FLUAZURON

First draft prepared by
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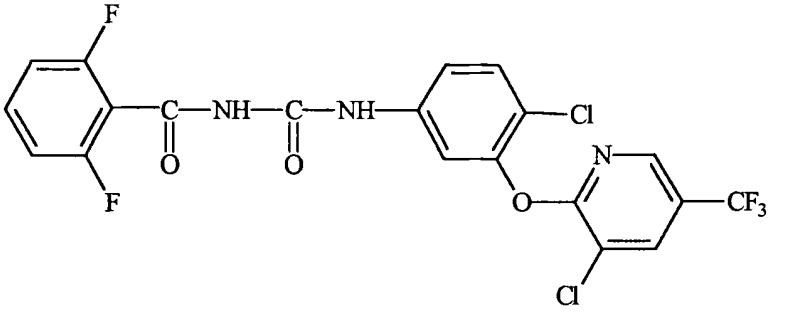
IDENTITY

Chemical name: IUPAC: 3-[3-(3-chloro-5-trifluoromethyl-2-pyridinyloxy)-4-chlorophenyl]-1-(2,6-difluorobenzoyl)-urea

CA: N-(3-(3-chloro-5-trifluoromethyl-2-pyridinyloxy)-4-chlorophenyl)-1-2,6-difluorobenzoyl)-urea

Synonyms: Fluazuron

Structural formula:



Molecular formula: $C_{20}H_{10}Cl_2F_5N_3O_3$

Molecular weight: 506.21

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient:

Appearance: White to pink fine crystalline powder, physical state at 20°C - crystalline, colourless and odourless

Melting point: 219°C

Partition coefficient in n-octanol/water: log P = 5.1

Solubility:

Water at 20° C	< 0.02 mg/L
Organic solvents at 20° C (w/v)	
Methanol	0.24%
Isopropanol	0.09%
n-Octanol	0.07%
Acetone	5.5%
Hexane	3 mg/L
Methylene Chloride	2.0%
Cyclohexanone	10.5%
N-Methyl-2-Pyrrolidone	35%

Stability to acids, bases:

	Half-lives
pH 3 at 25°C:	14 days
pH 5 at 25°C:	7 days
pH 7 at 25°C:	20 hours
pH 9 at 25°C:	0.5 hours

RESIDUES IN FOOD AND THEIR EVALUATION

CONDITIONS OF USE

General

Antiparasite, tick development inhibitor, insecticide, insect/acarine development inhibitor. Use in cattle is for the control of *Boophilus microplus*. The principle mode of action of fluazuron on the cattle-tick is by inhibition of chitin incorporation into tick cuticle. The inhibition is presumably against enzymes involved in the final stages of chitin synthesis (Kemp et al.,1990).

Dosage

The product is applied in two bands on each side of the spine between the shoulders and the rump by means of an applicator at the dose levels of 1.5 and 2.5 mg/kg b.w. In most situations the control can be achieved with a single treatment per season. When necessary, depending on the climatic region, an additional treatment is recommended after an interval of 3 to 6 months. The difference in dosing is due to the different sensitivity of the pest strains in different countries.

PHARMACOKINETICS AND METABOLISM

Pharmacokinetics

Rat

In rats, a daily dose of 0.5 mg/kg b.w. of [U-^{14}C] Cl-Phenyl labelled fluazuron was administered by stomach tube for 7 consecutive days. At 24 hours after final dose, approximately 60% of the administered radioactivity were absorbed (Schulze-Aurich, 1992). The metabolic pathway of fluazuron is shown in Figure 1.

Radiolabelled fluazuron and metabolites were released by first order kinetics with a half life of 13 days in rats, orally administered 0.5 mg/kg b.w. for 7 consecutive days. A total of 60% of the administered dose was eliminated in the urine and faeces during one week of repeated exposure and a subsequent one-week withdrawal period.

Based on the faeces metabolite pattern, it is estimated that about two-thirds of the dose was metabolized and one-third was eliminated unchanged. The metabolism is mainly by cleavage of the benzoyl ureido bridge. Hydroxylation of the metabolite at the phenyl ring leads to metabolite which was eliminated mainly with the faeces. The metabolism in rats proceeds by cleavage of the urea moiety, followed by hydroxylation in position 6 of the phenyl ring leading to 3-[3-(3-chloro-5-trifluoromethyl-2-pyridinyloxy)-4-chloro-6-hydroxyphenyl]urea. The primarily formed cleavage product 2,6-difluorobenzoic acid is partly conjugated with glycine to 2,6-difluorohippuric acid. The primary route of elimination was through the faeces as shown in Table 1.

