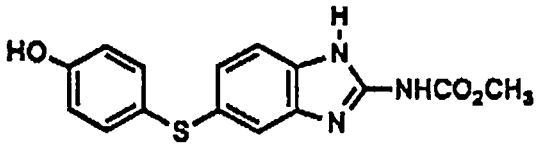
HOE 881 (fenbendazole)



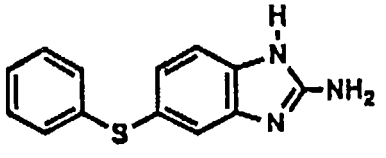
HOE 8105 (oxfendazole)



HOE 5151



HOE 2542



HOE 7391

Metabolites HOE 2542 and HOE 7391 were not detected in any of the samples. The trials demonstrated that markedly more fenbendazole was absorbed in the animals given pellets than after administration of the suspension. The levels of fenbendazole in milk peaked between 24 and 32 hours. The levels in milk showed large variations between animals, but generally the oxfendazole level exceeded the fenbendazole level. The sulfone level frequently was comparable to the lower of the fenbendazole or oxfendazole level. The maximum level of all three added together exceeded 1 μg/g. All three compounds were below their detection limits 4 days post administration. (Tiefenbach et al, 1984)

Sheep

No labeled studies of fenbendazole were reported in sheep.

Swine

^{14}C-Fenbendazole was administered to swine to determine its depletion from tissues and the elimination of fenbendazole and its metabolites in urine and feces. Five groups containing three pigs each were administered 3 mg/kg ^{14}C-fenbendazole as 2.5% suspension on each of three successive days Three additional pigs were used as controls. The treated groups were slaughtered on days 0.25, 1, 7, 11 and 21 following administration of the third daily dose. The control group was slaughtered after all other groups had been killed. The blood levels peaked at 0.83 μg/ml at ca. 6 hours after the third dose and was less than 0.1 μg/ml at 24 hours. The percent of dose eliminated in the urine and feces after three weeks post-administration was 45 and 30, respectively. The tissue levels are summarized in Table III. (Bevill et al, no date)

Table III. Tissue levels of fenbendazole and metabolites in swine with a dose at 3 mg/kg for three days.

Withdrawal	Tissue Concentration (μg/g)			
Time	Liver	Kidney	Muscle	Fat
6 hours	10.55	3.95	1.07	1.47
24 hours	10.18	4.30	0.52	0.59
7 days	0.63	0.06	0.01	0.01
11 days	0.39	0.03	0.01	0.02
21 days	0.11	0.02	0.01	0.01

Other Residue Depletion Studies (with Unlabeled Drug)

Cattle

Two groups of three cows each were given 7.5 and 10.0 mg/kg fenbendazole as a suspension. The levels of fenbendazole were determined in the serum and milk. The results are summarized in Table IV. (Duwel and Hajdu, 1974b)

Table IV. Fenbendazole levels (μg/ml) in milk and serum of cows.

Withdrawal (Hours)	7.5 mg/kg Serum	7.5 mg/kg Milk	10.0 mg/kg Serum	10.0 mg/kg Milk
1	0.13		0.15	
2	0.24		0.20	
4	0.30		0.26	
6	0.17		0.16	
8		0.07		0.22
24	0.90	0.20	0.94	0.27
30	0.92	0.27	0.97	0.22
48	0.66	0.25	0.79	0.28
54	0.55	0.18	0.59	0.28
72	0.18	0.10	0.28	0.20
78	0.13	0.05	0.24	0.13
96	0.13	0.01	0.07	0.07
102	0.02	0	0.06	0
120	0	0	0.06	0

Twelve cattle were dosed with 10 mg/kg fenbendazole suspension. Three animals wer slaughtered at withdrawal times of 2, 5, 7 and 14 days post dosing. The tissues wer analyzed by a fluorometric method for fenbendazole. The results are summarized i Table V. (Duwel and Hajdu, 1974c)

Table V. Fenbendazole levels in tissue of cattle dosed with 10 mg/kg.

