PERMETHRIN

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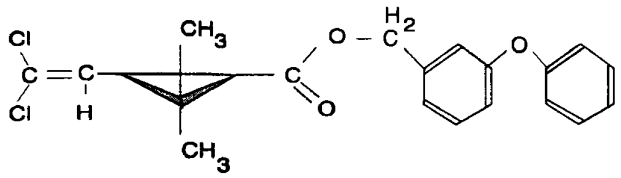
IDENTITY

Chemical Name: 3-phenoxy (±) *cis*, *trans* 3-(2,2-dichlorvinyl)-2,2-dimethylcyclopropane-1-carboxylate (IUPAC).
4-(phenoxyphenyl)-methyl (±) *cis*, *trans* 3-(2,2-dichlorethenyl)-2,2-dimethylcyclopropanecarboxylate (CAS), CAS No. 52645-53-1

Generic Name: Permethrin is an approved name.

Commercial Names: Swift, Rypospect, Flypor, Switch.

Structural formula:



Molecular formula: $C_{21}H_{20}Cl_2O_3$
Molecular weight: 391.3

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient: Permethrin 80:20 *cis : trans*
Appearance: Pale yellow crystals or yellow to brown oil.
Melting point: 34-39°C for 80:20 *cis*:*trans* mixture. Pure *cis* 63-65°C; *trans* 44-47°C
Boiling Point: 80:20 *cis*:*trans* mixture (220°C at 0.5mm Hg)
Solubility: Insoluble in water (0.2 mg/L at 30°C); soluble in hexane, benzene, chloroform, ethanol and acetone.
Partition Coefficient: n-octanol:water ($logP_{ow}$) at 20°C = 6.5
Stability: Moderately stable in the environment with a half lives of 28 days in soil and about 10 days on plants. It is stable in weak acid. Readily hydrolysed in strong acid and base.
Toxicity: The *cis* isomers are approximately 10 times more toxic in acute studies than the *trans* isomers.

RESIDUES IN FOOD AND THEIR EVALUATION

Conditions of use
The 40:60 *cis*:*trans* formulation is used mainly as an agricultural pesticide and also as an animal ectoparasiticide. The 80:20 *cis* : *trans* formulation is used as an ecto-parasiticide pour-on formulation for cattle at a dose rate of approximately 4 mg/kg BW up to a maximum dose of 1.6g per animal.

PHARMACOKINETICS AND METABOLISM

The pharmacokinetics and metabolism of orally administered permethrin in 40:60 *cis*:*trans* form has been extensively reviewed in the scientific literature and especially by a working party organised by IPCS and jointly sponsored by

UNEP, ILO and WHO (IPCS 1990). The data for farm animals is mostly associated with the administration of the 40:60 *cis*:*trans* form and limited data are available for the 80:20 *cis*:*trans* form.

The important aspect for laboratory animals is the pharmacokinetics and metabolism following oral administration, because this route is to be compared with human consumption. The pharmacokinetics in cattle should also review the fate of the drug when applied externally since this is the route of administration for the ecto-antiparasiticidal action of the drug. However, the target animals are also exposed to this compound in the 40:60 *cis*:*trans* form as a contaminant present on or in plant foods

Laboratory Animals

Rat

Excretion
Preparations of [1RS, *trans*] or [1RS, *cis*] -permethrin (^{14}C-labelled in the acid or alcohol moiety were administered orally to male rats at 1.6 – 4.8 mg/kg BW. The compounds were rapidly metabolised and almost all the radioactivity was eliminated in the urine or faeces within a few days. Within 12 days 79-82 % of the radiolabel residues of the 1RS, *trans*] form were eliminated in the urine and 16-18% in the faeces, whereas from the 1RS *cis* isomer 52-54% of the dose was eliminated in the urine and 45-47% in the faeces. The results are shown in table 1. Residues of the *trans* isomer were more rapidly eliminated than the *cis* isomer.

