FLUBENDAZOLE

IDENTITY

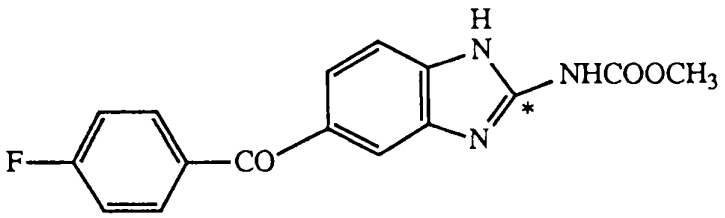
Chemical name: Flubendazole

CAS Number: 31430-15-6

CAS Nomenclature: [5-(4-Fluorobenzoyl)-1H-benzimidazol-2-yl]carbamic acid methyl ester

Synonyms: Fluvermal, Flubenol, Flumoxal, Flumoxane

Structural formula:



(* shows position of ^{14}C label for metabolism studies)

Molecular formula: $C_{16}H_{12}FN_3O_3$

Molecular weight: 313.30

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient: Flubendazole active ingredient contains not less than 95.0% of $C_{16}H_{12}FN_3O_3$, calculated on a dry basis.

Appearance: Grey-white to yellowish powder.

Melting point: 260°C

Solubility: Flubendazole is almost insoluble in water and most common organic solvents [diluted mineral acids, ethanol, ether, chloroform (0.014 g/100 ml)]. It is fairly soluble in formic acid (34.05 g/100 ml).

RESIDUES IN FOOD AND THEIR EVALUATION

CONDITIONS OF USE

General

Flubendazole is a member of a widely used chemical class of compounds known as the benzimidazoles. Its chemical structure and pharmacological properties are similar to other benzimidazoles such as thiabendazole, fenbendazole, oxibendazole, mebendazole, oxfendazole and triclabendazole.

Flubendazole is a broad-spectrum anthelmintic used for deworming dogs, cats, swine, and poultry. It is active against gastrointestinal nematodes and lungworms in swine and against gastrointestinal nematodes in poultry. For therapeutic treatment, pigs are given feed containing 30 g flubendazole per ton (30 ppm) of feed for 10 consecutive days. For poultry, the following treatments are recommended for 7 consecutive days: 20 g per ton (20 ppm) of feed for turkeys, 30 or 60 g per ton (30 or 60 ppm) for chickens and geese; and 60 g per ton (60 ppm) for pheasants and partridges. For disease prevention, chickens may be treated continuously with feed containing 4 g per ton (4 ppm) flubendazole.

Dosages

Flubendazole is administered as a feed additive to swine and poultry, or orally as a paste (44 mg/ml) to dogs and cats. Because of poor solubility in aqueous systems, the drug is suitable for oral administration and generally is not available for parenteral treatment.

METABOLISM

General

The absorption, distribution, metabolism, excretion and tissue residues of flubendazole have been studied using ^{14}C-labeled drug in rats, dogs, swine, and poultry. In all studies where the radioactive label site was identified, the molecule was labeled in the 2-position of the benzimidazole ring, as shown in the chemical structure above. Flubendazole is poorly absorbed and the metabolism is qualitatively similar in all species studied. Efficacy against gastrointestinal parasites has been attributed to the poor bioavailability of flubendazole, causing most of the drug to be eliminated in the feces as unchanged flubendazole. The portion of drug that becomes absorbed is rapidly metabolized, resulting in extremely low levels of parent drug in blood or urine. The major metabolites in urine of all species result from carbamate hydrolysis or ketone reduction. Metabolites were present in urine mainly as glucuronide or sulphate conjugates.

When swine or poultry are treated with flubendazole, the tissue with the highest residue concentration and slowest depletion rate is the liver. The major metabolite in swine liver is (2-amino-1H-benzimidazol-5-yl) 4-fluorophenyl-methanone. This compound is found at a much higher concentration than parent flubendazole and

could serve as a marker residue. Residues were higher and more persistent in egg yolk than egg white.