Withdrawal (Days)	Tissue Concentrations (μg/g) Liver	Kidney	Muscle	Fat
2	8.4	1.04	0.47	0.95
2	8.1	0.74	0.22	0.48
2	7.1	0.77	0.32	1.10
5	1.17	<0.1	<0.1	<0.1
5	1.49	<0.1	<0.1	<0.1
5	8.3	<0.1	0.40	1.31
7	0.14	<0.1	<0.1	<0.1
7	0.67	<0.1	<0.1	<0.1
7	0.14	<0.1	<0.1	<0.1
14	<0.1	<0.1	<0.1	<0.1
14	<0.1	<0.1	<0.1	<0.1
14	<0.1	<0.1	<0.1	<0.1

Three cattle were administered 7.5 mg/kg body weight fenbendazole in 1.5% pellets. Residue analyses of fenbendazole and its metabolites were performed 7 days after treatment and the following arithmetic means were calculated (µg/g): (Damm, 1985)

	HOE 8105	HOE 5151	HOE 881
muscle	ND	ND	0.09
fat	ND	ND	0.11
kidney	0.12	ND	0.18
liver	1.92	0.08	1.29

ND = Not detected, below detection limit
HOE 2542 was not detected at all.

Sheep

Fifteen sheep were administered 5.0 mg/kg fenbendazole orally as a suspension. Three animals each were slaughtered at withdrawal times of 2, 5, 7, 14 and 21 days post administration. The tissue levels of fenbendazole as measured fluorometrically are given in Table VI. (Duwel and Hajdu, 1974a)

Table VI. Tissue concentrations of fenbendazole in sheep.

Withdrawal	Tissue Concentration (µg/g)			
Time (Days)	Liver	Kidney	Muscle	Fat
2	3.85	0.37	0.27	0.75
5	1.09	0.1	0.16	0.1
7	0.91	0.1	0.1	0.2
14	0.2	0.1	0.1	0.1
21	0.1	0.1	0.1	0.1

Three sheep were administered 5 mg/kg body weight of fenbendazole as 1.5% pellets on five consecutive days. Residue analyses of fenbendazole and its metabolites were performed 7 days after the last dose was administered and the follow arithmetic means were calculated (µg/g): (Damm, 1985)

	HOE 8105	HOE 5151	HOE 881
muscle	0.07	0.10	0.13
fat	0.06	0.10	0.33
kidney	0.18	0.28	0.51
liver	7.30	0.72	4.03

HOE 2542 was not detected at all.

Goat

Three goats were administered 5 mg/kg fenbendazole by means of a nasal stomach tube. The milk from the goats was analyzed for fenbendazole by a fluorometric method with a detection level of 0.01 μg/ml of milk. The results are summarized in Table VII. (Klatt and Hajdu, 1975)

Table VII. Milk concentration of fenbendazole from goats.

Withdrawal (Hours)	Concentration of Fenbendazole in μg/ml of milk		
	Animal #1	Animal #2	Animal #3
5	0.16	0.07	-
22	0.20	0.10	0.10
30	0.30	0.08	-
47	0.18	0.05	0
54	0.07	0.02	-
70	0	0	0
78	0	0	-
94	0	0	0

Swine

Four piglets, ca. 20-25 kg body weight, were administered 1 mg/kg each on five consecutive days. Serum levels for fenbendazole were determined between 2 and 144 hours post-administration. Tissue levels were determined at 144 hours. The levels in serum varied between the detection limit and 0.37 μg/ml; at the time of sacrifice, 144 hours after the start of the trial, serum levels could no longer be measured. The results of the tissue assays are summarized below: (Duwel and Hajdu, 1976)

Liver	0.32 - 0.67 μg/g
Kidney	0.31 - 0.35 μg/g
Muscle	0.26 - 0.85 μg/g
Fat	0.24 - 0.52 μg/g

Four groups of three pigs (ca. 25 kg) were treated with 5 mg/kg fenbendazole and slaughtered at 2, 5, 7 and 14 days post dosing. The tissues were analyzed by a fluorometric method. The average results are summarized in Table VIII. (Duwel and Hajdu, 1975)

Table VIII. Tissue levels (μg/g) of fenbendazole in swine.

Withdrawal (Days)	Liver	Fat	Kidney	Muscle
2	0.67	0.20	0.53	0.22
5	0.25	0.15	<0.1	<0.1
7	0.28	<0.1	<0.1	<0.1
14	0.11	<0.1	<0.1	<0.1

The fate of residues of fenbendazole and its metabolites in swine was examined after relatively long periods of administration at a low dosage via medicated feed. The following mean values were determined one and five days after discontinuation of the fenbendazole feed (data in μg/g; detection limit: 0.05 μg/g) (Duwel, 1986)