Metabolism
Analysis of the excreta from the above studies revealed five principle sites of metabolic attack in both permethrin isomers, namely, ester cleavage, oxidation at the *trans* and *cis* methyl of the geminal dimethyl group of the acid moiety, and oxidation at the 2′- and 4′- positions of the phenoxy group. The major metabolite from the acid moiety was chrysanthemic acid (Cl_2CA) conjugated with glucuronic acid and excreted in the urine. This accounted for 50-63% of the dose for the *trans*-permethrin and 15-22% for the *cis* form. Oxidation at either of the gem-dimethyl groups was 4.3-10.4% (*trans*) and 12.2-14.9% (*cis*) and these oxidised products were eliminated in the both urine and faeces as such or as the lactone or glucuronide. The major metabolite from the alcohol moiety was 3-(4′-hydroxyphenoxy)benzoic acid (4′-OH-PBacid) sulfate, accounting for 31-43% of the dose for the *trans* and 20-29% for the *cis*. *Cis*-permethrin also yielded 2′OH-PBacid sulfate (ca. 3%). A major metabolite was Pbacid, either free or conjugated, and accounted for 25-31% of the dose for the *trans* isomer and 6-10% for the *cis* isomer. The metabolites are listed in table 2, comparing the profile in rats with those found in bovine excreta. The residues containing radioactivity were very low in tissues other than fat. In fat there was an accumulation of the *cis* derived compounds (0.46-0.62 mg/kg) but less from the *trans* isomer (Elliott et al., 1976, Gaughan et al., 1977).

Food Producing Animals

Cattle

The studies of Gaughan et al., (1978) examined the pharmacokinetics and metabolism of the *cis*- and *trans* permethrin isomers. Four lactating cows were given an oral dose of about 1 mg/kg BW with three consecutive doses of either ^{14}C-*trans*- or ^{14}C-*cis*-permethrin labelled in either the acid or alcohol moieties. Urine, faeces, milk and plasma samples were collected at regular intervals until the cows were slaughtered at 12 or 13 days after the first dose. Tissue samples were collected for residue analysis. The amount of radioactivity in the plasma reached transient peaks shortly after dosing and then declined to low levels (< 50 μg/L). Higher blood levels were attained with the ^{14}C-*trans*-permethrin labelled in the acid moiety than the other three radiolabelled isomers (Gaughan et al., 1978). More of the *trans* isomer was excreted in the urine than the *cis* isomer. More than half of the dose of both isomers was excreted in the faeces. The results are shown in table 1. The excretion pattern for the *trans* isomer for the cows differed from that of rats and goats in that less of the isomer is excreted in the urine and considerably more is excreted in the faeces. (Gaughan et al., 1978). Almost all the administered radioactivity was recovered in the excreta within 9-10 days after the last dose. Over a 12 day test period only 0.03-0.44% of the oral dose was recovered in the milk for either isomer (Gaughan et al., 1978).

Lactating cows were treated with a pour-on preparation of 80:20 *cis*:*trans* permethrin at a dose of 8 mg/kg BW (twice the recommended dose). Plasma (3 cows) and milk samples from 5 cows were collected at 6 and 24 hours after treatment. No residues were detected (LOD 5 μg/kg) in the plasma or in the milk (Robert Young and Co. Ltd., 1984a).

The absorption of 80:20 *cis*:*trans* permethrin following topical administration to cattle was studied using five bullocks weighing 252–313 kg. They were dosed with 40 mg/kg (approximately ten times the recommended dose) poured along the back-line, and bled at regular intervals up to 168 hours after dosing. No residues of parent drug were detected (LOD 5 μg/kg) in any plasma sample (Robert Young and Co. Ltd., 1985).

Metabolism
The metabolism of permethrin in cows follows the same principle routes as that found in the rat and goat. In comparison with rats (Elliott et al., 1976, Gaughan et al., 1977), cows excrete a larger proportion of ester metabolites including the glucuronides (unique in utilising glutamic acid for conjugation) of the carboxylic acid metabolites, and more extensive hydroxylation of the *trans* methyl group and less on the phenoxy moiety. The profile of metabolites in excreta, measured as recovered radioactivity, was: permethrin 5.6% (*trans*), 9.3% (*cis*), hydroxy-permethrin metabolites, 38-40%, metabolites of the acid moiety 54-56% (of which Cl_2CA-glucuronide was 19.2% for *trans* isomer and 4.1% for the *cis*) and metabolites of the alcohol moiety were 55-61% (Gaughan et al., 1978). One of the effects of these differences is that 4'-OH-PB-acid-sulfate is a major metabolite in rats but not in cows.

The calculation of the ratio of unmetabolised permethrin to the total radioactivity residues was not possible for the edible tissues. However, permethrin residues were present in liver, fat and milk.

Goat

Excretion
Goats were treated at a dose of 0.2-0.3 mg/kg BW on ten consecutive days with ^{14}C-*trans*- and ^{14}C-*cis*-permethrin labelled in either the acid and alcohol moiety. The goats excreted most of the *trans* isomer in the urine and at least half of the *cis* isomer in the faeces (Hunt & Gilbert, 1977). The results are shown in table 1.

