FLUMETHRIN (195)

IDENTITY

Flumethrin is pyrethroid acaracide composed of a mixture of two diasterioisomers (*trans-Z*-1 and *trans-Z*-2, with an approximate ratio 55:45) formed by the reaction of 4-fluoro-3-phenoxybenzaldehyde and *trans*-(*E*)-3-[2-chloro-2-(4-chlorophenyl)vinyl-2,2-dimethylcyclopropanecarboxylic acid chloride in the presence of cyanide.

ISO common name: flumethrin

Chemical name

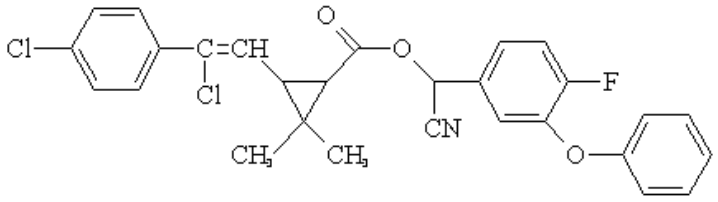
IUPAC: (*R,S*)-Æ-cyano-4-fluoro-3-phenoxybenzyl 3-(ß,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate

CA: cyano(4-fluoro-3-phenoxyphenyl)methyl 3-[2-chloro-2-(4-chlorophenyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate

CAS No.: 69770-45-2

Synonyms: Bayticol; Bay VI 6045; FCR 1622; BAY Vq 1950; FCR 2769

Structural formula:



Molecular formula: $C_{28}H_{22}Cl_2FNO_3$

Molecular weight: 510.4

Physical and chemical properties (Krohn, 1995)

Pure active ingredient (98%, except determination of density)

Vapour pressure:

Sum of *Z*-1 and *Z*-2 partial v.p.	at 20°C	$<10^{-11}$ hPa
	at 25°C	$<10^{-10}$ hPa
Sum of *Z*-1 and *Z*-2 saturation v.p.	at 20°C	$<2 \times 10^{-4}$ ì g/m^3
	at 25°C	$<2 \times 10^{-3}$ ì g/m^3

Melting point: not provided
Octanol/water
partition coefficient: P_{ow} 1,600,000; log P_{ow} = 6.2

Solubility:	*Z*-1	*Z*-2	*Z*-1 + *Z*-2
(20°C, ì g/l)			
water (pure)	0.1	0.1	0.2
water (1% NaCl)	<0.03	<0.03	
water (pH 4 or 7 buffered)	<0.03	<0.03	
(Decreased solubility stated to be due to salinity, not to pH)			
water (pH 9 buffered)	Hydrolysed		
(20°C, g/l)			
n-heptane	11	8	19
xylene			>250
1,2-dichloroethane			>250
2-propanol	36	29	65
1-octanol	69	56	130
polyethylene glycol			100-200
acetone			>250
dimethylformamide			>250
acetonitrile			>250
ethyl acetate			>250
dimethyl sulfoxide			>250

Density (95% material): 1.28 g/cm^3 at 20°C
Hydrolysis: hydrolysed at pH 9
Photolysis: No information
Boiling point: >250°C, under decomposition
Thermal stability:

Differential thermal analysis (DTA) and thermogravimetric analyses (TGA) were employed, using OECD Guidelines. DTA indicated exothermic reaction above 270°C under nitrogen and 220°C in air. With TGA, weight loss started above 200°C in air and above 230°C in nitrogen.

Technical material

Purity Assay 90-100%
Sum of all by-products max. 10%

Formulations

6% EC solution (UK label for treatment of sheep provided).
75 g flumethrin/l liquid hydrocarbon solvent (solvent density 745 g/l, so 10% w/v ai) cattle dip and spray for cattle tick (Australian label provided).
10 g flumethrin/l pour-on solution for cattle tick and Buffalo fly control (Australian label provided).
Strip for pest control in bee hives (label provided).

METABOLISM AND ENVIRONMENTAL FATE

Information on the fate of flumethrin in rats and cattle was provided. Because flumethrin is used only for ectoparasite control on animals the manufacturer did not consider information on the fate of residues in plants, soil, or water/sediment systems to be applicable.

Animal metabolism

Oral, i.v. and duodenally administered flumethrin is hydrolysed to the substituted cyclopropanecarboxylic acid component (flumethrin acid) and (possibly through intermediate cyanohydrin and aldehyde oxidations) 4-fluoro-3-phenoxybenzoic acid. Flumethrin acid is conjugated to form the glucuronide and the benzoic acid component is oxidized to 4-fluoro-3-(4-hydroxyphenoxy)benzoic acid; both the hydroxylated and unhydroxylated acids are conjugated with glycine. A proposed metabolic pathway is shown in Figure 1, which is based on the following studies.

Rats. Because the fate of flumethrin in rats is considered in detail in the toxicological evaluation (Evaluations Part II - Toxicology), it will be described here only to the extent needed to view the metabolism in cattle in the context of the general metabolism in mammals. Five reports were available on the fate of flumethrin in rats, all from oral, i.v. or duodenal administration (none from topical application).

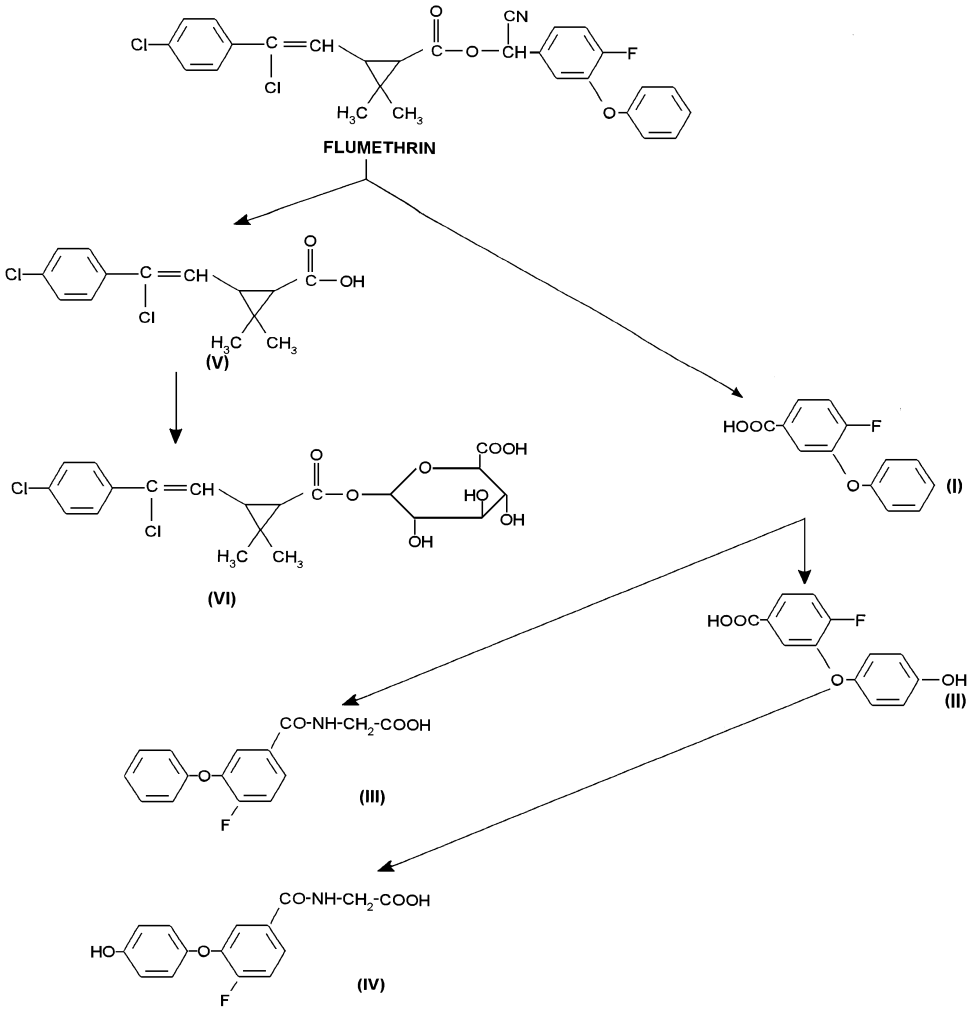
In a basic study on the elimination and metabolism of unlabelled flumethrin (Rauchschwalbe, 1980) rats were given a single oral dose. The author reported the presence of flumethrin and the metabolites I and V (Figure 1) in the faeces. The two metabolites were also eliminated in the urine, although the parent compound was not detected. Theoretical intermediates from the alcoholic portion of the molecule would also include the cyanohydrin (FCR 1271) and its oxidation product 4-fluoro-3-phenoxybenzaldehyde (FCR 1260), but their instability would make their detection unlikely and they were they reported.

The elimination of flumethrin and its metabolites in faeces peaked 3 or 4 days after administration, then dropped almost to zero. Residues of the two metabolites in urine dropped below the limit of detection within 5 days. Altogether 33% of the administered dose was eliminated in the urine and faeces.

A second study investigated the pharmacokinetics of the metabolism of fluorophenyl-labelled [^{14}C]flumethrin in rats after oral, i.v. and intraduodenal administration (Steinke *et al*., 1983). Approximately 50% of the ^{14}C was reported to be absorbed from oral administration, 45% of which was eliminated in the urine (the remainder in the faeces), compared with 75% renal elimination from i.v. administration. About 95% or more of the radioactive dose administered orally or intravenously was excreted within 48 hours. After 10 days only 1% of the administered ^{14}C was found in the animals. From duodenal administration, about 1/3 of the absorbed ^{14}C was eliminated via the bile.

In a study of the biotransformation of [U-*fluorophenyl*-^{14}C]flumethrin after oral administration (Ecker, 1983) the author reported the urinary elimination of two primary metabolites, 4-fluoro-3-(4-hydroxyphenoxy)benzoic acid (not reported by Rauchschwalbe) and 4-fluoro-3-phenoxybenzoic acid (found by Rauchschwalbe), 0-24 hours and 24-48 hours after administration. The hydroxyphenoxy metabolite accounted for 50 and 80% and the phenoxy metabolite for 35 and 10% of the radioactivity at these times. The glycine conjugates of the two primary metabolites were also reported, but accounted for at most 4 and 7.4% respectively of the urinary radioactivity.

Figure 1. Proposed metabolic pathways of flumethrin in rats and cattle.



(I) 4-fluoro-3-phenoxybenzoic acid
(II) 4-fluoro-3-(4-hydroxyphenoxy)benzoic acid
(III) 4-fluoro-3-phenoxybenzoylglycine (glycine conjugate of (I))
(IV) 4-fluoro-3-(4-hydroxyphenoxy)benzoylglycine
(V) 3-(ß,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylic acid (flumethrin acid, BNF 5533A)
(VI) flumethrin acid glucuronide

In a fourth study whole-body autoradiography was used to study the distribution of total radioactivity during 48 hours after single oral doses of [U-*chlorophenyl*-^{14}C]flumethrin (Klein, 1993a). The author reported slow or delayed absorption and only slowly decreasing residues in the organs and tissues, with the highest concentration in the liver. Towards the end of the experiment the highest residues were in the organs of excretion.