The rat and dog are exposed to nearly the same metabolites that are present in the edible tissues of swine. One minor metabolite found in the dog was not reported in swine or rats. This compound, 2-amino-α-(4-fluorophenyl)-1-methyl-1H-benzimidazole-5-methanol (Compound (5) in Figure 1), resulted from N-methylation. Metabolism information was not available for poultry. However, a radiolabeled residue depletion study included information on excretion. Rate of excretion in poultry was similar to that of rats and dogs. Of the total radioactive dose, 86 to 87% was excreted as unchanged drug within 24 hours of the last treatment. Absorption of flubendazole may be greater in swine than in rats and dogs. In swine, only 79% of the total radioactive dose had been excreted by the end of the 30 day withdrawal period. Within 4 days post-dosing, 96% and 88% of the total radioactive dose had been excreted by rats and dogs, respectively.

Rat

Twenty-four male Wistar rats (250 ± 10 g) were treated orally with a microcrystalline suspension of ^{14}C-flubendazole. The rats received a 10 mg/kg dose with specific activity of 2.03 μCi/mg (radiochemical purity and label position not-specified). Plasma levels of unchanged flubendazole reached 0.130 μg/ml one-half hour after treatment. In plasma, total drug related residue peaked at 0.504 μg/ml eight hours after treatment. The elimination half life was approximately 6 hours for unchanged drug, measured by HPLC with UV detection at 313 nm. Plasma clearance of labeled metabolites was much slower. At 24 hours post-treatment, approximately 50% of the total radioactive dose had been eliminated in the feces, primarily as unchanged flubendazole. Only about 4% of the total radioactive dose was excreted in the urine by 24 hours, all as metabolites. (Michiels et al., 1977a)

In a study comparing the excretion and metabolism of flubendazole and mebendazole, flubendazole was given to five male Wistar rats (275 to 285 g) at 10 mg/kg. Dosing was by oral injection with a microcrystalline suspension of ^{14}C-flubendazole labeled in the 2-position. The drug was radiochemically pure (exact purity not-stated) when tested by TLC, and had a specific activity of 6.7 μCi/mg. A high percentage of the total radioactive dose was recovered in the excreta within four days (89% feces, 7% urine) after treatment. Unchanged drug was measured using HPLC with detection at 254 nm. Metabolites were identified by TLC, comparing purified urine and fecal extracts with reference compounds. Radioactivity in the feces was almost entirely from unchanged drug, but urinary ^{14}C was primarily from metabolites. The main metabolite in feces and urine resulted from carbamate hydrolysis. In addition, another metabolic pathway was reduction of the ketone, resulting in additional metabolites in urine (Figure 1). The major metabolites in urine were unchanged flubendazole (9.8% of 0 to 48 h radioactivity in urine), methyl-[5-(α-hydroxy-α-(4-fluorophenyl) methyl)-1H-benzimidazol-2-yl] carbamate (19.0%), and (2-amino-1H-benzimidazol-5-yl) 4-fluorophenyl-methanone (15.8%). Another peak amounting to 15.8% of total radioactivity could not be identified. In feces, 87.3% of the 0 to 24 hour radioactivity was from unchanged drug and 2.5% from (2-amino-1H-benzimidazol-5-yl) 4-fluorophenyl-methanone. (Meuldermans et al., 1977)

A study was conducted to compare the absorption of flubendazole in Wistar and multimammate rats. Rats received an oral dose of 40 mg/kg ^{14}C-flubendazole. Treatment groups included 18 Wistar or 12 multimammate rats. Plasma levels of flubendazole measured by radioimmunoassay, reached 81 ng/ml by 4 hours after oral administration to Wistar rats. In the multimammate rats, plasma concentrations were approximately 4 times lower than in Wistar rats. Substantial differences in drug absorption were observed in these two rat strains. (Michiels et al., 1980)