Milk
The amount of radiolabel appearing in the milk was <0.7% of the administered dose. A larger amount of the *cis* isomer was present as parent compound than for the *trans* isomer.

Tissues
Most of the radioactivity in the fat tissues was parent compound(s) or ester metabolites (e.g., *trans*-OH-permethrin or the glucuronide) (Ivie & Hunt, 1980).

Metabolism
The principle metabolites found in the excreta were the same as those found in bovine excreta (Ivie & Hunt, 1980).

Table 1. Excretion of radioactivity as a percentage of dose in animals after oral dosing of either *cis*- or *trans*- ^{14}C-permethrin.

Species	*Cis* Isomer		*Trans* Isomer	
	Urine	Faeces	Urine	Faeces
Rat	52-54	45-47	79-82	16-18
Cow	22-28	60-76	39-47	52-57
Goat	25-36	52-68	72-79	12-15

Table 2. Metabolites as a percentage of dose in the excreta of rats and cows after oral dosing with either *cis*- or *trans*- ^{14}C-permethrin labelled in the acid or alcohol moieties.

Metabolite	*Cis*-isomer		*Trans*-isomer	
	Rat	Cow	Rat	Cow
Permethrin	12	9	5-7	6
OH-permethrins	17-19	29	0	34
$CACl_2$ (+conjugates)	15-22	5	50-63	21
OH- $CACl_2$	12-15	13	4-10	15
PB-alcohol (+ glucuronide)	20-29	9	31-43	11
PB-acid metabolites	6-10	17	25-31	41

TISSUE RESIDUE DEPLETION STUDIES

Radiolabelled Residue Depletion Studies

The radiolabelled studies in cattle to date have been associated with the oral administration of ^{14}C-labelled permethrin and no studies are yet available for the 80:20 *cis:trans* permethrin. Four lactating cows were treated at a dose of about 1 mg/kg BW with three consecutive doses of either ^{14}C-*trans*- or ^{14}C-*cis*-permethrin labelled in either the acid or alcohol moieties. Urine, faeces, milk and plasma samples were collected at regular intervals until the cows were slaughtered at 12 or 13 days after the first dose. Tissue samples were collected for residue examination (Gaughan et al., 1978). The total residues in muscle, kidney, brain, heart and skin were all below 56 µg/kg, the LOQ for the analytical method. Residues were present in fat and liver and are shown in table 3. The residues of the *cis* isomer were higher than those for the *trans* isomer.

The total residues in milk reached maximum levels around the time of the third dose (day3). The approximate maximum levels were 260 µg/kg and 150 µg/kg for the *trans* and *cis* isomers labelled in the alcohol moiety, respectively, and 20 µg/kg and 200 µg/kg for the *trans* and *cis* isomer labelled in the alcohol moiety, respectively. The levels declined to <10µg/kg by day 12-13 except for the *trans* isomer labelled in the alcohol moiety which declined to about 50 µg/kg by day 10, the last day measurements were made for this isomer (Gaughan et al., 1978). The authors concluded that most of the residues were likely to be unmetabolised permethrin.

Table 3. Residues of ^{14}C-permethrin in µg/kg equivalents in cows after oral dosing.

Tissue	*Trans*-isomer		*Cis*-isomer	
	^{14}C in acid	^{14}C in alcohol	^{14}C in acid	^{14}C in alcohol
Kidney Fat	<35[1]	109[1]	335[1]	119[1]
Subcutaneous. Fat		<56		101
Visceral Fat	<35[1]	96[1]	202[1]	95
Liver	72 (19)	122 (83)	210 (55)	158 (81)

Footnote 1. Mostly or entirely unmetabolised parent drug.
The value in parentheses is the amount of extractable permethrin residues in µg/kg equivalents.

Radiodepletion studies are ongoing for the topical administration of an 80:20 *cis:trans* permethrin mixture as a pour-on preparation for cattle (sponsor, private communication).

Residue Depletion Studies with Unlabelled Drug

Three early studies and two recent studies are reported by the sponsor in which a pour-on preparation using 80:20 *cis:trans*-permethrin was applied to female cattle (Robert Young and Co Ltd. 1984a, 1984b, 1985, Borthwick, 1995 and Gibson, 1996). The residues of 40:60 *cis:trans*-permethrin following topical and parental administration were reviewed by JMPR (1987) and IPCS (1990).