A fifth study investigated the biokinetic behaviour and metabolism of flumethrin in rats after single oral doses or after oral dosing for 7 consecutive days with flumethrin labelled with ^{14}C in the chlorophenyl ring. In a separate experiment a single dose was also administered duodenally (Klein, 1993b). Again, radioactivity was reported to be only partially absorbed from the intestine with 77-88% slowly eliminated,(68% in the faeces, 2% in the urine). The faeces were the source of residues for identification. The highest concentrations of ^{14}C were found in the plasma and the lowest in the brain. Nine to 20% of the dose was found in non-intestinal tissues. Multiple doses demonstrated the accumulation of residues. The only two compounds identified in the faeces were flumethrin and BNF 5533A (flumethrin acid, V in Figure 1). The ratio of flumethrin to BNF 5533A was 53:16 in males and 24:30 in females.

Cattle. Three studies were reported. The first two were of the distribution of radioactivity, one from a topical application and the second from i.v. administration. The third was a continuation of the i.v. study for the identification and quantification of the residues.

In the first study (Cameron and Phillips, 1986), in accordance with GLP principles, a single dose of 938.5 mg (6.56 mCi) of formulated [U-*fluorophenyl*-^{14}C]flumethrin was applied by syringe to a 60 cm x 15 cm section along the spine of a 530 kg lactating Friesian dairy cow (1.8 mg/kg bw). The GAP rates for pour-on applications are 1.8-3.6 mg/kg bw (generally $\leq$2.5 mg/kg bw) and for spray applications approximately 1.5-2 mg ai/kg bw. Milking was by machine twice daily, and blood samples were taken at frequent intervals until slaughter 48 hours after treatment. Samples were taken of liver, kidney, perirenal fat, subcutaneous fat (beneath and away from the dose area) and muscle at different sites, as well as of bile and bladder urine. All samples were stored at -20°C until analysis for total radioactivity by liquid scintillation counting.

Residues in the plasma peaked at 6.3 ng flumethrin equivalents/ml after 23 hours, slowly decreasing thereafter. No radioactivity was detected in the milk on the first day after treatment but 1, 3 and 2 ng equivalents/ml were reported at the first and second milkings on the second day and the first milking on the third day respectively. The levels of radioactivity in other samples are shown in Table 1.

Table 1. Total radioactivity in tissues and fluids of a lactating cow 48 hours after topical administration of fluorophenyl-labelled [^{14}C]flumethrin at 1.8 mg/kg bw (Cameron and Phillips, 1986).

Sample	^{14}C, ng flumethrin equivalent/g or ml
Whole blood	2
Plasma	4
Liver	9
Kidney	10
Renal fat	2
Subcutaneous fat	
below dose area	0 (<7.7 ng equiv./g)
away from dose area	0 (<7.7 ng equiv./g)
Skeletal muscle	
fore leg	0(<3.9 ng equiv./g)
rump	0(<3.9 ng equiv./g)
dorsal	0(<3.9 ng equiv./g)
cheek	1(3.9 ng equiv./g limit of determination)
Bile	70
Bladder urine	281
Application area (surface wash and solubilized skin)	4.7 mCi = 71.5% of administered dose

In the second study, also in accordance with GLP, [U-*chlorophenyl*-^{14}C]flumethrin (98.2% pure by TLC, 96.3% by HPLC) was formulated as a solution (specific activity 9 Ì Ci/mg) and administered as a single i.v. dose into the jugular veins of both a lactating cow (545 kg) and a steer (340 kg) at a nominal rate of 1 mg ai/kg bw (Gifford and Dunsire, 1994). The integrity of the dose solution was confirmed by TLC after dosing. Urine, milk and faeces samples were taken until slaughter 8 hours after treatment and milk also just before dosing. Tissue samples were taken at slaughter and all

samples were transported under dry ice and stored at -20°C until analysed. Total ^{14}C was determined by liquid scintillation.

The cumulative recovery of ^{14}C is shown as a proportion of the administered dose is summarized in Table 2 and as flumethrin equivalents/kg in the milk, blood and tissues in Table 3.

Table 2. Recovery of radioactivity from [^{14}C]flumethrin 8 hours after administration of a single intravenous dose to cattle at 1 mg ai/kg bw (Gifford and Dunsire, 1994).

Sample	^{14}C, % of injected	
	Dairy cow	Steer
Urine	4	8
Faeces	0.03	0.35
Milk	0.32	NA
Tissues		
liver	21.13	4.4
kidney	0.22	0.28
muscle	7.13*	6*
fat	3.1*	2.5*
Total	31.6	13.2
Total	35.9	21.5

* Assumes muscle and fat account for 30% and 20% of body weight respectively.

Table 3. Residues of ^{14}C as flumethrin equivalents 8 hours after administration of a single intravenous dose of [^{14}C]flumethrin to cattle at 1 mg ai/kg bw (Gifford and Dunsire, 1994).

Sample	^{14}C as flumethrin, mg/kg	
	Dairy cow	Steer
Milk	0.3	NA
Liver	13	3.4
Kidney	0.9	1.4
Muscle - loin	0.19	0.18
flank	0.25	0.19
round	0.30	0.23
Fat - subcutaneous	0.17	0.24
omental	0.37	0.19
Whole blood	1.5	1.8
Plasma	2.2	2.8

The third study (Klein, 1995), also in accordance with GLP, was a continuation of the 1994 study of Gifford and Dunsire described above, with the objective of identifying and quantifying the residues in the edible tissues and milk. Identifications were based on the characterization and fractionation of urinary extracts by HPLC, followed by GC-MS and NMR spectrometry. One HPLC

fraction was shown by MS and NMR to contain the glucuronic acid conjugate of metabolite BNF 5533A. The identification was confirmed by the detection of BNF 5533A in glucuronidase/arylsulfatase hydrolysates of the conjugate. Another major urinary component was shown by GC-MS and NMR after methylation to be unconjugated BNF 5533A.

Samples of loin, flank and round muscle and of omental and subcutaneous fat were composited for each animal before extraction for analysis. Tissues were extracted with acetonitrile/water, and the extracts concentrated and partitioned with n-heptane. The heptane fractions were concentrated, taken up in acetonitrile and analysed by HPLC. The aqueous fractions were diluted with water, adjusted to pH 3 (except liver extracts) and partitioned with acetonitrile which was concentrated for HPLC. Milk was extracted with methanol and the residues were partitioned into heptane: only the heptane fraction was analysed as it contained 89% of the radioactivity. Residues were quantified by HPLC with integration of ^{14}C signals, and identified by comparison with reference standards in two HPLC systems. Table 4 shows the efficiencies of extraction of from the milk and tissues and the levels of ^{14}C found. Table 5 shows the levels and percentages of the identified compounds.

Table 4. Concentrations and extractable proportions of total radioactivity in milk and tissues of cattle 8 hours after i.v. administration of [^{14}C]flumethrin at 1 mg/kg bw (Klein, 1995).

Sample	^{14}C			
	Dairy Cow		Steer	
	Flumethrin equivalent, mg/kg	Extractable, %	Flumethrin equivalent, mg/kg	Extractable, %
Liver	13	96	3.4	92
Kidney	0.9	92	1.4	90
Muscle	0.25	87	0.2	87
Fat	0.27	78	0.22	88
Milk	0.34	89	-	-

Table 5. Distribution of ^{14}C in flumethrin and metabolites in milk and tissues of a lactating dairy cow and steer 8 hours after i.v. administration of [^{14}C]flumethrin at 1 mg/kg bw (Klein, 1995).

Sample	Component or fraction	Total % and mg/kg as flumethrin in sample

		Flumethrin	BNF 5533A	BNF 5533A glucuronide	Unknown	
Liver (cow)	%	87.1	7.0	1.0		95.1
	mg/kg	11.31	0.91	0.13		12.4
Liver (steer)	%	28.9	39.9	7.2		76
	mg/kg	0.97	1.34	0.24		2.6
Kidney (cow)	%	35.1	47.4	5.7		88.2
	mg/kg	0.31	0.42	0.05		0.8
Kidney (steer)	%	15.5	46.5	24.8		86.8
	mg/kg	0.22	0.66	0.35		1.2
Muscle (cow)	%	29	57.5			86.5
	mg/kg	0.07	0.14			0.2
Muscle (steer)	%	35.9	51.1			87
	mg/kg	0.07	0.1			0.2
Fat (cow)	%	23.8	54.5			78.3
	mg/kg	0.06	0.15			0.2

Fat (steer)	%	27.8	59.8			87.6
	mg/kg	0.06	0.13			0.2
Milk (cow)	%	67.9			11.5	67.9
	mg/kg	0.23			0.04	0.2

METHODS OF RESIDUE ANALYSIS

Analytical methods

A multi-residue analytical method used by Australian national authorities for the determination of pyrethroids including flumethrin in animal fat, and methods for the determination of flumethrin and in some cases also its metabolite BNF 5533A (flumethrin acid) in cattle tissues and milk, and for the determination of flumethrin in sheep tissues, honey and honey wax were reported.

Multi-residue methods

The Australian multi-residue Method 2A for the determination of pyrethroids in animal fat (Webster *et al*., 1996) was used in the supervised trials carried out by the Queensland Department of Primary Industries (Queensland and New South Wales, 1996). It is based on and very similar to published methods (Mills *et al*., 1963; EPA, 1980) for organochlorine pesticides. In Method 2A finely sliced fat, is rendered, dissolved in hexane, and partitioned with acetonitrile. The acetonitrile is diluted with water and the residues partitioned into hexane. The extract is concentrated, cleaned up on a Florisil column eluted with 10% ethyl ether in hexane, and the residue determined after concentration by GLC with an ECD. The method calls for immediate storage of rendered fat samples at -40°C until analysis, although the Australian residue reports did not specify how this was done or the period of storage.

The limit of "detection" of flumethrin was reported as 0.01 mg/kg, with a mean recovery of 87% (n=5, s.d. 6.9) at 0.02 mg/kg, the lowest validated fortification level. Recoveries were similar (92%) at 0.05 mg/kg. Sample chromatograms were not provided for an independent estimate of the limit of detection or determination.

Specific methods

Cattle. The earlier methods were for the determination of flumethrin in milk. Riegner (1986a) described a method for the determination of flumethrin in cows milk which involved extraction with water/acetonitrile (1:4), clean-up on a silica gel column, and determination by HPLC with a 254 nm UV detector. Recoveries of 66 and 77% and a limit of determination of 0.005 mg/kg were reported (sample chromatograms suggest that 0.1 mg/kg might be more realistic). The reported limit of detection was 0.002 mg/kg. Saito (1988) described a method for flumethrin in milk and plasma which consisted in extraction with hexane/water (2:1), concentration, partitioning between hexane and acetonitrile, clean-up on a Sep-Pak cartridge, and HPLC determination. Recoveries of 92.4% were reported for milk fortified at 0.5 mg/kg and the limit of "detection" was reported to be 0.03 mg/kg, but this could not be confirmed in the absence of sample chromatograms.

In one of the first methods reported for flumethrin in cattle tissues (Werthmann and Kaiser, 1980), an acetonitrile extract of minced tissues is cleaned up on a silica column and the dichloromethane eluate is concentrated and analysed by reversed-phase HPLC with UV detection at 266 nm. A "limit of detection" of 0.05 mg/kg was reported, with 80-90% recoveries at 0.08 mg/kg, but these figures could not be confirmed with the information provided.