Dog

A 10 mg/kg oral dose of ^{14}C-flubendazole (labeled in 2-position) was given to three female Beagle dogs (weight 12.0, 13.2, and 14.2 kg). The ^{14}C-flubendazole (specific activity of 0.76 μCi/mg) was radiochemically pure when tested by TLC and inverse isotope dilution techniques. Plasma levels of total radioactivity reached a maximum of 0.23 μg/ml flubendazole equivalents at 24 hours post-dosing. Unchanged drug in plasma, measured by HPLC with detection at 313 nm, was below the detection limit of 0.01 μg/ml throughout the 96 hour post-treatment sampling period. About 88% of the total radioactive dose was excreted within four days, 81.5% with the feces and 6.3% in the urine. More than 90% of the radioactivity in the feces was from parent drug. Radioactivity in the urine was almost entirely from metabolites. Metabolites were characterized by HPLC with UV detection at 247 nm, MS, and NMR. The main metabolic pathways were the same for the dog as for the rat. These were reduction of the ketone and hydrolysis of the carbamate. The resulting basic metabolites were mainly present in urine as glucuronide or sulphate conjugates. In the dog, a novel (although minor) metabolite was detected, identified tentatively as 2-amino-α-(4-fluorophenyl)-1-methyl-1H-benzimidazole-5-methanol (compound (5) in Figure 1). (Meuldermans et al., 1978)

Swine

Metabolism in swine was studied using eighteen feeder pigs (weight 16.7 to 24.5 kg) treated orally with ^{14}C-flubendazole at 1.5 mg/kg daily for five consecutive days (total dose 7.5 mg/kg). This dose level was given to simulate treatment with 30 ppm flubendazole in the feed. The test substance, labeled in the 2-position of the benzimidazole ring, had a specific activity of 9.25 μCi/mg. The radio and chemical purity of the test compound was not-specified. Thirty days after the end of the medication period, 79% of the administered dose had been excreted, 23% with the urine and 56% with the feces. Metabolite analysis required first extracting tissue samples with methanol and water. Samples were cleaned up using Sep-Pak C_{18} cartridges and then analyzed by reverse phase HPLC with a radioactivity detector. The major metabolites in swine feces and urine were the same as for rats and dogs. The main urinary metabolite resulted from both carbamate hydrolysis and ketone reduction (compound (4) in Figure 1). In feces, the main metabolite was from carbamate hydrolysis (compound (3) in Figure 1). In tissues, the major metabolites were the same as those found in urine and feces. The major metabolite in swine liver was (2-amino-1H-benzimidazol-5-yl) 4-fluorophenyl-methanone (compound (3) in Figure 1). This metabolite might be suitable for regulatory monitoring. Actual numerical values for metabolite concentrations were not included in this report. When extrapolated from a graph at zero withdrawal, approximately 1.5 ppm or one-third of

total residue in liver was the metabolite (3) in Figure 1. Unchanged flubendazole levels were approximately 0.06 ppm or less than 2% of total residue. In kidney, similar ratios were found between total residue, parent flubendazole, and this metabolite (3). (Meuldermans et al., 1982)

TISSUE RESIDUE DEPLETION STUDIES

Radiolabeled Residue Depletion Studies

Rat

The following residue data were from one of the metabolism studies discussed above. Three rats were slaughtered at each time listed in Table 1, which includes a summary of total residues (TR) and unchanged flubendazole (UD) in plasma and tissues. Total residues were highest in liver and kidney during the 24 hour testing period. Unchanged drug is a minor proportion of total residue in all tissues except fat. In fat, UD represented 6% of TR at 1 hour and more than 100% at 6 hours withdrawal. (Michiels et al., 1977a)

Table 1. Total residue (TR) and Unchanged Flubendazole (UD) in Wistar rats after oral dosing at 10 mg/kg.