Duration of Dosing	Dissection (days after)		Liver	Kidney	Fat	Muscle
30 Days	+1	HOE 8105	0.28	0.05	0.08	ND
		HOE 5151	0.23	0.07	ND	ND
		HOE 881	0.40	0.16	ND	0.05
	+5	HOE 8105	0.13	0.06	0.07	ND
		HOE 5151	0.06	0.06	ND	ND
		HOE 881	0.21	0.09	ND	ND
60 Days	+ 1	HOE 8105	0.15	0.09	0.04	ND
		HOE 5151	ND	ND	ND	ND
		HOE 881	0.06	0.09	0.06	ND
	+ 5	HOE 8105	0.05	0.08	0.13	ND
		HOE 5151	ND	ND	ND	ND
		HOE 881	0.10	0.06	ND	0.07
90 Days	+ 1	HOE 8105	ND	0.05	ND	ND
		HOE 5151	0.05	0.05	0.06	ND
		HOE 881	0.09	0.05	0.06	ND
	+ 5	HOE 8105	0.07	ND	ND	ND
		HOE 5151	ND	ND	ND	ND
		HOE 881	0.06	ND	ND	ND
120 Days	+ 1	HOE 8105	0.11	0.07	0.06	ND
		HOE 5151	ND	ND	ND	ND
		HOE 881	0.18	ND	ND	ND
	+ 5	HOE 8105	0.05	0.08	ND	ND
		HOE 5151	ND	ND	ND	ND
		HOE 881	0.07	0.08	ND	ND

During the 30, 60, 90 or 120-day administration period of medicated feed, a mean compound intake of 0.2 to 0.3 mg fenbendazole/kg body weight per day was calculated. The study findings showed that, when administered in medicated feed for a period lasting from 30 up to a maximum of 120 days, no accumulation of fenbendazole was observed in host tissues and, during the study period from 1 to 5 days after discontinuation of the medicated feed, residues were found to be considerably reduced.

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

Fenbendazole can be determined in serum and milk at a level of 0.25 µg/ml by fluorometry. The serum or milk is extracted with ether and subsequently centrifuged. Part of the ether is evaporated, the residue is mixed with ethanol and measured on the fluorometer. (Duwel and Hajdu, 1974b)

Fenbendazole and its metabolites can be determined in serum and milk by HPLC. Two ml serum is mixed with internal standard and ammonia and extracted with diethyl ether. The ether extract is concentrated to dryness, taken up in solvent and separated by HPLC.

Two ml milk is mixed with internal standard and other protein removed with methanol. The supernatant is concentrated to dryness, the residue divided between ammonia solution and ether, and then between n-hexane and acetonitrile. The acetonitrile phase is concentrated to dryness, taken up in solvent and separated by HPLC. (Uihlein and Hack, 1979)

The method detects side by side the metabolites HOE 8105, HOE 5151, H0E 2542 and the sum of HOE 881 and H0E 7391. Detection limits are:

	HOE 881	HOE 8105	HOE 5151	HOE 2542
Serum	150 ng/ml	10 ng/ml	10 ng/ml	10 ng/ml
Milk	50 ng/ml	50 ng/ml	10 ng/ml	10 ng/ml

Fenbendazole can be determined in cattle and sheep tissue by fluorometry. The tissue is homogenised with methanol and subsequently centrifuged. The supernatant is evaporated until dry, mixed with phosphate buffer pH 7 and extracted with ether. After the ether extract has been evaporated the residue is mixed with chloroform and placed on a silica gel column. It is then eluted with chloroform; the eluate is evaporated until dry, mixed with ethanol and measured in the fluorometer. The limit of measurement is reported to be 0.1 µg/g tissue. (Duwel and Hajdu, 1974a and 1974c)

A method has been developed for the determination of fenbendazole at 0.8 µg/g concentration levels and above. Fenbendazole is extracted from homogenized tissues with ethyl acetate. The dried extract is then partitioned between hexane and acetonitrile to remove lipid components. The acetonitrile phase is evaporated, and the residue is dissolved in methanol and assayed quantitatively for fenbendazole by reverse phase high pressure liquid chromatography. The lower limit of sensitivity of the method is approximately 0.02 µg/g fenbendazole, which is equivalent to about twice the response

of control tissue. The method has been validated by interlaboratory studies.(Hoechst, 1983a)

Confirmation of fenbendazole in bovine liver is accomplished by further purifying the acetonitrile residue in the above method by thin-layer chromatography. The zone of interest is excised and eluted. The isolated fenbendazole is transformed to a benzyl derivative by phase transfer alkylation. Quantitation of the isolated derivative is performed by HPLC. (Hoechst, 1983b)

APPRAISAL

(See Annex 2 for a combined appraisal of Febantel, Fenbendazole and Oxfendazole).

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