Residues of 80:20 *cis:trans*-permethrin in Cattle

Cattle were treated with a pour-on preparation of 80:20 *cis:trans* permethrin at a dose of 8 mg/kg BW (twice the recommended dose). Plasma and milk samples were collected at 6 and 24 hours after treatment. Animals were slaughtered in treatment groups of three at 3 days and 7 days post dosing. No residues were detected (LOD 5 µg/kg) in the plasma or milk samples. No residues were detected in muscle, liver and kidney (LOD 5µg/kg) or in fat (LOD 10 µg/kg) (Robert Young and Co. Ltd., 1984a).

Thirty mixed breed female cattle about one year of age were dosed with a pour-on preparation of 80:20 *cis:trans* permethrin at a dose of 6 mg/kg BW (1.5 times the recommended dose). Groups of five heifers were slaughtered at 1, 7, 28, 42, 56 and 77 days after dosing. Tissue samples were collected and analysed for residues of permethrin by a gas chromatography technique. The residues in fat are shown in table 4. The residues persisted in all three fat types, subcutaneous (s.c.), renal and omental fat, but were not detectable in any kidney sample at any time nor in muscle and liver samples by day 28. Whereas there were no residues in the fat at 7 days post dosing in the 1984 study (see above) the residues were at their maximum levels in this study at 7 days; they were 100 ± 39, 157 ± 48 and 137 ± 41 µg/kg in s.c., omental and renal fat, respectively. Residues were only >LOQ (25 µg/kg) in one muscle sample (52 µg/kg) and in one liver sample (31 µg/kg) at day 7 in the same cow (Gibson,1996).

Table 4. Residues in the fat of heifers after treatment with a pour-on preparation of 80:20 *cis:trans* permethrin at a dose of 6 mg/kg BW.

Days after dosing	Subcutaneous fat (μg/kg)	Omental fat (μg/kg)	Renal fat (μg/kg)
1	<13, <13, <25, <13, <13	25, <25, <25, 49, <25	<25, <25, 43, <25, <25
7	120, 63, 53, 131, 135	172, 226, 136, 154, 96	144, 193, 147, 118, 81
28	31, 50, 25, 55, 80	121, 78, 149, 118, 86	146, 86, 227, 149, 120
42	<13, <25, <13, <25, 130	121, 127, 132, 129, 192	175, 211, 169,127, 241
56	41, <13, <13, <25, 95	117, 65, <13, 107, 177	110, 83, 39, 155, 216
77	<13, <13, <13, <13, <13	30, 62, 44, 36, 87	32, 44, 44, 31, 72

Note. <13 is <LOD; <25 is <LOQ.

Eight dairy cows, 500-695 kg, were treated with a pour-on preparation of 80:20 *cis:trans* permethrin at a dose of 1.6 g (2.3-3.2 mg/kg BW). Milk samples were collected twice daily after treatment up to 106 hours after dosing. A mid-sample was collected on the day of treatment (Borthwick, 1995). The individual milk samples and pooled milk samples at a given time after dosing were analysed for residues of permethrin by a gas chromatography method. The results are shown in table 5. The dose used is that recommended by the sponsor but because of the high weight of the dairy cows the dose is much lower than 4 mg/kg B.W. recommended for lighter animals.

Table 5. Residues in milk samples (μg/kg) after treatment of dairy cows with 1.6 g of a pour-on preparation of 80:20 *cis:trans* permethrin.

Cow	Hours after Dosing											
	0	1	6	10	25	34	49	58	73	82	97	106
1	<2.5	<2.5	<2.5	6.1	7.1	11.3	<5.0	9.5	10.0	5.2	<5.0	<2.5
2	<2.5	<2.5	<2.5	<2.5	<2.5	<5.0	<2.5	5.4	<5.0	<5.0	<2.5	6.7
3	<2.5	<2.5	<2.5	<2.5	<2.5	<5.0	<2.5	<5.0	<2.5	<2.5	<2.5	<2.5
4	<2.5	<2.5	<2.5	<5.0	<5.0	<5.0	<2.5	<5.0	<5.0	<5.0	<2.5	<2.5
5	<2.5	<2.5	<2.5	6.7	8.4	10.6	6.5	11.8	11.2	8.1	6.3	<2.5
6	<2.5	<2.5	<2.5	<2.5	<2.5	<5.0	<2.5	<5.0	<2.5	<2.5	<2.5	10.0
7	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5
8	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5
Pooled	<5.0	<5.0	<5.0	<5.0	3.5	6.7	4.4	6.2	2.6	5.0	<5.0	2.9