Time	Plasma		Liver		Kidney		Muscle		Fat	
(h)	(μg/ml)					(μg/g)				
	TR	UD	TR	UD	TR	UD	TR	UD	TR	UD
0.5	0.309	0.130	1.61	0.016	1.38	0.039	0.197	NG*	0.239	NG
1	0.304	0.110	1.90	0.015	1.65	0.028	0.253	0.080	0.793	0.049
2	0.223	0.076	1.67	0.034	1.75	0.05	0.202	0.066	0.465	0.283
4	0.363	0.085	1.78	0.018	1.77	0.062	0.198	0.048	0.277	0.186
6	0.449	0.083	2.68	0.014	2.99	0.032	0.312	0.050	0.227	0.250
8	0.504	0.071	2.84	≤0.01	3.09	0.041	0.296	0.034	0.223	0.120
16	0.278	0.011	1.68	<0.01	0.881	<0.01	0.129	NG	0.164	0.068
24	0.296	≤0.01	1.29	<0.01	1.29	0.022	0.111	NG	0.140	0.039

*NG = No value given.

Swine

A radiolabeled residue depletion study was conducted using the same eighteen pigs used for the metabolism study described above. Dosing information is included in the

section above on metabolism. Data for the total residue portion of the metabolism study in swine tissue (see above) are summarized in Table 2. At each withdrawal time, values are means from three pigs. Total residues were highest in liver throughout the 30 day withdrawal period. (Meuldermans et al., 1982); (Lee, 1981)

Table 2. Total Residues of ^{14}C-Flubendazole in Swine Tissue (ppb ± SD).

Withdrawal Time	Liver	Kidney	Muscle	Fat
6 hours	3865 ± 1046	2678 ± 488	262 ± 69	212 ± 94
5 days	1863 ± 1453	435 ± 448	35.5 ± 34.9	50.1 ± 52.3
10 days	529 ± 212	78.2 ± 23.0	10.5 ± 4.8	16.3 ± 9.0
16 days	433 ± 66	76.6 ± 44.3	8.66 ± 4.29	15.6 ± 10.0
23 days	194 ± 85	49.9 ± 23.8	8.67 ± 2.74	13.5 ± 7.2
30 days	106 ± 44	22.5 ± 6.2	2.51 ± 0.32	3.38 ± 0.92

Poultry

Twenty-eight laying hens (average weight 3.6 kg, 34 weeks old) received gelatin capsules containing ^{14}C-flubendazole at a dose equivalent to 30 ppm in the food for seven consecutive days. Flubendazole was labeled in the 2-position of the benzimidazole ring. Drug with a radiochemical purity of 98.5% was mixed with unlabeled flubendazole to give a final specific activity of about 8 μCi/mg. At all withdrawal times tested from 1 to 14 days post-treatment, radioactive equivalents of flubendazole in blood and plasma were less than 0.01 μg/ml, suggesting that absorption was poor. Within 24 hours of the final dose, 86 to 87% of the administered radioactivity had been excreted, primarily as unchanged flubendazole. After total radioactivity levels reached steady state in 5 to 6 days, eggs contained an average of 0.11 to 0.12 μg equivalents flubendazole/g. Radioactivity in the yolks was much higher than in the egg white. The highest observed levels of radioactivity in tissue were 0.21 μg equivalents/g in liver and 0.08 μg/g in kidney at 24 hours past the last dose. Table 3 includes a summary of total radioactive residues of flubendazole in eggs and Table 4 summarizes residues in plasma and tissue. Days 0 through 6 are on treatment and 7 through twenty represent the withdrawal period. (Michiels et al., 1983)

Table 3. Total Residue of Flubendazole μg/g (SD) in Eggs.

Time (days)	Egg White	Egg Yolk	Total Egg
0	≤0.001	≤0.001	≤0.001
1	0.016 (0.009)	0.030 (0.012)	0.020 (0.009)
2	0.014 (0.008)	0.048 (0.033)	0.026 (0.016)
3	0.017 (0.009)	0.098 (0.058)	0.045 (0.024)
4	0.017 (0.006)	0.184 (0.062)	0.073 (0.024)
5	0.020 (0.008)	0.279 (0.082)	0.109 (0.033)
6	0.018 (0.010)	0.294 (0.120)	0.116 (0.048)
7	0.015 (0.006)	0.306 (0.078)	0.117 (0.031)
8	0.009 (0.008)	0.309 (0.103)	0.115 (0.043)
9	0.004 (0.003)	0.339 (0.098)	0.121 (0.038)
10	0.002 (0.001)	0.268 (0.088)	0.095 (0.032)
11	≤0.001	0.220 (0.091)	0.077 (0.036)
12	≤0.001	0.161 (0.076)	0.059 (0.034)
13	≤0.001	0.117 (0.053)	0.041 (0.020)
14	≤0.001	0.074 (0.050)	0.031 (0.018)
15	≤0.001	0.026 (0.026)	0.010 (0.009)
16	≤0.001	0.010 (0.010)	0.003 (0.004)
17	≤0.001	0.004 (0.004)	≤0.001
18	≤0.001	≤0.001	≤0.001
19	≤0.001	≤0.001	≤0.001
20	≤0.001	≤0.001	≤0.001