Maasfeld (1989) described a method for the determination of flumethrin in cattle tissues and milk. Tissues are homogenized with acetonitrile, and the homogenate is partitioned successively with hexane (which is discarded) and dichloromethane before clean-up by silica gel chromatography. Milk is extracted with 1:4 water/acetonitrile (as in the Riegner method) and partitioned with dichloromethane. The extract is cleaned up on silica gel (elution with 55:45 hexane/dichloromethane). Determination is by HPLC with UV detection at 266 nm. Recoveries were generally about 80% or better from tissues at 0.01 mg/kg fortification levels and from milk at 0.005 mg/kg. The limit of detection (based on noise levels) was estimated to be approximately 0.004 mg/kg for tissues and 0.001 mg/kg for milk. The limit of determination was reported to be 0.01 mg/kg for tissues and 0.005 mg/kg for milk. Sample chromatograms support those estimates, at least for the author's laboratory. Permethrin, cypermethrin and cyfluthrin do not interfere.

Three more recent methods (Bohm and Paul, 1994a,b,c) for flumethrin in tissues and milk and for flumethrin acid (BNF 5533A) in tissues are based on the method of Maasfeld. Tissues are analysed in the same way, except that fat samples are ground and mixed with sea sand before extraction with acetonitrile. Milk solids are removed by the addition of acetone and centrifugation before extraction with dichloromethane, partitioning into acetonitrile and washing with hexane (which is discarded).

The determination of flumethrin acid in tissues is similar to that of flumethrin, except that extraction is with 8:1 acetonitrile/0.1% phosphoric acid instead of acetonitrile, and the silica gel column treatment is followed by further clean-up on a C-18 solid-phase extraction column.

The mean recoveries of flumethrin were 80 to 90% from tissues at 0.01 mg/kg fortification levels and 86% from milk at 0.005 mg/kg. A limit of determination of 0.01 mg/kg was reported for both flumethrin and flumethrin acid in tissues. Sample chromatograms suggest that this limit may be possible in the authors' laboratory for flumethrin and perhaps for flumethrin acid, except in kidney and liver where it is questionable. The reported limit of detection for flumethrin was 0.002 mg/kg and for flumethrin acid 0.002 mg/kg in kidney and muscle but 0.004 mg/kg in liver and fat. A limit of determination of 0.005 mg/kg was reported for flumethrin in milk and sample chromatograms suggest that this is possible in the authors' laboratory. The limit of detection was reported as 0.001 mg/k.

Two recent HPLC methods similar to those of Bohm and Paul have been reported for the determination of flumethrin and flumethrin acid in cattle tissues (Krebber, 1994a) and milk (Krebber, 1994b). In the tissue method flumethrin and flumethrin acid are extracted together from homogenates by the procedure used in the Bohm and Paul method for flumethrin acid (extraction with acetonitrile/phosphoric acid). The compounds are separated on a silica gel cartridge by eluting flumethrin with dichloromethane/hexane and flumethrin acid with dichloromethane/methanol. As in the Bohm and Paul method the flumethrin acid fraction is further cleaned up on a C-18 solid-phase cartridge and both fractions are analysed by HPLC.

Mean recoveries of flumethrin at 0.01 mg/kg were 92-104% from tissues except fat, and 68% from fat. Mean recoveries of flumethrin acid at 0.02 mg/kg from tissues were 87 to 110%. The limits of determination were reported to be 0.01 mg/kg and 0.02 mg/kg for flumethrin and flumethrin acid respectively. No response for flumethrin was seen in controls, but a limit of detection of 0.005 mg/kg was reported for flumethrin acid. Sample chromatograms were consistent with the reported limit of determination for flumethrin but were not as conclusive for flumethrin acid.

The Krebber (1994b) method for the determination of flumethrin and flumethrin acid in milk is essentially the same as that for tissues. At 0.005 and 0.2 mg/kg fortification levels the mean recoveries of flumethrin were 73 and 85% respectively and of flumethrin acid 102 and 90%. The limits of

determination were reported to be 0.005 and 0.01 mg/kg for flumethrin and flumethrin acid respectively. Again, sample chromatograms were consistent with the reported limit of determination for flumethrin, but were less conclusive for flumethrin acid.

Sheep. Separate methods have been reported for the determination of flumethrin, but not flumethrin acid, in sheep. The oldest of the methods provided to the Meeting was for the determination of flumethrin in sheep milk (Palermo, 1987). It involves extraction with a 1:1:2 solution of petroleum ether(PE)/acetone/acetonitrile, discarding the PE, extraction of the aqueous layer with chloroform, concentration, dissolution in PE and clean-up on a silica gel column before determination by HPLC with UV detection at 266 nm. The mean recovery was only 66% and a limit of "detection" of 0.01 mg/kg was reported. No sample chromatograms or details of recovery experiments were provided.

The method reported by Inveresk (1996) as "the method for flumethrin determination in sheep tissues" is a modification of method 00366 developed for the determination of flumethrin in rat serum (Krebber, 1994c) and later modified for serum analyses (Krebber, 1995).

In the original method serum was extracted with ethyl acetate, the extract was cleaned up on a silica gel column, eluted with n-hexane/dichloromethane (55:45), concentrated, taken up into acetonitrile and determined by HPLC with UV detection. The 1995 modification for serum consisted in acidification of serum in water with phosphoric acid and elution from an "Extrelut" cartridge with ethyl acetate before the silica column clean-up.

For the analysis of sheep tissues extraction with acetonitrile is followed by partitioning with hexane, silica gel column clean-up and HPLC determination (Inveresk, 1996). Only a summary of the modified method for sheep was provided. From the summary, the modified method seems similar to the method described by Maasfeld (1989) for cattle tissues, although the summary does not indicate whether tissues are ground before extraction. Limits of detection and determination of 0.01 mg/kg and 0.02 mg/kg were reported, with recoveries of 88, 82, 115 and 99% from liver, kidney, muscle and fat respectively at 0.02 mg/kg. The lack of details and sample chromatograms precluded independent confirmation of the reported limits.

Honey and wax. In the method of Riegner (1986b) for the determination of flumethrin in honey and beeswax honey is extracted with a mixture of toluene, dichloromethane and methanol (5:4:1), the solvent is evaporated and the residue taken up in 1:1 ethyl acetate/cyclohexane for clean-up by gel permeation followed by silica gel column chromatography. Wax is melted, dissolved in hot 2-propanol, and precipitated with methanol/water. The extract is further purified by partitioning between water and 1:1 ethyl acetate/cyclohexane, the solvent is evaporated and the residue taken up in acetonitrile, which is washed with hexane. The acetonitrile is evaporated and the residue taken up in toluene for silica gel chromatography. Determination is by HPLC with UV detection at 254 nm.

The mean recoveries were about 63% from honey at 0.003 to 0.004 mg/kg and from wax at 0.03 to 0.1 mg/kg. The "lower practical working range" was reported to be 0.002 mg/kg for honey and 0.025 mg/kg for wax. Sample chromatograms indicated that these levels were achievable in the author's laboratory.

Two more recent methods (Heukamp, 1993; Heukamp and Krebber, 1993) are very similar to and appear to be based on the Riegner (1986) method. Modifications include the use of an ultra sound bath for re-dissolving the residues from extracts which have been taken to dryness and of a variable wavelength detector, used at 266 nm, instead of the 254 nm detector. The reported mean recoveries from honey were 74% at 0.003 mg/kg, 87% at 0.013 mg/kg and 86% at 0.85 mg/kg, and from wax

60% at 0.026, 79% at 0.051, and 76% at 0.1 mg/kg. The reported limits of detection and determination were 0.001 and 0.003 mg/kg for honey and 0.02 and 0.026 mg/kg for wax. Sample chromatograms were consistent with these levels.

Stability of pesticide residues in stored analytical samples

No substantive studies of storage stability were provided. In one supervised trial milk fortified with 0.037 mg/kg flumethrin was stored for 40 days at -18°C and analysed after 10 and 40 days (Dorn and Maasfeld, 1989b). Since the recoveries, 74 and 77% respectively, were normal for the method the authors concluded that flumethrin was stable in milk under the conditions of storage.

Residue Definition

Although the metabolite BNF 5533A (flumethrin acid) was found in metabolism studies to occur at 1 to 1.5 times the level of flumethrin in cattle tissues, it was not reported in milk. If flumethrin is of significantly greater toxicological concern than the metabolite, if it is observed that it may occur in tissues at comparable levels to the metabolite, that only flumethrin was reported in milk and is the residue of concern in honey, flumethrin *per se* is a suitable indicator residue for regulatory purposes. Other issues relevant to expressing MRLs for meat are discussed in the appraisal.

USE PATTERN

Flumethrin is applied to cattle (including lactating cows), sheep, goats, horses and dogs as a spray, dip or pour-on treatment for the control of mange, mites, lice, biting lice and ticks. The only information provided on nationally approved uses (GAP) was on an Australian 75 g ai/l formulation for dips or sprays for cattle and horses, an Australian 1% ai pour-on for cattle and a UK 6% EC formulation for sheep dipping, all supported by labels. The submission made further general reference to a 6% EC for sprays or dips for sheep and dip for goats (Inveresk, 1996) but no labels, countries, withdrawal periods or treatment intervals were provided. The Inveresk reference to the 6% EC dip reported application rates of 44-66 mg ai/l to sheep (after milking if lactating) and 30-48 mg ai/l to goats. The application rate for sheep is consistent with the UK label. Flumethrin-impregnated plastic strips (3.6 mg/strip) are also available for the control of Varroa in bee colonies, 2 to 4 strips per chamber. This use is approved in the UK (Inveresk, 1996), but again labels and other details were not provided.

UK GAP for sheep. The 6% EC formulation for dipping sheep for scab and tick control is used at a rate of 1l product/900-1300 l water (46-67 mg ai/l). Sheep are dipped for at least one minute with total immersion (including the head and ears) at least twice. Re-dipping after 14 days is recommended if scabies is confirmed. A 3-month interval before shearing is recommended. No withdrawal period is required before consumption of tissues or milk, but lactating sheep must be dipped after milking.

Australian GAP for cattle and horses is summarized in Table 6.

Table 6. Australian uses of flumethrin on farm animals.

Application			Treatment interval, days	Withholding period, days	Notes
Method	Solution concn., g/l	Rate, mg/kg bw			
Dip and spray formulation, 75 g ai/l (cattle and horses)					
Plunge dip	75		10-21 (pest-dependent)	cattle 0 horses 1	Replenish at same concn.[1] before 1/4 volume loss; 20-25 animals used as stirrers (need re-dipping).
Recirculating spray	75		same	same	Replenish same concn. every 250 l vol. loss or after 1000 l, then after 500 l, then after every 250 l loss. Max. 750 adults before emptying and recharging.
Constant replenishment spray	75		same	same	Replenish at same concn. Max. 750 adults before emptying and recharging.
Hand spray or non-recirculating spray	75	1.2-1.5 (assuming 500 kg animal)	same	same	Minimum 8-10 l/animal
Pour-on Formulation 10 g/l (Cattle)					
Pour-on	10 g/l	2.3* 1.8-3.6** 1.5-2.5*** 1.5-2.2****	14-42[3]	"Nil"[2]	Applied along mid-line of back from front of shoulder to tail. * ≤ 150 kg; (33 ml product); ** 151-300 kg; (55 ml product); *** 301-500 kg; (75 ml product); **** 501-750 kg; (112.5 ml product

[1]It has been demonstrated over 40-70 week periods of practical cattle dipping that replenishments of flumethrin EC plunge dips at the initial rate maintain a concentration near the target without the need for replenishment at rates higher than the initial charge. For example an initial 50 mg/l will be stabilized between 40 and 50 mg/l (Terblanche, 1980c)

[2]A 56-day withholding period is "suggested" for exports and may be required by some meat processors, but is not a statutory requirement

[3]Implied treatment interval ("Control can be attained"). Pest-dependent for ticks. Controls Buffalo fly up to 10 days

RESIDUES RESULTING FROM SUPERVISED TRIALS

Supervised trials data were available on residues of flumethrin in the milk of cattle, sheep and goats and the tissues of cattle and sheep, and for residues of the metabolite flumethrin acid (BFN 553A) in the tissues of cattle. Data were also provided on residues in honey and beeswax from supervised trials in bee hives.