Table 1. Excretion of Radioactivity in Rats (% of Total Dose) During Days 0-7 and Days 8-14

	Days 0-7		Days 8-14	
	Male	Female	Male	Female
Urine	1.6	2.1	1.1	1.5
Faeces	37.2	38.1	21.5	20.8
Total	**38.8**	**40.2**	**22.6**	**22.3**

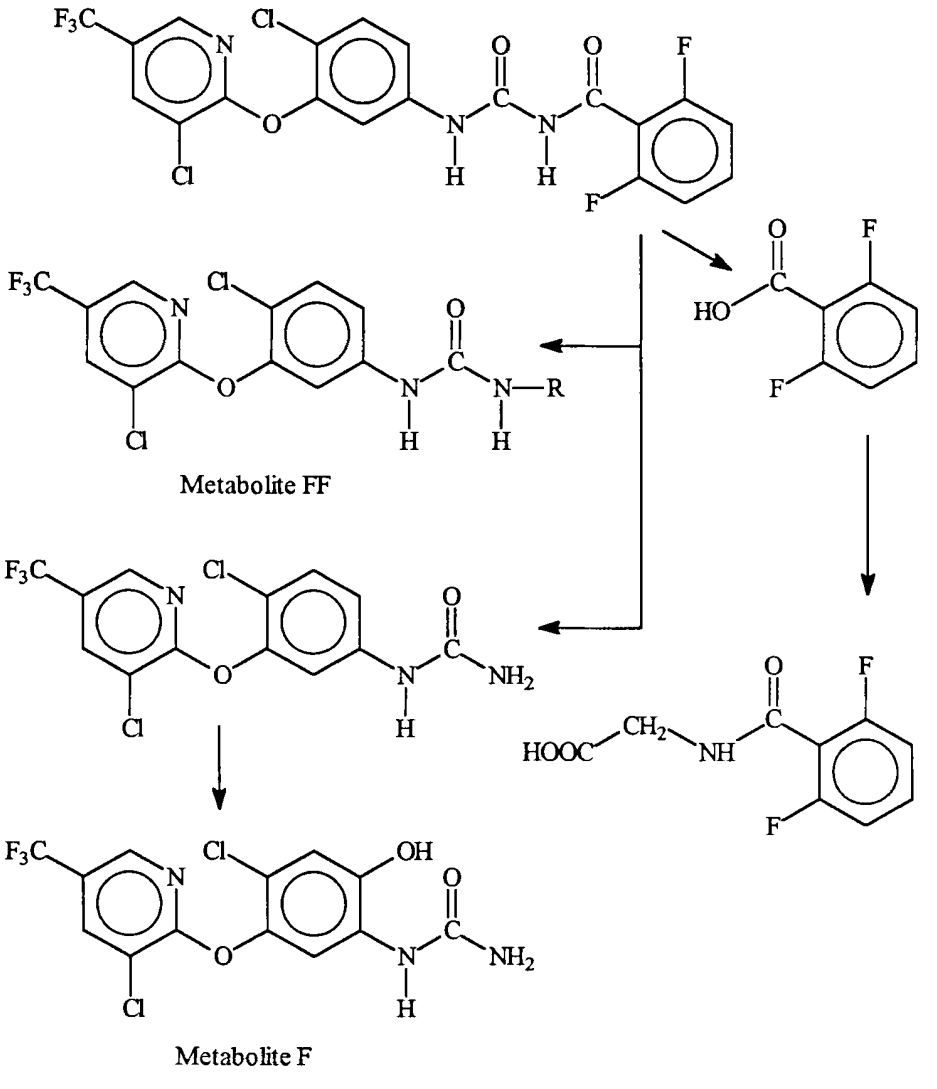


Figure 1. Proposed Metabolic Pathway of Fluazuron in Rats

Cattle

Oral application of 2.0 mg/kg b.w. of fluazuron gives rise to more rapid absorption and maintains higher level of fluazuron in the bloodstream of cattle than a dermal treatment at the same dose level (Bull and Strong, 1994). The compound distributed to the tissues such as muscle, kidney, liver, lung and brain but deposited preferentially in the fat. When the radiolabelled fluazuron was administered subcutaneously to cattles at 1.5 mg/kg b.w., the mean maximum plasma level of total radioactivity was reached in 48 hours post dose. The radioactivity was absorbed slowly from the site of injection. Half life of the radioactivity in the blood was around 78 days (Cameron et al., 1992).