Table 4. Total Residues of Flubendazole μg/ml or g (SD) in Tissues and Plasma of Laying Hens.

Study day (withdrawal day)	Plasma	Liver	Kidney	Muscle	Fat
7 (1)	0.007 (0.002)	0.210 (0.047)	0.080 (0.044)	≤0.01	≤0.01
8 (2)	0.005 (0.003)	0.146 (0.032)	0.054 (0.028)	≤0.01	≤0.01
10 (4)	0.002 (0.001)	0.069 (0.026)	0.010 (0.001)	≤0.01	≤0.01
13 (7)	0.001 (0.000)	0.073 (0.033)	≤0.01	≤0.01	≤0.01
17 (11)	≤0.001	0.030 (0.013)	≤0.01	≤0.01	≤0.01
20 (14)	≤0.001	0.016 (0.013)	≤0.01	≤0.01	≤0.01

OTHER RESIDUE DEPLETION STUDIES

Residue Depletion Studies with Unlabeled Drug

Swine

Three male pigs (20 to 25 kg) received flubendazole at 30 ppm in the feed for five consecutive days. Flubendazole levels measured by HPLC (UV detection at 254 nm) were less than 0.01 μg/g (method sensitivity) in plasma, liver, kidney, muscle, and fat at all slaughter times of 16, 30, and 54 hours withdrawal. In an additional study, seven sows (weight 121 to 163 kg) were treated with feed containing 30 ppm flubendazole for ten consecutive days. At 30 ppm in feed, the sows received about 0.5 mg/kg body weight per day. The sows were slaughtered at seven days after the last treatment with flubendazole. Mean levels of flubendazole were 0.059, 0.067, 0.013, and 0.033 μg/g for liver, kidney, muscle, and fat, respectively. (Michiels et al., 1976)

When a single dose of 5 mg flubendazole (by capsule) per kg was given to three male pigs (20 to 25 kg), measurable residues were detected in fat. Analysis by HPLC with UV detection at 313 nm showed 0.06, 0.06, and 0.07 μg/g flubendazole in fat at 24, 48, and 72 hours withdrawal, respectively. Residues in muscle and liver were 0.01 μg/g (method sensitivity) or less at all slaughter times. In kidney, 0.02 μg/g flubendazole was determined at 48 and 72 hours withdrawal. These data are summarized in Table 5 below (one animal per slaughter time). (Michiels et al., 1977b)

Table 5. Flubendazole μg/ml or g (SD not given) in Swine Tissue after a Single Oral Dose

Withdrawal Time (h)	Plasma	Liver	Kidney	Muscle	Fat
24	0.02	<0.01	<0.01	<0.01	0.06
48	0.03	0.01	0.02	<0.01	0.06
72	<0.01	0.01	0.02	0.01	0.07

Another residue study was conducted using single 5 mg/kg dosing in three groups of five male pigs (weight 20 to 25 kg). Tissues and plasma were analyzed using a radioimmunoassay (RIA) with quantitation limits of 1 ppb in plasma and 5 ppb in tissue. Animals were slaughtered in groups of five at 24, 72, and 168 hours after dosing. Slightly higher levels of flubendazole in tissue were found in this study with a single 5 mg/kg dose than when pigs received 30 ppm in the feed for 5 days. The difference in results could be attributed to either the dosing method or differences in the analytical method (RIA vs HPLC). Results are summarized in Table 6. (Michiels et al., 1979)