Note. The LOQ = 5μg/kg; the LOD = 2.5 μg/kg

Residues of 40:60 *cis:trans*-permethrin in Cattle

Oral Administration. Groups of three cows were dosed orally with 40:60 *cis:trans* permethrin at rates of 0.2, 1, 10, 50 or 150 mg/kg BW for 28-31 days. Mean plateau levels in whole milk were <10 μg/kg at the lowest dose and 300 μg/kg at the highest dose. The residues in milk from the highest dose treatment declined to <10 μg/kg 5 days after dosing. The cattle were sacrificed at the end of the dosing period and residues of permethrin in perirenal fat were <10-40 μg/kg and 2800-6200 μg/kg for the lowest and highest doses, respectively (Edwards and Iswaran, 1977).

Topical Administration. Cows were given six whole body sprays of 1g permethrin per cow at 14 day intervals and also exposed to a self-oiler containing a solution of 0.3 g permethrin/litre. The cows were housed in premises that were sprayed six times at 0.06 g per square meter at 14 day intervals. This treatment is almost certainly at the high end of normal husbandry practice. The cows were sacrificed 5 days after the last topical dose. Residues in muscle, liver and kidney were <10 μg/kg, 100 μg/kg in intestinal fat and 40 μg/kg in subcutaneous fat (Ussary and Braithwaite, 1980).

BOUND RESIDUES AND THEIR BIOAVAILABILITY

The extractable and non-extractable residue portions of ^{14}C-permethrin in edible tissues were measured only in bovine liver by Gaughan et al. (1978). Using the results for the extractable fractions shown in table 3 the non-extractable fractions in liver at 12-13 days after initial oral administration of ^{14}C-permethrin are shown in table 6. The results were similar for the *cis* and *trans* isomers although the nature of the non-extractable residues was not investigated. There was accumulation of non-extractable residues in the liver particularly if the label was in the acid moiety. The rapid metabolism of permethrin in the liver may be followed by either the smaller molecules being incorporated into other molecular components of the liver or a very strong binding of the metabolites to the cellular components. There is no information on the bound residues of the 80:20 *cis:trans* permethrin preparation.

Table 6. The non-extractable residues in bovine liver after oral administration of ^{14}C-permethrin isomers labelled in the acid or alcohol moiety.

Metabolite	Total Residues (µg/kg)	Extractable (µg/kg)	Non-extractable (µg/kg)	% Non-extractable
Trans acid ^{14}C	72	19	53	74%
Cis acid ^{14}C	210	55	155	74%
Trans alcohol ^{14}C	122	83	39	32%
Cis alcohol ^{14}C	158	81	77	49%

METHODS OF ANALYSIS

Two reports have been submitted by the sponsors; Hanif, Z.P. (1995a and1995b). In addition an Expert Report, produced as part of a Codex submission, includes comments on the analytical methodology.

Bovine Tissue

Method Summary. Samples were extracted in boiling hexane/acetone and subjected to various solvent partitions before further clean-up on a florisil column and gas chromatographic analysis with an electron capture detector.

QA System. No mention was made of GLP, NAMAS, or any other system in the documentation.

Matrices. The assay was applied to bovine muscle, liver, kidney and fat.

Accuracy/Recovery. Three fortification concentrations were used for recovery determinations, 25.4, 50.8 and 101.6 µg/kg. For muscle the recoveries and coefficient of variation (CV), at each respective level, were 85.5% (17.0%), 85.4% (13.2%) and 85.7% (14.1%). Similarly, for liver, the recoveries were 109.2% (13.9%), 105.2% (9.1%) and 106.9% (10.6%). For kidney tissues, the recoveries were 105.0% (10.2%), 91.6% (7.4%) and 88.4% (13.9%). For fat, the recoveries were 76.2% (13.9%), 103% (12.4%) and 78.1% (18.6%). (n=6, at each fortification level).

Linearity. The linearity of response of the detector was assessed with standard solutions over the range of 2-500µg/l. The units of the graph of the regression analysis are not clear and, therefore, it is difficult to establish linearity at the lower range.

Sensitivity. Fortifying blank tissue with 12.7 µg/kg of permethrin gave recoveries of 100.7% (muscle; n=3), 115.9% (liver; n=3), 101.6% (kidney; n=3) and 112.7% (fat; n=3). The sensitivity was defined as 12.7 µg/kg.