Cattle (Tables 7-10). Supervised trials were reported from Australia, South Africa, Germany and Japan, with applications by dipping, spraying and pour-on. The Meeting was informed of additional Australian studies to be completed in 1996.

Table 7. Flumethrin residues in cattle fat from 1994-95 Australian trials. Australian government submission.
Table 8. Flumethrin residues in cattle tissues (including older Australian trials). Submissions by the manufacturer.
Table 9. Flumethrin acid (metabolite BNF 5533A) residues in cattle tissues. Submission by the manufacturer (trials conducted in accordance with GLP).
Table 10. Flumethrin residues in cattle milk. Submission by the manufacturer.

Table 7. Flumethrin residues in loin (subcutaneous) and renal fat of cattle from 1994-95 supervised trials in Australia (Webster *et al*., 1996; Queensland and New South Wales, 1996)

Pre-slaughter interval, days	Sample	Residues, mg/kg, after indicated treatment			
Plunge Dips[1]		Treatment[2]			
		D1	D2	D3	D4
2	Loin fat	<0.005	--	<0.005	<0.005
		<0.005	--	<0.005	<0.005
		0.041	--	<0.005	<0.005
	Renal fat	<0.005	--	<0.005	<0.005
		<0.005	--	<0.005	<0.005
		0.047	--	<0.005	<0.005
4	Loin fat	<0.005 (3)[3]	<0.005 (3)	<0.005 (3)	<0.005 (3)
	Renal fat	<0.005 (3)	<0.005(2) 0.006	<0.005 (3)	<0.005 (3)
7	Loin fat	<0.005 (3)	<0.005 (3)	<0.005 (3)	<0.005 (3)
	Renal fat	<0.005 (3)	<0.005 (3)	<0.005 (3)	<0.005 (3)
15	Loin fat	<0.005 (3)	<0.005 (3)	<0.005 (3)	<0.005 (3)
	Renal fat	<0.005	<0.005	<0.005	<0.005
		0.008	<0.005	<0.005	<0.005
		<0.005	<0.005	<0.005	<0.005
21	Loin fat	All 12 residues <0.005			
	Renal fat	All 12 residues <0.005			
30	Loin fat	<0.005	<0.005	<0.005	0.009
		<0.005	<0.005	<0.005	<0.005
		<0.005	<0.005	<0.005	<0.005
	Renal fat	<0.005	<0.005	0.011	0.013
		<0.005	<0.005	<0.005	<0.005
		<0.005	<0.005	<0.005	<0.005

Pour-on applications[4]		Treatment	
		P1	P2
2	Loin fat	<0.005	0.015
		<0.005	0.014
		<0.005	0.013
	Renal fat	<0.005	0.04
		<0.005	0.034
		<0.005	0.023
4	Loin fat	0.023	0.028
		<0.005	0.025
		0.029 [0.04][5]	0.023
	Renal fat	0.032	0.058
		<0.005	0.022
		0.026 [0.04][5]	0.035
7	Loin fat	0.013 [0.015][5]	0.031
		0.011	0.018
		0.008	0.019
	Renal fat	0.015 [0.015][5]	0.037
		0.020	0.036
		0.015	0.022
10	Loin fat	<0.005	0.022
		0.014	0.022
		0.009	0.029
	Renal fat	<0.005	0.044
		0.019	0.038
		0.014	0.097
15	Loin fat	0.011	0.052
		0.007	0.020
		0.011	0.020
	Renal fat	0.012	0.14 (confirmed)
		0.014	0.038
		0.034	0.035
21	Loin fat	0.006	0.017
		0.008	0.011
		0.040 [0.06][5]	0.016
		0.017 [0.025][5]	0.015
		0.010	0.022
		0.029	0.019
	Renal fat	0.014	0.036
		0.021	0.026
		0.11 [0.06][5]	0.049
		0.024 [0.025][5]	0.026
		0.014	0.054
		0.042	0.033
30	Loin fat	0.020	0.014
		0.008	0.017
		0.008	0.020
	Renal fat	0.027	0.027
		0.029	0.030
		0.011	0.027
Pour-on applications[4]		Treatment	
		P1	P2
45	Loin fat	<0.005	0.023
		<0.005	0.012

		0.009	0.029
	Renal fat	0.018	0.051
		0.024	0.028
		0.020	0.044

[1]Generally 3 animals for each treatment and pre-slaughter interval, each sample from a different fat depth and the renal fat values corresponding successively to the loin fat values.

[2]D1: dipped once according to GAP.
D2: dipped twice, but the animals were also used to stir the dip. Complied with GAP.
D3: dipped twice. Not strictly GAP because retreatment interval was 3 days and GAP minimum is 10 days.
D4: dipped twice, but the animals were used as stirrers for both dips. Not strictly GAP because the retreatment interval
was 7 days instead of minimum of 14 days implied by label.
P1: one application according to GAP.
P2: two applicatons at 7-day interval. GAP interval is 14 days.

[3]Numbers in parentheses are the numbers of samples with the same residues.

[4]At GAP rate of 10 g ai/l and according to label instructions requiring 1.5 to 3.6 mg/kg bw, according to the weight of
the animals (see Table 6).

[5]Values in square brackets are means of replicate analyses of fat from core samples of cartons of frozen product (same
carcases) as distinct from loin and renal fat samples taken at slaughter.

Dip concentrations were checked by analysis before treatment. The multi-residue GLC method used is described in "Analytical methods". Although the reported limit of detection was 0.01 mg/kg, undetectable residues are recorded as <0.005 mg/kg. No information was provided on the length of time from slaughter to analysis, although the time from the start of the study until the final report was less than 14 months. The protocol called for sample storage at -40°C.

Figure 2 shows the variation of residues of flumethrin in loin and renal fat with time after one or two pour-on applications at GAP rates.

Figure 2. Average residues of flumethrin in loin (subcutaneous) fat and renal fat from one or two pour-on applications to cattle at GAP rates (Queensland and New South Wales, 1996).

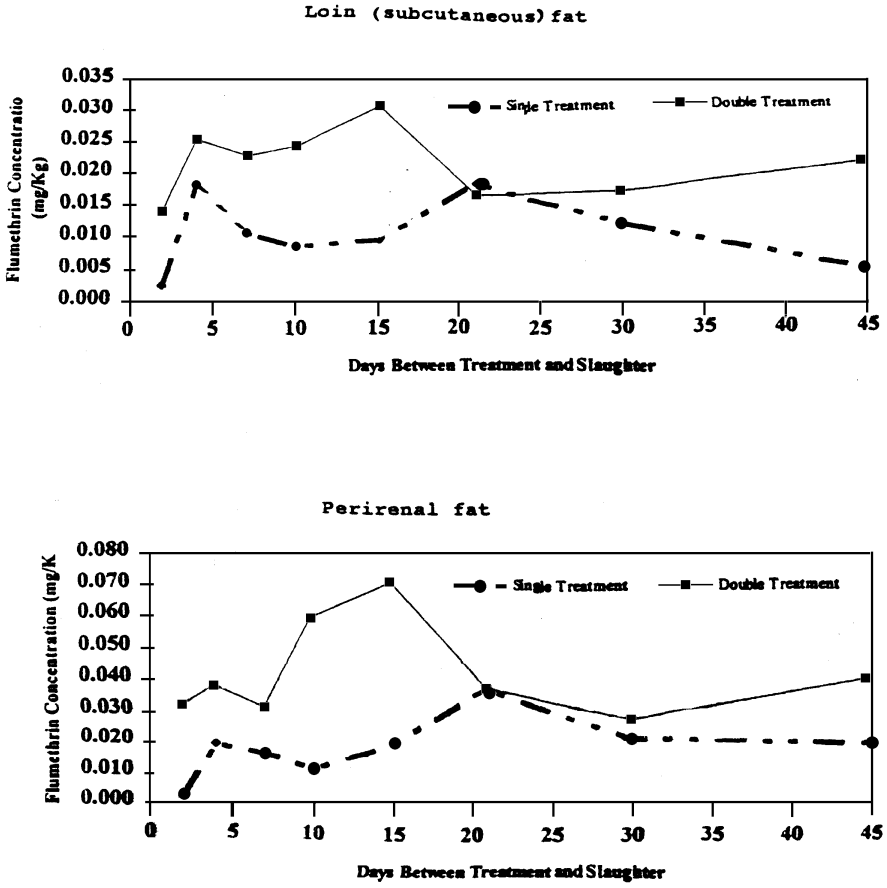


Table 8. Residues of flumethrin in cattle tissues from supervised trials.

Country, year, Formln.	Application			No. of cattle	Pre-slghtr. (days)	Flumethrin, mg/kg, in				Ref[1]
	Concn., ai	No. & (days intvl.)	mg/kg bw			fat[3]	liver	muscle	kidney	
Dip										
S. Africa 1980 7.5% EC (dip wash)	75 mg/l No GAP	4 (14)		3	3	<0.1(3)	<0.1(3)	<0.1(3)	<0.1(3)	40
				3	7	<0.1(3)	<0.1(3)	<0.1(3)	<0.1(3)	
				3	14	<0.1(3)	<0.1(3)	<0.1(3)	<0.1(3)	

Australia 1983 7.5% (plunge dips)	67 mg/l (within GAP)	1		3	1	0.007 <0.005(2)	<0.005(3)	0.01 <0.005(2)	<0.005(3)	36
				3	3	<0.005(3)	<0.005(3)	<0.005(3)	<0.005(3)	
Pour-on										
Germany 1989 1% pour-on	10 g/l No GAP	1	2	2[2]	1	0.05(2)	≤0.01, 0.03	nd, <0.01 nd = <0.01 = limit determ.	nd, <0.01	28
				2	4	0.07, 0.05	nd,0.013	nd,0.01	nd,0.01	
				2	7	0.07, 0.08	nd(2)	nd(2)	nd(2)	
				2	14	0.06(2)	nd(2)	nd(2)	nd(2)	
				2	21	0.03, 0.08	nd(2)	nd(2)	nd(2)	
				2	28	0.07, 0.06	nd(2)	nd(2)	nd(2)	
S. Africa 1984 0.5% pour-on No GAP	5 g/l	6 (7)	1.2	3	0.5	<0.05(2), 0.07	<0.05(3)	<0.05(3)	<0.05(3)	25
S. Africa 1984 1% pour-on No GAP	10 g/l	6 (7)	1.2	2	0.5	<0.05(2)	<0.05(2)	<0.05(2)	<0.05(2)	26
Australia 1984 0.5% pour-on	5 g/l (within GAP)	1	1 GAP?	3 3	1 3	max./av. 0.01/ 0.007 0.005/ <0.005	max./av. <0.005(3) 0.01/ <0.007	max./av. 0.005/ <0.005 <0.005(3)	max./av. <0.005(3) <0.005(3)	34
	5 g/l	1	2 (GAP)	3 3	1 3	0.005/ <0.005 0.005/ <0.005	<0.005(3) <0.005(3)	<0.005(3) <0.005(3)	<0.005(3) <0.005(3)	
	5 g/l	1	4	3 3	1 3	0.13/ <0.09 0.005/ <0.005	0.01/ <0.007 <0.005(3)	0.02/ <0.01 <0.005(3)	0.005/ <0.005 <0.005(3)	
1% pour-on	10 g/l (GAP)	1	1 (within GAP)	3 3	1 3	0.01/ <0.007 0.025/ <0.01	<0.005(3) <0.005(3)	0.005/ <0.005 <0.005(3)	0.01/ <0.007 <0.005(3)	34
	10 g/l	1	2 (GAP)	3 3	1 3	<0.005(3) 0.005/ <0.005	<0.005(3) <0.005(3)	<0.005(3) <0.005(3)	<0.005(3) <0.005(3)	
	10 g/l	1	4	3 3	1 3	0.015/ <0.01 0.055/ <0.02	0.005(3) 0.005/ <0.005	0.005/ <0.005 <0.005(3)	<0.005(3) 0.01/ <0.007	
	Median for ref. 34 (N=36):				GAP treatments All treatments	<0.005 0.005	<0.005	<0.005	<0.005	