Table 6. Flubendazole μg/ml or g (SD) in Swine Tissue after a Single Oral Dose

Withdrawal Time (h)	Plasma	Liver	Kidney	Muscle	Fat
24	<0.001	0.12 (0.16)	0.12 (0.16)	0.07 (0.05)	0.10 (0.08)
72	<0.001	0.03 (0.01)	0.02 (0.01)	0.02 (0.01)	0.07 (0.03)
168	<0.001	≤0.005	≤0.005	0.01 (0.0)	0.02 (0.01)

Poultry

When chickens (number not stated) were treated with 60 ppm flubendazole for 7 days, residues were detectable in egg yolk for 11 days after treatment ended. Residues were higher in yolk than white. Eggs and tissues were analyzed using an HPLC method (detection method not-specified) that was sensitive to 0.010 μg/g. Of the tissues, liver had the greatest amount of residue at zero withdrawal, although flubendazole could not be detected in any tissue by 6 (n=1) and 7 (n=6) days withdrawal. Residue data are summarized in Table 7. (Tornoe and Christensen, undated)

Table 7. Residue μg/g (SD) in Chicken Tissue and Eggs after Treatment with feed containing 60 ppm flubendazole

Withdrawal Time, days	Egg Yolk	Egg White	Muscle	Kidney	Liver
0 (n=6)	0.592 (0.148)	0.036 (0.008)	0.079 (0.031)	0.173 (0.079)	0.198 (0.082)
4 (n=1)	NA	NA	0.071	0.236	0.200
6 (n=1)	NA	NA	ND	ND	ND
7 (n=6)	0.318 (0.128)	ND	ND	ND	ND
11 (n=6)	0.019 (0.010)	ND	NA	NA	NA
28 (n=6)	NA	NA	ND	ND	ND

Pheasants (20 males and 20 females) were treated with feed containing 60 ppm flubendazole for 7 consecutive days. Tissues and plasma were analyzed for flubendazole by HPLC with UV detection at 312 nm. Only skin with adhering fat contained measurable residues by 1 day of withdrawal. Results are summarized in Table 8. (Van Leemput and Heykants, 1991)

Table 8. Residues of Flubendazole in Pheasants. Values (ng/g) are Median of Ten Birds per Slaughter Time.

Withdrawal Time	Plasma	Liver	Kidney	Muscle	Skin/Fat
6 hours	16.5	35	57.5	18.5	76
1 day	≤10	≤10	≤10	≤10	29.5
4 days	≤10	≤10	≤10	≤10	22.5
7 days	≤10	≤10	≤10	≤10	12

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

Plasma and tissue levels of flubendazole in swine were measured using an HPLC method with UV detection at 313 nm. An internal standard, nocodazole, was added to plasma or tissue, followed by extracting twice with chloroform. The combined organic layers were dried, re-extracted several more times with organic solvents, and several pH adjustments were made. The final extracts were measured by HPLC. This method is sensitive to 0.01 ppm. (Michiels et al., 1977a)

A similar HPLC procedure with UV detection at 312 nm was used to measure flubendazole in plasma and tissue of pheasants. This procedure requires adding ammonium acetate and ammonia to samples, followed by extracting with a mixture of 95% heptane and 5% isoamyl alcohol. Extracts are dried and re-solubilized before analysis. The claimed detection limit is 0.01 μg/g. (Van Leemput and Heykants, 1991)

Another HPLC method was developed for flubendazole using UV detection at 254 nm. This procedure shows excellent separation between flubendazole and the major metabolite resulting from carbamate hydrolysis ((3) in Figure 1). The procedure was described for analysis of pure substances and did not include extraction procedures for tissues. (Fujisawa, 1981)