Fluazuron was applied to various species of cattle by single or repeated administration of pour-on in two strips along the backline from the shoulder to the loins. There were relatively consistent range of ratio for residues in plasma and fat as shown in Table 2. When subcutaneous injection was administered to male cattle at 1.5 mg/kg b.w., elimination of unchanged fluazuron occurred via bile and faeces (23%), whereas metabolized products were excreted via urine (1%). More than 96% of the radioactive compounds present in the faeces were extractable. The major fraction (62-81%) of the radioactivity present in the extract, was identified as unchanged compound.

Table 2. **Levels of Fluazuron in Blood Plasma and Fat of Cattle Following a Single or Repeated Administration of Pour-on Formulations**

Species of Cattle and Their Body Weights (kg)	Method of Application	No. of Cattle	Application Rate per Treatment (mg a.i. per kg bw)	Residue (Mean ± SD)		Sampling Time (days)	Reference
				Plasma (µg/L)	Fat (mg/kg)		
Hereford Weaner heifers, b.w. 150-200 kg	Pour-on, two strips along the backline, one single treatment	4 (plasma) 1 (fat)	1.5 2.5	9 ± 4 10 ± 3	1.2 1.6	84 d	Thomas et al., 1992
Hereford x Braham heifers, b.w. 271-277 kg	Pour-on, two treatments 16 weeks apart	4	1.5	12 ± 5	2.5 ± 0.9	42 (after first treatment)	Swindale et al., 1993a
Braham Steers, b.w. 280 kg	Pour-on, two treatments 24 weeks apart	4	1.5	13 ± 5	1.4 ± 0.4	42 (after first treatment)	Swindale et al., 1993b
Friesian, Guernsey dairy heifers, b.w. 200 kg	Pour-on, one single treatment	2 (selected out of 49 treated)	1.25	6 ± 2	1.2	42	Swindale et al., 1993d
Hereford, Hereford x Santa Gertrudis, Hereford x Braham heifers, b.w. 217 kg	Pour-on, one single treatment	3 (selected out of 59 treated)	1.25	<2 ± 0.5	0.73 ± 0.14	42	Swindale et al., 1993c

The parent compound and/or its metabolites had a high affinity for fat. There were persistent depot of the compound at the injection site.

There is a transfer and accumulation of fluazuron in calves suckling cows which have been treated with fluazuron pour-on (Strong and Swindale, 1993).

Metabolism in Food Animals

Radiolabelled fluazuron was given as a single subcutaneous injection to cattle at 1.5 mg/kg b.w. The extent of metabolism in cattle was found to be lower than in rats. The TLC radiograms from cattle showed less radioactive spots than those from rats. In all tissues, and at all time points, unchanged fluazuron was the only metabolite, accounting for more than 90% of the total residues (Schulze-Aurich, 1992a). The nature of metabolites eliminated with urine, faeces and bile were more polar than the parent compound. Following single topical administration of radiolabelled fluazuron pour-on preparation, unchanged fluazuron was almost the only radioactive compound detected. In the faeces, the parent compound accounted for 92% of the radioactivity of the investigated samples.

TISSUE RESIDUE DEPLETION STUDIES

Radiolabelled Residue Depletion Studies

Twelve steers were treated with a single s.c. dose of ^{14}C-fluazuron at a dose level of 1.5 mg/kg b.w. Three animals were sacrificed at each of the sampling times of 2 days, and 2, 6 and 16 weeks post-dosing. Fluazuron residue levels in fat were consistently about 10 times higher than those in liver and kidney. Fat contains the highest residue levels at all times. The distribution of the total residues (mg/kg) in edible tissues for all of the treatment groups are shown in Table 3 (Cameron et al., 1992).

Table 3. Ranges of the Total Residues Expressed as Fluazuron Equivalents (mg/kg) in Steers Treated with a Single Subcutaneous Dose of 1.5 mg of ^{14}C-Fluazuron per kg of Body Weight

Withdrawal time	Muscle (mg/kg)	Liver (mg/kg)	Kidney (mg/kg)	Fat (mg/kg)
2 days	0.094 - 0.210	0.640 - 0.903	0.269 - 0.585	0.37 - 6.89
2 weeks	0.027 - 0.121	0.238 - 0.353	0.098 - 0.214	1.43 - 4.63
6 weeks	0.032 - 0.082	0.230 - 0.326	0.114 - 0.206	1.76 - 3.20
16 weeks	0.010 - 0.035	0.090 - 0.140	0.071 - 0.171	0.51 - 1.17