Spray										
S. Africa 1984 6%EC	30 mg/l No GAP	4 14		2	3	<0.05(3)	<0.05(3)	<0.05(3)	<0.05(3)	24
				2	7	<0.05(3)	<0.05(3)	<0.05(3)	<0.05(3)	
				2	14	<0.05(3)	<0.05(3)	<0.05(3)	<0.05(3)	
Australia 1981 7.5% EC	50 mg/l (2/3 max. GAP)	1		3	1	<0.05	<0.05	<0.05	<0.05	32
	50	1		3	3	<0.05	<0.05	<0.05	<0.05	
	100 (1.3X GAP)	1		3	1	<0.05	<0.05	<0.05	<0.05	
	100	1		3	3	<0.05	<0.05	<0.05	<0.05	
	200	1		3	1	<0.05	<0.05	<0.05	<0.05	
	200	1		3	3	<0.05	<0.05	<0.05	<0.05	
Australia 1981 7.5% EC + 16% coumaphos	100	1		3 3	1 3	<0.05 <0.05	<0.05 <0.05	<0.05 <0.05	<0.05 <0.05	32

[1]Numbers correspond to tab numbers in 1996 Bayer submission, Vol. III:
24. Amelsfoort, 1984a; 25. Amelsfoort, 1984b; 26.Amelsfoort, 1984c; 28. Dorn and Maasfeld, 1989a; 32. Hopkins and Lindsay, 1981; 34. Lindsay and Hopkins, 1984; 36. Lindsay, 1983b; 40. Terblanche, 1980a.
[2]Duplicate analyses on each cow. Results are means of duplicates.
[3]Reference 40 fat was described as perirenal fat, references 28 and 36 as "fat" and the rest "minced fat".

Table 9. Residues of flumethrin acid (BNF 5533A) in cattle tissues from supervised trials with a 1% pour-on flumethrin formulation, Germany, 1994 (Tesch and Doberschütz, 1994).

Treatment	No. of cattle	Pre-slaughter (days)	Flumethrin acid (BNF 5533A), mg/kg[1]			
			fat (suet)[2]	liver	muscle	kidney
2 x 10 g ai/l, 10 days apart (2 mg/kg bw)	6	1	0.03 0.02 (2) <0.01 (2) <0.004	0.05 0.04 0.03 0.02 <0.01	0.01 <0.01(4) <0.002	0.03(2) 0.02(2) <0.01 (2)
	6	2	0.04 0.02 (3) 0.013 0.01	0.06 0.05 0.04 0.03(2) 0.02	0.01 <0.01(3) <0.002(2)	0.05 0.03 0.02 0.01(3)
	6	4	<0.004(6)	0.02 0.01(2) <0.01	<0.01(3) <0.002(3)	0.03 <0.01(5)

Treatment	No. of cattle	Pre-slaughter (days)	Flumethrin acid (BNF 5533A), mg/kg[1]			
			fat (suet)[2]	liver	muscle	kidney
				<0.002(2)		
	6	7	0.02 <0.01 <0.004(4)	0.01 (2) <0.004 (4)	<0.01 <0.002(5)	0.02 <0.01 <0.002(4)
	6	21	<0.004(6)	<0.004(6)	<0.002(6)	<0.002(6)
	6	35	<0.004(6)	<0.004(6)	<0.002(6)	<0.002(6)

[1]Limit of detection 0.002 mg/kg in kidney and muscle and 0.004 mg/kg in liver and fat; limit of determination 0.01 mg/kg in all tissues.

[2]Suet = loin or kidney fat

Table 10. Residues of flumethrin in cattle milk from supervised trials with pour-on and spray applications.

Country, year formln.	Application			No. of cattle	Flumethrin, mg/kg, at intervals after last application[3]						Ref[1]
	Concn., ai	No. & (days intvl.)	mg/kg bw		Hours	Days					
					4	2	4	7	10	10	
Pour-on											
Germany 1989 1% Pour-on	10 g/l (withers to tail base)	2 (14)	2	5	<0.005 (4h) 0.03 M[2] 0.07 E	0.06	0.04	0.01	0.006		29
Germany 1989 1% Pour-on	10 g/l (hip pt. to tail base)	2 (14)	2	5	0.005 (4 h) 0.02 M 0.04 E	0.04	0.02	0.01	0.006		30
					Hours						
					6	8-9	18-19	22-25	30	≥42	
Australia 1984 1% pour-on	10 g/l	2 (3)	2[3]	3		9 h 0.01 <0.01 (2)[4] *	* From bulked milk: skim milk <0.01 mg/kg milk fat 0.14 mg/kg				31
Australia 1984 1% pour-on	10 g/l	1	1 (GAP)	3		9 h 0.01 <0.01 (2)		24 h 0.01 <0.01 (2)		72 h 0.01 <0.01 (2)	37

Country, year formln.	Application			No. of cattle	Flumethrin, mg/kg, at intervals after last application[3]						Ref[1]
	Concn., ai	No. & (days intvl.)	mg/kg bw		Hours	Days					
					4	2	4	7	10	10	
	10 g/l	1	2 (GAP)	3		0.04 0.01 <0.01		0.01 0.02 <0.01		0.01 0.01 <0.01	
	10 g/l	1	4	3		0.1 0.05 0.04		0.01 0.01 <0.01		0.01 0.03 0.01	
Australia 1984 0.5% pour-on	5 g/l	1	1 (GAP)	3		0.04 0.03 <0.01		0.03 0.04 0.01		0.02 0.01 <0.01	38
	5 g/l w/in GAP	1	2 (GAP)	3		0.03 0.01 0.01		0.03 <0.01 0.01		0.01 <0.01 <0.01	
	5 g/l	1	4	3		0.04 0.02 <0.01		0.01 0.01 0.02		<0.01 <0.01 0.01	
Japan 1987 1% pour-on	10 g/l	1	1	3		8 h <0.03 (3)		25 h <0.03 (3)			39
	10 g/l	3 (7)	1	3		1 h <0.03 (3) 8 h <0.03 (3)		25 h <0.03 (3)			
S. Africa 1984 0.5% Pour-on	5 g/l (withers to loins) [7]	6 (7)	1.2	3		8 h <0.05 (3)	19 h <0.05 (3)		30 h <0.05 (3)	42 h <0.05 (3) 66 h <0.05 (3)	27
Spray											
Australia 1984 7.5% EC	75 g/l (≤8 l/cow)	2 (3)		3		0.01 (2) <0.01					31
Australia 1981 7.5% EC (bulked samples)	75 g/l (10 l/cow) (GAP)	1		10		9 h <0.1		22 h <0.1			33

Country, year formln.	Application			No. of cattle	Flumethrin, mg/kg, at intervals after last application[3]						Ref[1]
	Concn., ai	No. & (days intvl.)	mg/kg bw		Hours	Days					
					4	2	4	7	10	10	
	150 (10 l/cow)	1		10		0.6		0.2			
Australia 1983 7.5% EC	100 (10 l/cow) (1.3 x GAP)	1		6		<0.01 (6)		<0.01 (6)			35
S. Africa 1980 7.5%[5]	75 g/l	4 (14)		9	<0.01 (9)		18 h <0.01 (9)	24 h <0.01 (9)		48 h <0.01 (9)	41

[1]Numbers correspond to tab numbers in 1996 Bayer submission, Vol. III:
27. Amelsfoort, 1984d; 29. Dorn and Maasfeld, 1989b; 30. Dorn and Maasfeld, 1989c; 31. Gyr, 1984; 33. Lindsay and Gyr, 1981; 35. Lindsay, 1983a; 37. Lindsay, 1984a; 38. Lindsay, 1984b; 39. Ohta, 1988; 41. Terblanche, 1980b.

[2]For refs. 29 and 30 the residues are the means of the means of the morning and evening milkings of the 5 cows, except on day 1 where morning (M) and evening (E) means are recorded separately because they differed significantly. After day 2 there were no significant differences between the morning and evening milkings.

[3]Calculated by authors from surface areas. Calculation from actual weights gives 1.4-1.6 mg/kg bw.

[4]Numbers in parentheses following the residues are the numbers of samples with those values.

[5]This trial is listed here as a spray. The submitted working paper summary lists it as a dip. The original report states that the cattle were "sprayed" with Bay L 6045 "dipwash" using a power spraypump.

Sheep and goats (Tables 11 and 12). Data were available from trials in Australia, South Africa, Italy and the UK, although information on national GAP was available only for Australia and the UK. Residues in sheep tissues and in sheep and goat milk are shown in Tables 11 and 12 respectively.

Table 11. Residues of flumethrin in sheep tissues from supervised trials with one application of pour-on or dip formulations.