An HPLC method that has detection limits of 20 to 50 ppb has been developed for simultaneously determining eight benzimidazoles in meat. This method might be suitable for measuring flubendazole and the major metabolite found in swine tissue, (2-amino-1H-benzimidazol-5-yl) 4-fluorophenyl-methanone. Samples of ground tissue are homogenized with acetonitrile and then centrifuged. The supernatant was subjected to a series of organic extractions, followed by clean-up with Sep-Pak C_{18} and fluorosil cartridges. Solutions containing purified benzimidazoles were dried, re-dissolved, and assayed by HPLC using a reverse phase C_{18} column and UV detection at 298 nm. Individual benzimidazoles were confirmed using GC/MS. Before GC analysis, purified samples prepared for HPLC were used to form methyl and pentafluorobenzyl derivatives. Using spiked samples (0.1 μg/g), typical recoveries were above 70% for flubendazole in liver, kidney, or muscle. (Marti et al., 1990)

A radioimmunoassay (RIA), which was originally developed to measure mebendazole, was used to determine flubendazole in plasma and tissues. Mebendazole differs from flubendazole only by a fluorine substitution in the benzoyl portion of the molecule. Tissues were homogenized in a solution containing 10% formic acid in methanol. After centrifuging, a portion of the supernatant was added to control plasma, the antiserum, and ^{3}H-mebendazole. Following a 2 hour incubation at room temperature, a dextran-charcoal suspension was added to separate the bound and free drug. Samples were centrifuged again and radioactivity in the supernatant was determined by liquid scintillation counting. Radioactivity in the supernatant is from antibody-bound ^{3}H-mebendazole. Tissue concentrations were calculated using a standard curve prepared by adding flubendazole to control liver tissue. (Michiels et al., 1979)

The mebendazole antibodies used in the RIA procedure show a high degree of cross-reactivity with flubendazole, making it a suitable method for both drugs. Metabolites (2), (3), and (4) of Figure 1 did not bind well with the mebendazole antibodies. Thus the RIA assay would be reasonably specific for parent drug, but unlikely to measure other flubendazole related metabolites. (Michiels et al., 1978).

APPRAISAL

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

An ADI of 0-12 μg/kg of body weight was established. This would result in a maximum ADI of 720 μg for a 60 kg human.

Assuming a total daily food intake from zero-withdrawal swine tissue (Table 2) and eggs (based on 30 mg/kg body weight study, Table 3), the daily intake of flubendazole-related residues would be 620 μg:

> {(3865 μg/kg x 0.1 kg of liver) + (2678 μg/kg x 0.05 kg of kidney) + (262 μg/kg x 0.3 kg of muscle) + (212 μg/kg x 0.05 kg of fat) + (120 μg/kg x 0.1 kg of egg)} = 620 μg

Eggs

The daily intake of flubendazole-related residues would likely remain below the ADI even when considering the large increase in residues in eggs resulting from the use of flubendazole at 60 mg/kg body weight. However, the argument that increased doses of flubendazole would not increase residue levels because of the low systemic availability appears not to be true for eggs. The levels of parent flubendazole in egg yolk from the 60 mg/kg body weight study are double the residue levels of all flubendazole-related residues from the 30 mg/kg body weight study.

A MRL for the whole egg of 400 μg/kg flubendazole is recommended.

Poultry

As no withdrawal period is required for poultry, parent flubendazole is an adequate marker residue.

MRLs of 500 and 200 μg/kg are recommended for poultry liver and muscle, respectively.