Other Residue Depletion Studies (with Unlabelled Drug)

Table 4. Residue Depletion Studies in Cattle Using Unlabelled Fluazuron as Pour-on Formulation

Tissue	Dose (mg/kg bw)	Sampling time*	Reference
M, L, K, SF, KF	2.0, single treatment	4, 6, 8, and 16 weeks	Strong and Bull, 1992a
M, L, K, SF, KF	2.0, two treatments 9 weeks apart	6, 8, and 16 weeks	Strong and Bull, 1992b
SF	2.0 or 4.0, three treatments at intervals of 12 weeks	6 weeks after each treatment	Strong and Bull, 1993
F	1.5, two treatments 16 weeks apart	6 weeks after 1st treatment**	Swindale et al., 1993a
F	1.5, two treatments 24 weeks apart	6 weeks	Swindale et al., 1993b
SF	1.5 or 2.5, single treatment	6 and 12 weeks	Thomas et al., 1992
F	1.25, single treatment	6 weeks	Swindale et al., 1993c
F	1.25, single treatment	6 weeks	Swindale et al., 1993d
F	2.0 or 4.0, three treatments at intervals of 12 weeks, first treatment to cows carring calves to be born 6 weeks later. During the 2nd and 3rd years of treatment the calves received the same treatment as their respective mothers had received the previous year.	6 weeks post each treatment	Bull, 1995a
M, L, K, SF, KF, OF	2.5, single treatment	32 weeks (calves), after treatment of mothers	Strong and Swindale, 1993
M, L, K, SF, KF	3.0, single treatment	4, 6, 8 and 16 weeks	Strong and Bull, 1992c
M, L, K, SF, KF	3.0, two treatments 9 weeks apart	6, 8 and 16 weeks	Strong and Bull, 1992d
SF	2.0, single treatment pour-on and orally	25 and 52 weeks	Bull and Strong, 1994

* After last treatment, if not otherwise indicated; ** After 2nd treatment blood drawn only; M=Muscle, L=Liver; K=Kidney; F=Fat; SF=Subcutaneous Fat; KF=Kidney Fat; OF=Omental Fat

Results of four pour-on formulation studies in which fluazuron was applied in two strips along the backline from the shoulder to the rump using a calibrated plastic syringe, are summarized in Figures 2 and 3, and Table 5 (Strong and Bull, 1992a; 1992b; 1992c; 1992d). Residues in these studies were determined using an HPLC-UV method with a LOD of 0.02 mg/kg for muscle, liver and kidney, and 0.01 mg/kg for fat. These studies are consistent with previous studies showing that fluazuron does not accumulate in tissues. However, the residue levels rise with increasing doses.

Table 5. Residues of Fluazuron (mg/kg) in Muscle, Liver, Kidney, and Fat of Cattle Following Pour-on Dosing at 2 or 3 mg/kg of Body Weight

Dose (mg/kg bw)	No of Animals	Sampling time	Muscle (mg/kg)	Liver (mg/kg)	Kidney (mg/kg)	Fat (kidney) (mg/kg)	Fat (subcut) (mg/kg)
2, single treatment	3	4 weeks	0.07±0.01	0.10±0.03	0.07±0.02	2.1±0.1	2.4±0.2
		6 weeks	0.04±0.01	0.08±0.03	<0.02	0.9±0.3	0.9±0.2
		8 weeks	0.03	0.04±0.01	<0.03	0.8±0.3	0.9±0.3
		16 weeks	<0.03	0.02±0.01	<0.02	0.4±0.08	0.5±0.1
2, two treatments 9 weeks apart	3	6 weeks*	0.04±0.02	0.09±0.04	<0.04	1.10±0.60	1.10±0.61
		8 weeks*	<0.03	0.07±0.03	<0.03	0.83±0.49	0.89±0.54
		16 weeks*	0.05±0.02	0.10±0.06	<0.02	0.90±0.23	0.97±0.27
3, single treatment	3	4 weeks	0.08±0.02	0.12±0.02	0.05±0.01	2.4±0.1	2.4±0.1
		6 weeks	0.06±0.03	0.14±0.04	0.07±0.03	2.2±0.95	2.3±0.95
		8 weeks	0.04±0.02	0.06±0.02	0.04±0.02	1.2±0.15	1.3±0.2
		16 weeks	<0.02	0.03	<0.02	0.6±0.07	0.6±0.07
3, two treatments 9 weeks apart	3	6 weeks*	<0.04	0.09±0.10	0.04±0.03	1.18±1.15	1.06±1.0
		8 weeks*	0.03	0.07±0.02	0.03	0.94±0.10	0.93±0.14
		16 weeks*	0.06±0.03	0.09±0.05	<0.04	1.31±0.72	1.29±0.87