Country, year formulation	Concn., ai	No. of sheep	Pre-slaughter (days)	Flumethrin, mg/kg, in				Ref.[5]
				fat[1]	liver	muscle	kidney	
Pour-on								
Australia 1986 Bay 1950 1% pour-on	10 g/l (2 mg/kg bw) mid back (wool parted)	3	0.5	<0.05 (3)[2]	<0.05 (3)	<0.05 (3)	<0.05 (3)	58

Country, year formulation	Concn., ai	No. of sheep	Pre-slaughter (days)	Flumethrin, mg/kg, in				Ref.[5]
				fat[1]	liver	muscle	kidney	
		3	14 hours	<0.05 (2) 0.06	<0.05 (3)	<0.05 (3)	<0.05 (3)	
		3	1	<0.05 (3)	<0.05 (3)	<0.05 (3)	<0.05 (3)	
		3	2	<0.05 (3)	<0.05 (3)	<0.05 (3)	<0.05 (3)	
		3	3	<0.05 (3)	<0.05 (3)	<0.05 (3)	<0.05 (3)	
South Africa 1990 1% pour-on[3]	10 (1 mg/kg bw)	2	1	0.007, 0.003	0.003, 0.002	<0.002 (2)	<0.002 (2)	60
		2	3	<0.002 (2)	<0.002, 0.004	<0.002 (2)	<0.002 (2)	
		2	5	0.06, 0.01	0.008, <0.002	0.009, 0.004	<0.002 (2)	
		2	7	0.02, 0.003	0.01, 0.002	0.002, 0.007	<0.002 92)	
		2	10	0.004, 0.008	<0.002, 0.005	<0.002, 0.004	<0.002 (2)	
Dip (Australia plunge dip)								
Australia 1983 Bay 6045 7.5% EC 1 min. dip	60 mg/l	2	1	0.005, 0.02	<0.005 (2)	<0.005 (2)	<0.005 (2)	59
		2	3	<0.005 (2)	<0.005 (2)	<0.005 (2)	<0.005 (2)	
	90 mg/l	2	1	<0.005, 0.04	<0.005 (2)	<0.005 (2)	<0.005 (2)	
		2	3	<0.005 (2)	<0.005 (2)	<0.005 (2)	<0.005 (2)	
Australia 1983 Bay 6045 6% SLC 1 min. dip	60 g/l	2	1	0.02, 0.03	<0.005 (2)	<0.005 (2)	<0.005 (2)	
		2	3	<0.005 (2)	<0.005 (2)	<0.005 (2)	<0.005 (2)	
	90 g/l	2	1	<0.005, 0.01	<0.005 (2)	<0.005 (2)	<0.005 (2)	
		2	3	<0.005 (2)	<0.005 (2)	<0.005 (2)	<0.005 (2)	
U.K. 1992 5.9% EC dip 1 min. dip	70 g/l	4	0.5	<0.01 (4) (omental) <0.01(3), 0.02/0.03 (subcut.)[4]	<0.01 (4)	<0.01 (4)	<0.01 (4)	61

Country, year formulation	Concn., ai	No. of sheep	Pre-slaughter (days)	Flumethrin, mg/kg, in				Ref.[5]
				fat[1]	liver	muscle	kidney	
		4	1	<0.01 (4) (omental) <0.01(3), 0.01/0.01 (subcut.)[4]	<0.01(3), 0.02/ <0.01[4]	<0.01 (4)	<0.01 (4)	

U.K. 1992 5.9% EC dip 1 min. dip		4	2	<0.01 (4) (omental) <0.01 (4) (subcut.)	<0.01 (4)	<0.01 (4)	<0.01 (4)	61
		4	4	<0.01 (4) (omental) <0.01(3), 0.01/0.02 (subcut.)[4]	<0.01(3), 0.01/0.01[4]	<0.01 (4)	<0.01 (4)	

[1]Unspecified except in UK
[2]Numbers in parentheses following the residues are the numbers of samples with those values.
[3]The report only states that applications were dermal. It was a pour-on formulation as indicated.
[4]Positive samples were re-analysed (the analyses separated by /).
[5]Numbers correspond to tab numbers in 1996 Bayer submission, Vol. IV:
58. Hopkins and Gyr, 1986; 59. Lindsay, 1983c. 60. Nieuwenhuis, 1990. 61. Redgrave, 1992.

Table 12. Residues of flumethrin in sheep and goat milk from supervised trials with 1 application of pour-on or spray formulation.

Species Country, year Formln.	Concn., ai & area treated	No. of Ani-mals	Flumethrin, mg/kg, at interval, hours, after last application								Ref.[3]
			8	12	18	24	36	48	60	72	
Pour-on											
Goats Australia 1984 1950 0.5% Pour-on	5 g/l (6 mg/kg bw) back mid-line	3		0.01 (2)[1] 0.02		0.01, 0.02, 0.04					IV,56
1950 1% Pour-on	10 g/l (4.6-6 mg/kg bw) back mid-line	3		<0.01 (3)		<0.01 (3)					
Sheep Australia 1986 1740 1% pour-on	10 g/l (2 mg/kg bw) back, neck to tail	6	<0.01 (3)		<0.01 (3)[2]	<0.01 (3)				<0.01 (3)	IV,57
1950 1% Pour-on	10 g/l (2 mg/kg	6	<0.01 (3)		<0.01 (3)[2]	<0.01 (3)				<0.02 (3)	

	bw) back, neck to tail										
Italy 1987 1% Pour-on	10 g/l (2 mg/kg bw)	5		<0.01 (5)		<0.01 (5)	<0.01 (5)	<0.01 (5)	<0.01 (5)	<0.01 (5)	III,21
Spray											
Italy 1987 6% EC	60 mg/l (2 mg/kg bw)	5		<0.01 (5)		<0.01 (5)	<0.01 (5)	<0.01 (5)	<0.01 (5)	<0.01 (5)	III,21

[1]Numbers in parentheses following the residues are the numbers of samples with those values.
[2]A different group of 3 animals was used for the 18 hour samples.
[3]Numbers correspond to tab numbers in 1996 Bayer submission, Vols. III & IV:
III,21. Palermo, 1987 IV,56. Griffin, 1984 IV,57. Griffin, 1986

Residues in honey and beeswax

Eleven supervised trials have been conducted in Germany, Switzerland and the UK with flumethrin used for mite control in honey-bee colonies by means of impregnated strips (0.5 mg flumethrin per cm^3, equivalent to 3.6 mg/strip, 4 strips/frame of 8-10 combs). Several seasonal periods were represented. The residues found in honey and beeswax are shown in Tables 13 and 14 respectively.

Table 13. Residues of flumethrin in honey from bee colonies treated with 4 strips/frame at 3.6 mg flumethrin/strip according to UK GAP.

Country/year	No. Colonies/ No. Samples	Treatment		Time of sample collection	Residues, mg/kg	Ref.[3]
		Duration (weeks)	Period			
Germany 1987-88	6/3[1]	6	early Sept. to mid-Oct. (pre-winter storage period)	June 1988 (after early nectar flow)	nd (<0.002) (3)[2]	49
Germany 1987-88	6/6	18	late Oct. 1987 to mid-March 1988	June 1988 (after early nectar flow)	nd (<0.002) (6)	50
Germany 1986	7/15	not given	early May (1985?)to mid- April 1986	not given	nd (<0.002) (15)	51
Germany 1988	4/4	20	May to Sept. 1988 (during nectar flow)	August 1988 (last wk.)	nd (<0.002) (4)	52
Germany (Lindlar) 1992-93	24/1	23	Oct. 12, 1992 to March 8, 1993	June 15, 1993	nd (<0.001)	47
Germany (Leverkusen) 1991-92	12/4	56	early Sept. 1991 to mid-Oct. 1992	1993 (end fruit at dandelion flowering)	nd (<0.001) (4)	47

Country/year	No. Colonies/ No. Samples	Treatment		Time of sample collection	Residues, mg/kg	Ref.[3]
		Duration (weeks)	Period			
UK	not given/1	not given	not given	1993 (spring)	nd (<0.001)	48

[1]Three 2-colony samples
[2]Numbers in parentheses following the residues are the numbers of samples with those values
[3]Numbers correspond to tab numbers in 1996 Bayer submission, Vol. IV:
47. Krebber, 1994f; 48. Krebber, 1994g; 49. Krieger and Riegner, 1990a; 50. Krieger and Riegner, 1990b; 51. Krieger and Riegner, 1990c; 52. Krieger and Riegner, 1990d.

Table 14. Residues of flumethrin in beeswax from bee colonies treated with 4 strips/frame at 3.6 mg flumethrin/strip[1]

Country, year	No. Colonies/ No. Samples	Treatment		Time of sample collection	Residues, mg/kg[1]	Ref.[3]
		Duration (weeks)	Period			
Germany 1986	2/4	6	early March to mid-April 1986 (before nectar flow)	April 1986	<0.015, 0.017, 0.015, 0.04	53
Germany 1987	6/3	6	early Sept. to mid-Oct. 1987	June 1988 (after early nectar flow)	<0.02, 0.04, 0.05	54
Germany 1988	4/4	20	May to Sept. 1988	Sept. 1988	0.03, 0.1 (2), 0.13	55
Switzerland	not given/13 (3 regions)	not given	not given	1993	<0.03 (4), 0.03 (2), 0.04, 0.05 (2), 0.06, 0.07(2), 0.2	45
Germany 1991	4/4	4	June 28 to July 23, 1991	August 1991	0.07, 0.1 (2), 0.15[2]	46

[1]Numbers in parentheses following the residues are the numbers of samples with those values.
[2]The treatment for these samples was with 40 strips/hive: 10 times the recommended rate.
[3]Numbers correspond to tab numbers in 1996 Bayer submission, Vol. IV:
45. Krebber, 1994d; 46 Krebber, 1994e; 53. Krieger and Riegner, 1990e; 54. Krieger and Riegner, 1990f; 55. Krieger and Riegner, 1990g.

FATE OF RESIDUES IN STORAGE AND PROCESSING

No information was provided.

Residues in the edible portion of food commodities

All the residues from supervised trials were in edible items.

RESIDUES IN FOOD IN COMMERCE OR AT CONSUMPTION

Information was provided on residues of flumethrin in the perirenal fat of animals from an Australian random survey from July 1993 to December 1995. No residues (<0.02 mg/kg) were found in the fat of 2545 pigs, 801 horses, 642 goats, 158 deer, 154 buffalo 94 game pigs, 93 kangaroos, or 27 game goats. Flumethrin is not registered in Australia for use on these animals, but data were available because multi-residue methods were used. Although flumethrin is not registered for use on sheep in Australia, one of 4675 samples of sheep fat contained a residue in the range >0.1-0.2 mg/kg. Residues were also detected in perirenal beef fat in 59,6657 samples (0.9%), distributed as shown below.

	Residue range, mg/kg					
	0.02	>0.02-0.04	>0.04-0.1	>0.1-0.2	>0.2	Total
No. of samples in range	1	16	36	5	1	59
% of 6657 samples analysed	0.02	0.24	0.54	0.08	0.02	0.9

As a follow-up, treatment histories were obtained in 26 cases. Although details of the treatments were not recorded (except that they were pour-on treatments) they were reported to have complied with GAP. Residues were detected up to 1.1 mg/kg (Table 15).

Table 15. Flumethrin residues in perirenal fat[1] of Australian cattle treated on the farm with a flumethrin pour-on formulation (Webster *et al*., 1996).

Residue range, mg/kg	Number of samples within residue range at indicated interval between treatment and slaughter							
	<2 weeks	3-4 weeks	1-2 months	3-6 months	6-9 months	9-12 months	>12 months	?
0.05-0.1	2		6		1		1	
0.11-0.2			3	3	1	1	1	1[2]
0.21-0.5		3						
>0.5		1 (0.56)	2 (0.61, 1.1)					

[1]The nature of the samples was not specified but they were presumably perirenal fat because the study was to follow up positive results in random monitoring of perirenal fat and because it is Australian regulatory practice to analyse perirenal fat (Webster *et al*., 1996).

[2]This sample was from a cow which was not known to have been treated.

NATIONAL MAXIMUM RESIDUE LIMITS

The following national MRLs for flumethrin in animal products were reported for Australia (Webster *et al*., 1996).

	mg/kg[1]	
Cattle meat	0.05	Temporary
Cattle, edible offal of	0.05	Temporary
Milks	0.05	Temporary
Horse, edible offal	0.1	
Horse meat	0.1	

[1]Assumed to be whole-product basis (not indicated otherwise).

APPRAISAL

Flumethrin, (*R,S*)-Æ-cyano-4-fluoro-3-phenoxybenzyl 3-(ß,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate, is a pyrethroid acaracide composed of a mixture of two diasterioisomers (*trans*-*Z*-1 and *trans*-*Z*-2, with an approximate ratio 55:45) formed by the reaction of 4-fluoro-3-phenoxybenzaldehyde and *trans*-(*E*)-3-[2-chloro-2-(4-chlorophenyl)vinyl]-2,2-dimethylcyclopropanecarboxylic acid chloride in the presence of cyanide. It is widely used as a topical pesticide for the control of ectoparasites such as ticks and buffalo flies on farm animals by spraying, dipping or other treatments. It was reviewed by the present Meeting for the first time. The focus was on the uses against animal ectoparasites, although flumethrin residues in honey and beeswax from supervised trials on honey bee colonies were also provided and reviewed.