Specificity. Blank tissue samples were extracted and shown to be free of interfering peaks.

Conclusion. The sponsor method has not been validated to modern standards according to the data provided. Similar analytical methodology for determination of permethrin in bovine tissues reported in the literature has been collaboratively tested.

Bovine Milk

Method Summary. Milk samples were extracted with hexane, cleaned-up with solvent elution from a florisil cartridge and subjected to gas chromatographic analysis using an electron capture detector.

QA System. No mention was made of GLP, NAMAS, or any other system in the documentation.

Accuracy/Recovery. Four fortification concentrations were used for recovery determinations, 4.95, 9.9, 19.8 and 49.5 µg/l. Recoveries and coefficient of variation (CV) were, respectively (lowest level first), 85.1% (7.9%), 73.2% (14.6%), 82.1% (15.8%) and 88.0% (12.6%). (n=6 at each level).

Linearity. The linearity of detector response was examined with standards over the range of 2-500 µg/kg.

Sensitivity . Fortifying blank milk with 2.48 µg/l permethrin gave a mean recovery of 97.5% (n=3). The sensitivity was defined as 2.48 µg/kg

Specificity. Blank milk samples were extracted and shown to be free of interfering peaks.

Conclusion. The method has not been validated to modern standards according to the data provided.

APPRAISAL

Important data are missing. In particular, the toxicity data on a different isomer ratio and a radiodepletion study using the proposed formulation(s). The majority of the older data has been submitted for the 40:60 *cis:trans* permethrin preparation. This was extensively reviewed by JMPR and the IPCS. An ADI of 0-300 μg/60 kg person was established in 1987. MRLs were recommended for a variety of plant foods but not for meat and milk because of insufficient data. However, the sponsor is submitting data for the 80:20 *cis:trans* permethrin preparation that it has developed and is a more toxic and more active mixture than the 40:60 *cis:trans* permethrin. The *cis* form is much more active and more toxic than the *trans* and thus ADIs and MRLs may be different for the two preparations.

The residue depletion data using radiolabelled permethrin is weak for both preparations. In the case of 40:60 *cis:trans* permethrin much of the information is obtained following oral treatment with only one study where the animals and their premises were treated with a large excess of the recommended dose. There is virtually no information on the nature of the total residues in edible tissues or milk for either preparation, except they do appear to be at low levels. This information would assist in choosing a Marker Residue. The Committee was made aware of an ongoing radiodepletion study for the 80:20 *cis:trans* permethrin preparation.

The studies with unlabelled permethrin using a pour-on preparation indicate that residues as the sum of the *cis* and *trans* parent isomers are almost not detectable in muscle, liver and kidney at doses 1.5-2 times higher than the recommended dose. In the most recent residue study the residues persisted in all three fat types, subcutaneous (s.c.), renal and omental fat. This is in contrast with the 1984 study where no residues were detected in the fat at 7 days post dosing, while the residues were at their maximum levels in this 1996 study (100 ± 39, 157 ± 48 and 137 ± 41 μg/kg in s.c., omental and renal fat, respectively). Residues were only above the LOQ (25 μg/kg) in one muscle sample (52 μg/kg), and in one liver sample (31 μg/kg) at day 7 in the same cow (Gibson, 1996). Residues were not detectable in any kidney sample at any time nor in muscle and liver samples by day 28. It is not clear why there are residues in the fat of one study and not the other. The older studies did not find residues in the milk after topical administration but the new study found low concentration of permethrin residues in the milk of 4 of the 8 cows treated with the pour-on preparation. The Committee should consider the two new GLP compliant studies the more reliable.

If an ADI is established and the majority of the metabolites can be shown to have very low toxicity then practical MRL for the parent drug could be recommended in fat. Otherwise if the metabolites are toxic or their toxicity is unknown no MRL can be recommended until the ratios of MR to TR are established in the edible tissues of cattle. No information is yet available on the nature of the bound residues.

The analytical methodology is satisfactory for measuring the residues of parent drug.

MAXIMUM RESIDUE LEVELS

JMPR (1987) established an ADI in 1985 of 0-50 μg/kg BW for the 40:60 *cis:trans* permethrin formulation. The Committee concluded that the available JMPR database was not adequate to assess the toxicity of the 80:20 mixture proposed for use as a veterinary drug. In the absence of an ADI, the Committee was unable to recommend MRLs for the 80:20 *cis:trans* mixture of permethrin.

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