* After 2nd treatment

Figure 2. **Tissue Residues in Cattle Receiving Pour-On Formulation Given at a Rate of 2 or 3 mg a.i./kg bw by a Single or Double Application 9 Weeks Apart**

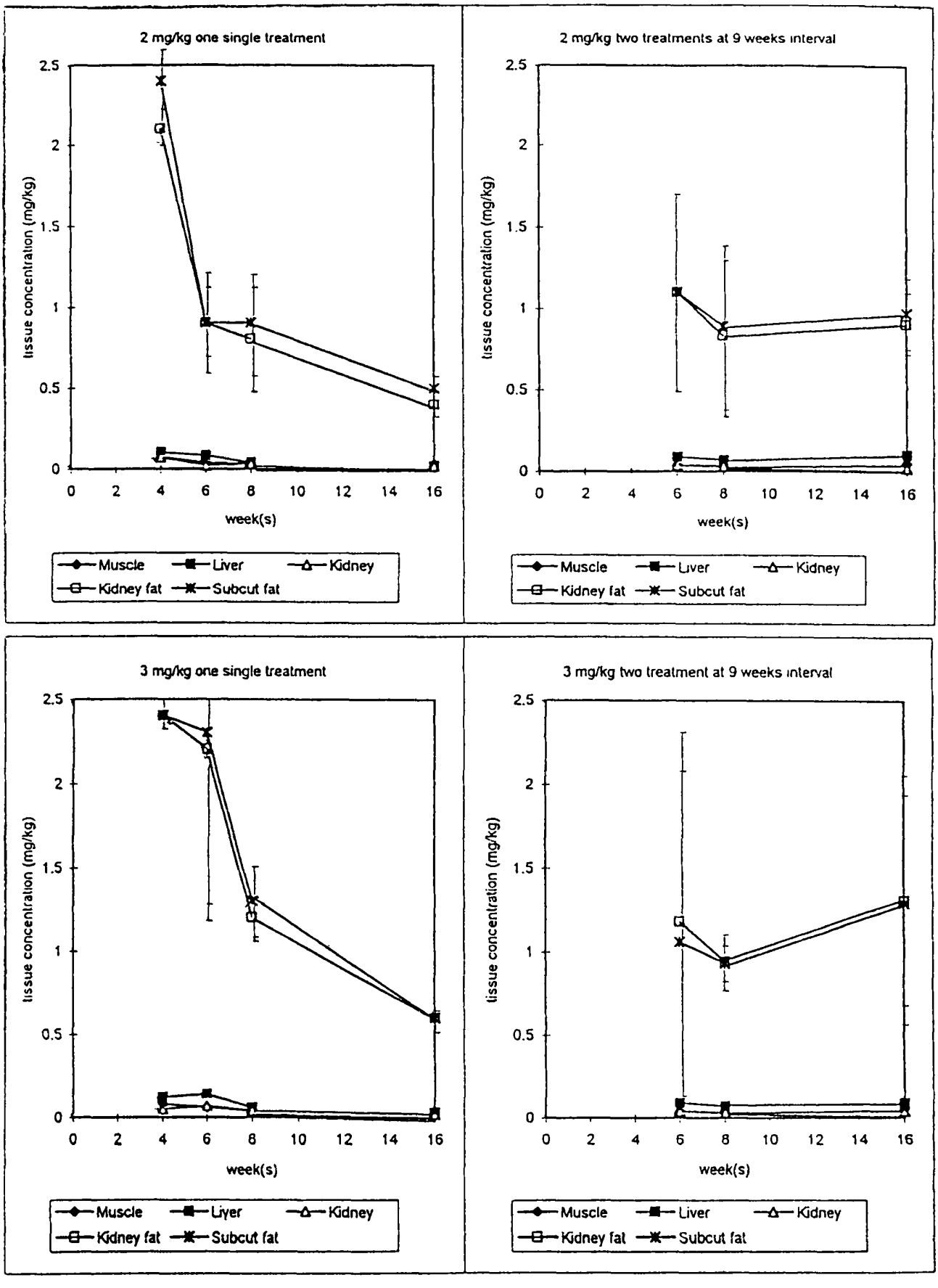
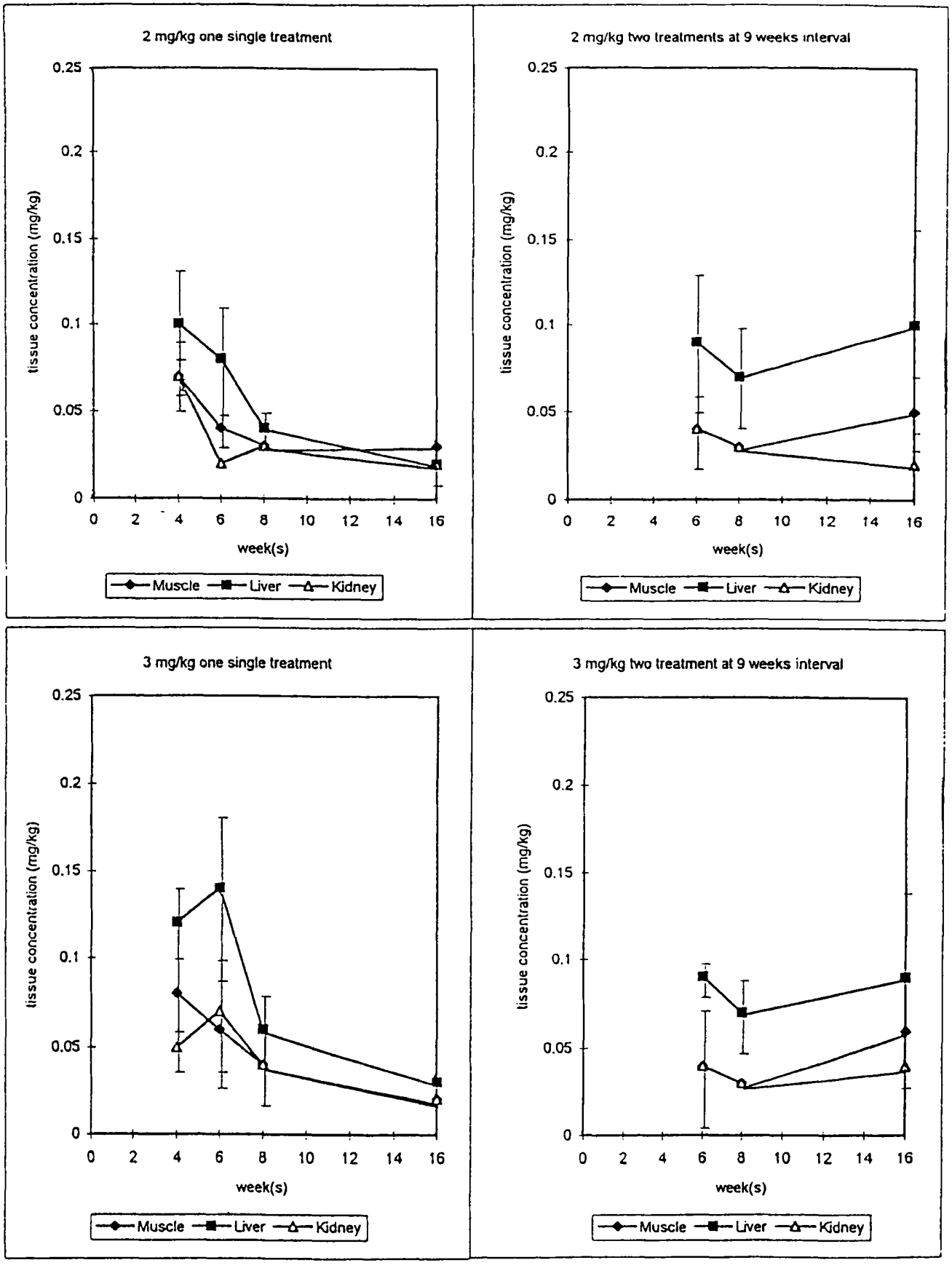