The Meeting agreed that data on environmental fate were not required in relation to potential flumethrin residues in animal products from uses as an ectoparasiticide, but considered such information to be desirable for assessing the potential for undesirable environmental effects.

The mammalian metabolism of flumethrin was reported for rats and cattle. Flumethrin administered orally, i.v. and duodenally showed ester hydrolysis to 3-(ß,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylic acid (flumethrin acid, BFN 5533A) and (through the probable cyanohydrin (FCR 1271) and 4-fluoro-3-phenoxybenzaldehyde (FCR 1260) intermediates) to the other main identified metabolite 4-fluoro-3-phenoxybenzoic acid. Flumethrin acid is conjugated to form the glucuronide and the fluorophenoxybenzoic acid component is further oxidized to 4-fluoro-3-(4-hydroxyphenoxy)benzoic acid, the last two compounds being conjugated to glycine. The studies indicate substantially greater ^{14}C elimination in the faeces than in the urine from chlorophenyl-labelled flumethrin and roughly equal elimination in faeces and urine from the fluorophenyl-labelled compound, with faster elimination of the fluorophenyl label.

Although the rat metabolism studies with labelled or unlabelled flumethrin are useful for identifying metabolites and provide useful information on the mammalian metabolism of orally, i.v. or

duodenally administered flumethrin, they do not fully reflect exposure from topical application which is relevant to the approved uses on cattle, horses, goats or sheep.

A 1986 material balance and distribution study on cattle was based on the administration of fluorophenyl-labelled ^{14}C-flumethrin as a back treatment, approximately at approved rates. After 48 hours 71% of the administered dose remained in or on the skin in the application area with $\leq$10 ng flumethrin equivalents/g in the tissues and $\leq$3 ng equivalents/ml in the milk through 31 hours, demonstrating slow absorption within this short test period.

In a similar study on cattle in 1994 chlorophenyl-labelled flumethrin was administrated at approximately an approved rate intravenously as opposed to topically and samples were analysed to study metabolism. Relatively little radioactivity was eliminated within the short period of 8 hours before slaughter, but significant amounts of the administered dose (32% in a lactating cow, 13% in a steer) were detected in edible tissues in the decreasing order liver (in the cow) or muscle (in the steer), fat and kidney. Residues as mg/kg flumethrin equivalents in the tissues were highest in liver (13.4 mg/kg cow, 3.4 mg/kg steer), with 0.2-0.3 mg/kg in muscle, 0.2-0.4 mg/kg in fat and 0.3 mg/kg in milk. The liver residues suggest greater metabolic activity in the steer (lower radioactivity in the liver) than in the cow. This is reinforced by the ratios of flumethrin to BNF 5533A of 87:7 and 29:40 in cow and steer livers respectively and by the higher levels of glucuronide found in the liver and kidney of the steer. The opposite may be seen in male and female rats if flumethrin to metabolite ratios in faeces are compared: the proportion of the metabolite is higher in female faeces.

Of the measured radioactivity, 76 to 95% of the residues were identified in tissues and 68% in milk. Only flumethrin was identified in the milk but an unidentified metabolite constituted almost 12% of the milk radioactivity. BNF 5533A glucuronide was identified only in the liver and kidney. Residue levels of BNF 5533A were 1-1.5 times those of flumethrin in muscle and fat with no pronounced difference between the cow and steer. While the log P_{ow} of 6 for flumethrin indicates fat-solubility, residue levels of flumethrin *per se* from the i.v. injections in this study are comparable in the muscle and fat of both steers and cows, actually slightly higher in the muscle. However, as will be discussed later, residues from topical applications in the supervised trials were higher in the fat.

Analytical methods are available for the determination of flumethrin and flumethrin acid (BNF 5533A) in the tissues of cattle and sheep and of flumethrin in milk. Only flumethrin and, at lower levels, an unidentified metabolite were reported in milk in cattle metabolism studies. In recent analytical methods homogenized tissues are generally extracted with acetonitrile or acetonitrile/phosphoric acid solution, partitioned into dichloromethane and/or hexane, cleaned up on silica gel columns and determined by HPLC using UV detectors. In some cases the flumethrin acid metabolite is further cleaned up on C-18 solid phase cartridges after separation from flumethrin on silica gel before HPLC determination. Analysis of milk is similar, although in some cases milk solids are removed by the addition of acetone before partitioning into acetonitrile.

Multi-residue methods for organochlorine compounds have also been modified for the determination of pyrethroids, including flumethrin, in animal fat. The modified method involves the partition of rendered finely sliced fat between acetonitrile and hexane, dilution of the acetonitrile, Florisil column clean-up and determination by GLC with EC detection. Information was not sufficient for an independent estimate of a limit of determination for this method, although satisfactory recoveries were achieved at fortification levels of 0.02 mg/kg.

Generally, analytical recoveries are 80% or better by the more recent methods in tissues and milk with fortification at or near the reported limits of determination. Limits of determination of 0.005 mg/kg for flumethrin in milk, 0.01 mg/kg for flumethrin acid in milk, 0.01 mg/kg for flumethrin in

tissues, and 0.01 or 0.02 mg/kg for flumethrin acid in tissues are generally reported, depending on the method. For the most part these limits are supported by sample chromatograms from the authors' laboratories, although in some cases sample chromatograms do not convincingly support a 0.01 mg/kg limit of determination in liver and kidney.

While the reported limits of determination may be achievable in the authors' laboratories, the Meeting concluded that limits of determination of 0.01 mg/kg for flumethrin in milk and 0.02 mg.kg for flumethrin and flumethrin acid in tissues are more realistic for routine enforcement among different laboratories. However, for dietary intake estimates the use of half these levels would be appropriate where no residues are detected.

Analytical methods have also been reported for residues of flumethrin in honey and beeswax, with recoveries generally about 75% or better. The reported limits of detection and determination were 0.001 and 0.003 mg/kg for honey and 0.02 and 0.026 mg/kg for wax, and the authors' sample chromatograms were consistent with these levels.

The manufacturer's working paper considered information on the stability of residues in stored analytical samples not to be necessary and no such studies were submitted, except relevant information incidentally included in one supervised trial report which showed flumethrin residues in milk to be stable for 40 days at -18°C. On the basis of this report and the persistence of flumethrin residues in fat even in live cows, the Meeting considered that the information provided was adequate to support estimates of maximum residue levels in cattle meat (fat) and milk. The Meeting further concluded that information on the stability of flumethrin in stored samples of other tissues (liver, kidney) was needed before maximum residue levels estimated for these tissues could be recommended for use as MRLs.

Data were available on supervised trials in a number of countries of ectoparasite control in cattle, sheep or goats using a variety of flumethrin formulations, as well as on mite control in beehives.

Data on supervised trials of ectoparasite control on cattle were available from Australia, Germany, South Africa and Japan. Approved uses (including labels) were provided only for Australia (on cattle and horses). The most recent, comprehensive and best described studies of flumethrin residues in cattle from plunge dipping or pour-on applications are 1994-1995 Australian trials submitted by the Australian government, but there was no information on whether GLP was followed in them. For example, no information was provided on the interval from slaughter to analysis, and actual storage conditions were not reported although the protocol called for storage at -40°C. An exception was a GLP study to determine the potential for residues of flumethrin acid from the treatment of cattle with a flumethrin pour-on formulation.

The 1994-95 Australian studies did not include data from spray applications, which are approved in Australia, although older Australian (and other) studies submitted to the Meeting included data from some types of approved spray applications. The older studies for the most part were also not reported to have been conducted under GLP, although in many cases essential information was available to give a reasonable degree of confidence in the data. Because only Australian approved uses for ectoparasite control in cattle were available, the Meeting based its analysis of the cattle data primarily on the Australian trials. That situation was not ideal since in the most recent and best documented studies residues were determined only in fat whereas some of the older trials included analyses of fat, liver, muscle, kidney and milk.

In the 1994-95 Australian trials low residues ($\underline{\leq}$0.008 mg/kg from one dip, $\underline{\leq}$0.013 mg/kg from two dips) were reported for plunge dip treatments, except in one of 84 test animals which showed 0.04 and 0.05 mg/kg flumethrin in loin and renal fat respectively. The treatments were in accordance with

approved uses, except that the interval between the two treatments was 3 days compared to the recommended minimum of 10 days. Higher residues were reported from approved pour-on applications to a total of 56 animals, with maximum residues of 0.04 mg/kg in loin fat from one application and 0.05 mg/kg from two applications 7 days apart, as compared with an implied minimum approved interval of 14 days. The maximum residues in renal fat were 0.11 mg/kg from one treatment and 0.14 mg/kg from two applications at the 7-day interval. The combined data from dip and pour-on trials at approved rates in the 1994-95 and 1981-84 Australian trials are shown below. The numbers of samples with the same residue or within the same ranges are shown in parentheses.

Single dips

Fat <0.005 (67), 0.006, 0.007, 0.008, 0.041, 0.047 mg/kg.
Liver <0.005 (6) mg/kg.
Muscle <0.005 (5), 0.01 mg/kg.
Kidney <0.005 (6) mg/kg.

2-dips

Fat <0.005 (69), 0.009, <0.011, <0.013 mg/kg (3-day interval as compared with the approved 10-day).

Single pour-on

Fat <0.005 (24), 0.005 (9), 0.006-0.01 (11), 0.011-0.015 (13), 0.017-0.020 (6), 0.023-0.029 (9), 0.032, 0.034, 0.04, 0.042, 0.11 mg/kg. Total number = 77.
Liver <0.005 (23), 0.01 mg/kg.
Muscle <0.005 (22), 0.005, 0.01 mg/kg.
Kidney <0.005 (23), 0.01 mg/kg.

2 pour-ons

Fat 0.011-0.015 (8), 0.016-0.020 (9), 0.022-0.025 (9), 0.026-0.03 (9), 0.031-0.051 (15), 0.052-0.058 (3), 0.097, 0.14 mg/kg (7-day interval as compared with the approved 14-day). Total number = 55.

"Fat" includes renal and subcutaneous fat.
The double-underlined ranges within which the median residues fall.

In the Australian spray trials in 1981 at 0.7-2.6 times GAP rates, the residues in fat, liver, muscle and kidney (24 samples of each) were all <0.05 mg/kg.

On the basis of the single pour-on applications according to GAP the Meeting estimated an STMR of 0.01 mg/kg for the fat of meat and <0.005 mg/kg for whole meat.

As noted above, information on approved uses on cattle was provided only for Australia, but it is useful and of interest to relate the results of trials in other countries to Australian approved uses. In such trials the maximum residues from applications approximating Australian approved uses were 0.08 mg/kg (or <0.1 mg/kg depending on the study) in fat, and <0.01 to <0.1 mg/kg, again depending on the study, in liver, muscle and kidney. In one German study residues in liver were 0.03 mg/kg. While such a comparison may be questionable, it suggests that the maximum flumethrin residues in cattle are likely to be similar if approved uses in those countries are similar to those in Australia. The German studies also show that flumethrin residues in fat from pour-on applications reach their highest level after about

4 days and stay at or near that level for up to 28 days. This confirms the finding in the Australian trials.