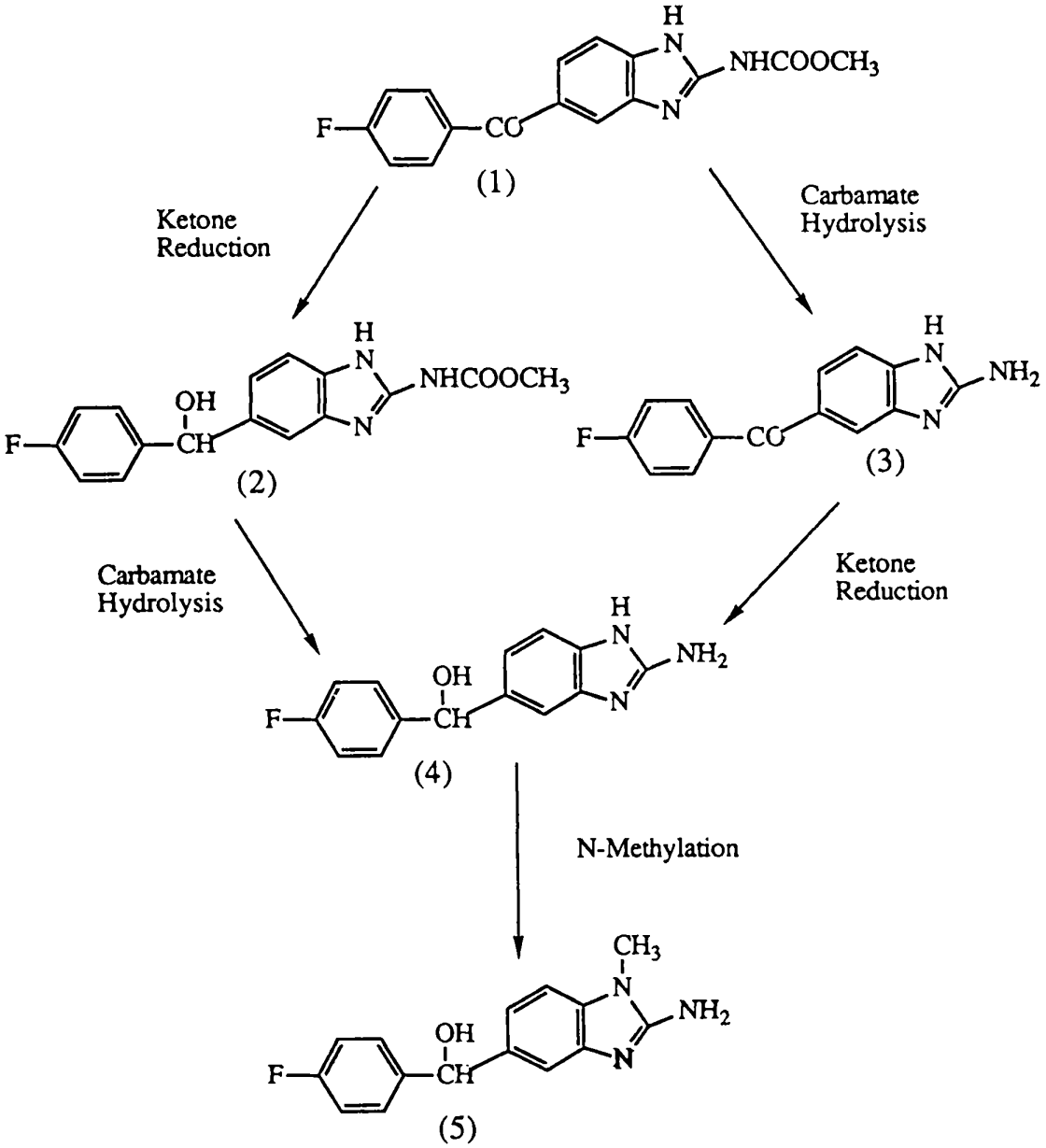
Swine

Although edible tissues from swine require no withdrawal period from a human food safety perspective, a withdrawal period will be used for swine based on good animal husbandry practices.

Parent flubendazole is a marginal marker residue for swine liver. However, methods are available for flubendazole and the residue data indicate that misuse will be detected by monitoring for parent flubendazole in swine tissue.

A MRL of 10 μg/kg is recommended for swine liver and muscle.

FIGURE 1
METABOLITES OF FLUBENDAZOLE



(1) flubendazole
(2) methyl-{5-[*α*-hydroxy-*α*-(4-fluorophenyl) methyl]-1H-benzimidazol-2-yl} carbamate (R 38 758)
(3) (2-amino-1H-benzimidazol-5-yl)-4-fluorophenyl-methanone
(4) 2-amino-*α*-(4-fluorophenyl)-1H-benzimidazole-5-methanol
(5) 2-amino-*α*-(4-fluorophenyl)-1-methyl-1H-benzimidazole-5-methanol

REFERENCES

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