Figure 3. **Tissue Residues in Muscle, Liver and Kidney of Cattle Receiving Pour-On Formulation Given at a Rate of 2 or 3 mg a.i./kg bw by a Single or Double Application 9 Weeks Apart**



Strong and Bull (1993) applied three treatments each at intervals of 12 weeks applying two strips along the backline from the shoulder to the rump. Six weeks after each treatment, fat samples were collected from each of the six animals. The mean fat levels 6 weeks after each treatment were 1.8, 1.8 and 1.6 mg/kg, respectively in the 2 mg/kg dose-group and 3.0, 2.4 and 2.1 mg/kg, respectively, in the 4 mg/kg dose-group. This study did not suggest accumulation following the dosing regimen.

Cows with calves *in utero* at the time of the first treatment were treated three times with a pour-on formulation at 12 weekly intervals at dose rates of either 2 or 4 mg a.i./kg (Bull, 1995a). The calves, born 6 weeks after the first treatment, had subcutaneous fat biopsy samples taken 6 weeks after their respective cows received their second and third treatments. In the second and third year of treatments, the calves received direct treatments with the pour-on formulation at the same rates and treatment intervals as their mothers had received the previous year. Again biopsy samples of fat were collected 6 weeks after each treatment. Peak concentrations of fluazuron in the fat occurred in the spring of each year of treatment. At the end of the three years of three treatments per year no accumulation of residues of fluazuron occurred in the fat of the cattle. At the treatment rates of 2 and 4 mg a.i./kg the initial maximum residues in the fat of 12 weeks old calves were 4.2 and 6.8 mg/kg, respectively, and after three years of applications, cattle (now approximately 2.5 years old), the maximum levels were 1.6 and 2.3 mg/kg, respectively.

Bound Residues/Bioavailability

The majority of the radiolabeled residues were extractable with mild solvents. In cattle, in all tissues at all time points, unchanged fluazuron accounted for more than 90%of the residues.

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

Four methods were described which allow for the determination and quantification of residues of parent fluazuron in bovine muscle, liver, kidney, and fat. One method that was presented (Bull, 1995b; Shume, 1990) involves cattle tissues being extracted with acetonitrile. From an aliquot of filtered extract the analyte is partitioned into methylene chloride in the presence of acidified sodium chloride solution. The organic phase is evaporated to dryness and the residue dissolved in a mixture of hexane/acetone. The solution is cleaned up by chromatography on deactivated basic alumina. The analyte is eluted with a mixture of hexane/acetone and the elute evaporated to dryness. The residue is dissolved in the mobile phase and quantitated by reverse phase High Performance Liquid Chromatography (HPLC) using UV-detection at 260 nm. The overall recovery of the method was 95±5%. Levels of quantification of this method were 0.01 mg/kg for fat and 0.02 mg/kg for muscle, liver and kidney.

In another method (Lanter, 1990a; 1991a), animal tissues were extracted with acetonitrile. From an aliquot of the centrifuged extract, the analyte is partitioned into a mixture of n-hexane/diethyl ether in presence of saturated sodium chloride solution and hydrochloric acid. The organic phase is evaportated to dryness and the residue dissolved in n-hexane. The solution is cleaned up by solid phase extraction on a Bond Elut^{R} cyanopropyl cartridge. The analyte is eluted with a mixture of n-hexane/diethyl ether and the eluate evaporated to dryness. The residue is quantitated by HPLC using UV-detection at 270 nm and column switching technique. The overall mean recovery was 92±7% (n=27). Levels of quantification of this method were 0.01 mg/kg for fat and 0.02 mg/kg for muscle, liver and kidney, respectively (Ciba-Geigy, 1990a).

APPRAISAL

Fluazuron had not been previously evaluated by the Committee. Fluazuron is an insect growth regulator that belongs to the chemical class of benzoylphenyl urea derivatives that inhibits chitin synthesis. It is indicated for the use on beef cattle for the control of the tick *Boophilus microplus*. Fluazuron is applied as a pour on at the recommended dose of 1.5 and 2.5 mg/kg b.w. in Australia and in Latin American countries, respectively. The difference in dosing is due to the different sensitivity of the Boophilus microplus strains in these two regions. A second treatment is frequently recommended after an interval of 3 to 6 months. However, current labeling of the commercial product permits a maximum of three treatments per year.

Table 6 shows the distribution of residues of fluazuron in the edible tissues of cattle in the studies performed by Cameron et al, 1992 and Schulze-Aurich, J., 1992a.

Table 6. **Mean Total Residues as Fluazuron Equivalents (mg/kg) as Determined by LSC and Mean Residues of Fluazuron (mg/kg) as Determined by TLC in Tissues of Cattle (3 Animals per Time Point) Following a Single Subcutaneous Injection of ^{14}C-Fluazuron at Dose Level of 1.5 mg/kg of Body weight**