It is clear that the potential for residues in cattle tissues is greater from approved pour-on uses than from spray or dip applications and, in contrast to metabolism studies with i.v. administration, field trials indicate that flumethrin residues from topical applications are likely to be significantly greater in fat than in other tissues. It is also of interest to note that the maximum residues of 0.11 to 0.14 mg/kg found in cattle fat in the pour-on trials are consistent with residues up to 0.2 mg/kg found in random Australian monitoring and less than some residues (as high as 1.1 mg/kg) found in follow-up investigations prompted by the finding of residues in random monitoring.

The supervised trials data are consistent with MRLs of 0.2 mg/kg in the carcase fat of cattle and 0.01 mg/kg in cattle muscle and kidney. The Meeting noted maximum flumethrin residues of 0.01 mg/kg in liver in the Australian trials, took into account residues up to 0.03 mg/kg in German trials approximating approved Australian uses and <0.05 or <0.1 mg/kg in other non-Australian trials, and concluded that prudence required a 0.05 mg/kg level for liver.

In the absence of studies of the storage stability of residues in tissues other than fat and in view of differences between the ratios of flumethrin residues in fat to those in non-fatty tissues found in metabolism studies and supervised trials, the Meeting was unwilling to recommend the use of the maximum residue levels estimated for liver and kidney as MRLs. This could be reconsidered at a future JMPR if relevant studies of storage stability with tissues other than fat become available.

The monitoring data suggest that residues in fat may occasionally exceed 0.2 mg/kg, especially from pour-on applications. For dietary intake purposes a level of 0.005 mg/kg (generally the lowest reported limit of determination) would be reasonable for flumethrin in the muscle, liver, fat and kidney of cattle.

A ratio of 1.9 (0.84 correlation coefficient) was reported for the residues in perirenal to those in subcutaneous fat arising from pour-on applications. Residues were also reported to be up to 32% lower in the fat of animals with greater fat deposits, presumably indicating fat dilution of the residues. In selected samples, analysis of extracted fat from core samples from cartons of frozen carcases correlate well with renal and loin fat samples taken at slaughter from the same animals.

Flumethrin residues in loin and renal fat from single approved pour-on applications increased rapidly from 2 days after treatment through the fourth day, then declined slowly until a second increase after 21 days, then declined gradually to 45 days. A similar pattern of two peaks was noted for two applications, although residues were higher and the second peak later owing to the second application. The pattern confirms the persistence of flumethrin in animal fat.

Supervised trials of ectoparasite control in sheep were available from Australia, South Africa and the U.K. Because information on approved uses was available only from the UK, the Meeting based its conclusions on sheep primarily on the single UK study. Sheep were dipped once (re-dipping is permitted after 14 days) approximately according to approved uses and samples of fat, liver, muscle and kidney were taken for analysis at intervals from 0.5 to 4 days after treatment. Although residues were low, they tended to be higher in subcutaneous than in omental fat. The maximum residues were 0.03 and <0.01 mg/kg in subcutaneous and omental fat respectively, 0.02 mg/kg in liver and <0.01 mg/kg in muscle and kidney.

Maximum residues in the relatively old Australian dip trials at 0.9 to 1.3 times UK approved use rates were 0.04 mg/kg in fat and <0.005 mg/kg in liver, kidney and muscle. Relatively old data were also available from Australia and South Africa from pour-on applications, but no relevant

approved uses were provided. The maximum residues found in the Australian sheep dipping trials were comparable to those found in the dip treatments of Australian cattle, and reasonably consistent with the UK dipping results when the use rates were similar. However, because only one well-documented sheep study was available which reflected approved uses, because only one dip was represented and because sheep are generally expected to have higher residues than cattle, the Meeting concluded that the data were insufficient to estimate maximum residue levels for sheep.

Data on residues in milk were available from supervised trials on cattle, sheep and goats. Data on residues in cattle milk were available from Australia, Germany, Japan and South Africa. As with cattle tissues information on approved uses was available only for Australia and the Meeting placed most emphasis on the Australian trials. Although the Australian studies were relatively old, they were for the most part acceptably documented, included pour-on and spray applications and covered a range of intervals after treatment. The maximum residues approximately reflecting Australian approved uses after various intervals were as follows.

Single Pour-on	GAP rate	Ratio to 9 h	24 h	72 h
		0.5	0.01	0.01
	0.01			
		1.0	0.04	0.02
	0.01			
		0.5	0.04	0.04
	0.02			
		1.0	0.03	0.03
	0.01			
Single Spray				
		1.0	<0.1	<0.1
		1.0	0.01 (2 applications)	
		1.3	<0.01	<0.01

The combined results from the pour-on treatments at 0.5 and 1 times the GAP rate gave the following residues at 9-72 hours: <0.01 (14), 0.01 (13), 0.02, 0.02, 0.03 (4), 0.04 (3).

The Meeting estimated an STMR for flumethrin in milk of 0.01 mg/kg.

Although no information on German approved uses was provided, two pour-on applications at approved Australian use rates resulted in maximum residues in 2 trials of 0.04 and 0.06 mg/kg after 2 days, decreasing to 0.02 and 0.04 mg/kg after 4 days and then continuing to decrease slowly.

As in the case of tissues it is clear that higher residues result from pour-on applications than from other types of application. The results suggest that multiple applications produce higher residues and point to the need for additional trials with multiple applications at approved use rates.

Supervised trials data on residues of flumethrin in sheep and goat milk were also available, but without information on relevant approved uses. At rates approved for pour-on applications to cattle in Australia, the maximum residues were 0.04 mg/kg and <0.01 mg/kg in goat and sheep milk respectively.

On the basis of the available information a maximum residue level of 0.05 mg/kg for cattle milk is reasonable, although additional data from trials with multiple treatments at approved use rates

are needed to confirm that estimate.

In addition to residues of flumethrin *per se* in cattle tissues, data were also available from one trial on residues of flumethrin acid in tissues at intervals of 1 to 35 days after the second of two pour-on applications of flumethrin at approved application rates. The maximum flumethrin acid residues, found after 2 days were 0.04 mg/kg in fat, 0.06 mg/kg in liver, 0.01 mg/kg in muscle, and 0.05 mg/kg in kidney. These indicate that the acid metabolite is less soluble than the parent compound in fat.

Honey and beeswax. Eleven supervised trials were conducted in Switzerland, the UK, and Germany (mostly Germany) to determine the potential for flumethrin residues in honey and beeswax from the treatment of bee colonies for mite control. Applications were in the form of flumethrin-impregnated strips. The trials varied in duration from 4 to 56 weeks and covered a variety of periods of honey production, including pre-winter storage periods and before or during nectar flow. At the recommended rate of 4 strips/frame (3.6 mg ai/strip) approved in the UK, no residues (<0.001 or <0.002 mg/kg, depending on the analytical method) were measured in any of the 34 honey samples analysed. The Meeting concluded that a maximum residue level of 0.005 mg/kg (limit of determination) would be suitable for use as an MRL for honey.

Residues in beeswax were <0.02 (2), 0.02 (2), <0.03 (4), 0.03, 0.04 (3), 0.05 (3), 0.06, 0.07 (2), 0.1 (2), 0.13 and 0.2 mg/kg. The maximum residues in each of the four trials were 0.02, 0.05, 0.13 and 0.2 mg/kg with a mean of 0.1 mg/kg and an estimated median of 0.09 mg/kg. In one trial with treatment at ten times the recommended rate the maximum residue was 0.15 mg/kg. Information was lacking on many aspects of the Swiss trial which gave the maximum residue of 0.2 mg/kg.

Residue Definition. The flumethrin acid metabolite BNF 5533A was found in cow metabolism studies (8 hours after the i.v. injection of flumethrin) to occur at 1 to 1.5 times the level of flumethrin in animal tissues, but was not reported in milk. The Meeting assumed that flumethrin would be of significantly greater toxicological concern than the metabolite, noted that only flumethrin *per se* was reported in milk and was the main residue in tissues (especially in fat) found in supervised trials, and concluded that flumethrin was the preferred indicator residue for regulatory purposes.

For the estimation of dietary intake, it is useful to note that metabolism studies suggest that the total residues (or flumethrin *per se*) in meat (muscle) could be similar to or slightly higher than in fat, although that did not occur in the supervised trials where flumethrin residues were higher in fat than in muscle, essentially in all instances. The total residues of flumethrin and flumethrin acid in tissues could be expected to be at most about three times those of flumethrin.

Fat-solubility and expression of residues in meat. The log P_{ow} of 6 for flumethrin indicates high fat-solubility. This is supported by a metabolism study with back treatments of a lactating cow, where measurable residues were found in renal fat but not in muscle or subcutaneous fat. Metabolism studies with i.v. dosing, however, indicate that once flumethrin residues enter the blood stream, levels of flumethrin *per se* or of total radioactivity are similar in the muscle and fat of both steers and cows. If there is a difference residues in muscle under these conditions appear to be slightly higher. The same is true for BNF 5533A, the flumethrin acid metabolite. Analytical methods are available for the determination of flumethrin residues in carcase meat or fat. Residues in edible offal can conveniently be on a whole-commodity basis.

The manufacturer expects to propose limits to the European Union for liver (0.04 mg/kg), milk (0.12 mg/kg) and fat (0.1 mg/kg), but none for muscle or kidney, since no residues were reported in these tissues in cattle or sheep. However, the procedures for sampling and analysis in the field trials and for the regulation of residues in meat (muscle) are key factors in determining how residues in meat

should be expressed.

The most relevant, recent and comprehensive supervised trials (Australian 1994-95) involved the determination of residues in fat rendered from finely sliced loin (subcutaneous) and renal fat. In the older studies, even though mean residues were at or below the limit of detection or determination, residues in the meat (muscle) of individual cows were measurable in some cases (up to 0.02 mg/kg). In older trials on cattle and sheep the type of fat was not defined, except in a 1980 South African trial where it was renal fat. No information on approved uses was provided for the older (1980-1989) trials, except those in Australia.

Since meat is often regulated at the international level on the basis of residues in subcutaneous fat, as a practical matter it is convenient to propose limits for meat on a fat basis (in the carcase fat) derived from residues in loin and subcutaneous fat found in supervised trials, noting that residues can be higher in renal than in subcutaneous fat. For these reasons the Meeting recommended that limits for flumethrin in meat be expressed on the carcase fat.

RECOMMENDATIONS

The residue levels recorded below are recommended for use as MRLs or for the estimation of dietary intakes.

Definition of the residue for compliance with MRLs and for estimation of dietary intake: flumethrin

The residue is fat-soluble.

Commodity		Recommendations, mg/kg	
CCN	Name	MRL	STMR
MM 0812	Cattle meat	0.2 (fat) V	0.01 (fat) 0.005 (whole muscle)
ML 0812	Cattle milk	0.05 F V	0.01
	Honey	0.005*	0.005

* At or about the limit of determination

FURTHER WORK OR INFORMATION

Desirable

1. Information on the stability of flumethrin residues in stored analytical samples of liver and kidney in relation to the periods and conditions of storage of the samples from supervised trials.

2. Submission of data from new supervised trials on animals expected to be available in June 1996 (Webster, *et al*., 1996).

3. Results of analyses of tissues and milk from additional supervised trials on cattle in which

multiple, especially pour-on, applications have been made in accordance with approved uses.

4. Studies on the fate of flumethrin in the environment, especially its persistence and mobility in soil.

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