Withdrawal Time	Tissue	Total Residues (TR) as Fluazuron Equivalents (mg/kg)	Residues of Fluazuron (FL) (mg/kg)	Ratio FL/TR (%)
2 days	Muscle	0.148	0.138	93
	Liver	0.800	0.701	90
	Kidney	0.479	0.438	92
	Fat	4.580	4.527	99
2 weeks	Muscle	0.072	0.066	92
	Liver	0.278	0.223	80
	Kidney	0.141	0.131	93
	Fat	2.660	2.604	98
6 weeks	Muscle	0.064	0.062	97
	Liver	0.283	0.249	94
	Kidney	0.164	0.147	90
	Fat	2.670	2.596	97
16 weeks	Muscle	0.027	0.024	90
	Liver	0.116	0.093	80
	Kidney	0.121	0.109	90
	Fat	0.970	0.945	97

The residue levels in fat were consistently about 10 times those in liver and kidney. Maximum residue levels were reached in all tissues at 2 days after drug withdrawal. Fat contained the highest amounts of residues at all sampling times. The residue levels in fat samples from the site of administration of the pour-on formulation were no higher than in fat samples taken from other sites.

Five residue depletion studies in cattle treated with a pour-on formulation of fluazuron were considered. In the first and second studies, fluazuron was administered once, at a dose of 2 and 3 mg/kg of body weight, respectively. In the remainig studies, the drug was administered as follows: 2 mg/kg of body weight repeated after 9 weeks; 3 mg/kg of body weight, repeated after 9 weeks; 2 or 4 mg/kg of body weight, repeated after 12 and 24 weeks. All these studies confirmed that the highest levels of residues occurred in fat. Residue levels were similar from 6 to 16 weeks after treatment. Table 7 shows the distribution of residues in tissues of cattle given two doses of 3 mg/kg of body weight at an interval of 9 weeks. This dosing regimen exceeds that recommended for therapeutic use. The results of this study are consistent with those of previous residue depletion studies using multiple-dose regimens, in which there was no evidence of bioaccumulation of the drug, but residue levels were shown to increase in a dose-dependent manner.

Table 7. **Residue Levels of Fluazuron (mg/kg) in Tissues of Cattle Given Two Pour-on Applications of Fluazuron at 3 mg per kg of Body Weight 9 Weeks Apart***

Withdrawal Time (weeks)	Muscle (mg/kg)	Liver (mg/kg)	Kidney (mg/kg)	Fat (mg/kg)
6	<0.02-0.08	0.02-0.20	0.02-0.07	0.37-2.50
8	0.03-0.03	0.05-0.08	0.03-0.03	0.84-1.10
16	0.04-0.10	0.05-0.14	<0.02-0.06	0.60-2.26

*Three animals per time point

Data on the depletion of fluazuron residues in fat from studies in cattle indicate that the residue concentrations increase significantly as the body-fat content decreases. Therefore, these studies suggest that the MRLs for fat should be higher than those derived solely on the basis of traditional residue depletion studies.

Fluazuron residues can be measured by HPLC with UV-detection. The method has been used for the analysis of residues in tissues of animals following treatment with fluazuron as well as in tissues fortified with the drug. The

method has limits of quantification of 0.02 mg/kg in muscle, liver and kidney and 0.01 mg/kg in fat. The recoveries in muscle, liver, kidney and fat were 107±7, 94±9, 102±8, and 94±5%, respectively.

Maximum Residue Limits

In recommending MRLs, the Committee took into account the following factors:

- An ADI of 0-40 μg per kg of body weight was established. This would result in a maximum daily intake of 2400 μg for a 60-kg person.

- The marker residue is the parent drug.

- The parent drug accounts for at least 80% of the total residues in all tissues.

- Fat and liver or kidney are recommended as the appropriate target tissues.

- Suitable analytical methods are available for monitoring the proposed MRLs.

On the basis of the maximum observed residues in cattle treated with fluazuron in accordance with good practice in the use of veterinary drugs, the Committee recommended MRLs in cattle of 200 μg/kg for muscle, 500 μg/kg for liver and kidney and 7000 μg/kg for fat, expressed as parent drug. From these values the theoretical maximum daily intake of fluazuron residues is 606 μg (Table 8).

Table 8. Theoretical Maximum Daily Intake of Fluazuron Residues

Tissue	Recommended MRL (μg/kg)*	Estimate of Total Residues (μg/kg)**	Theoretical Daily Intake (μg fluazuron equivalents)***
Muscle	200	250	75
Liver	500	625	62.5
Kidney	500	625	31.25
Fat	7000	8750	437.5
Total			**606**

*Expressed as parent drug; **The marker residue accounted for at least 80% of the total residues in muscle, liver, kidney and fat; ***Based on a daily intake of 300 g of muscle, 100 g of liver, and 50 g each of kidney and fat.

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