DELTAMETHRIN

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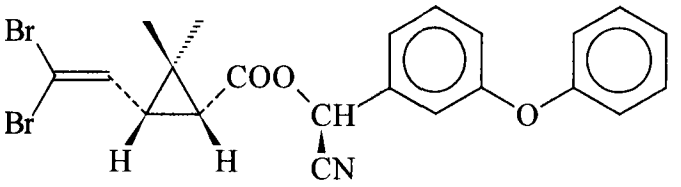
IDENTITY

Chemical name: S-cyano-3-phenoxybenzyl-cis-(1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxylate

Synonyms: RU 22974, Decamethrin, BUTOX®

Structural formula:



Molecular formula: $C_{22}H_{19}Br_2NO_3$

Molecular weight: 505.2

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient: deltamethrin

Appearance: white crystalline powder

Melting point: 98 - 101°C

Solubility: insoluble in water (<0.002 mg/kg)
soluble in acetone, DMSO, DMF, benzene, xylene, cyclohexanone, HMTP, ethyl acetate, THF, dioxan, acetonitrile (90 g/L); slightly soluble in ethanol, isopropanol,

Optical rotation: $[\alpha]_D$ +61° (c = 40 g/L, benzene)

Stability: Stable in acidic and neutral solutions. Unstable in alkaline solutions. Stable at 40°C in the dark and at room temperature in light.

RESIDUES IN FOOD AND THEIR EVALUATION

CONDITIONS OF USE

General

Deltamethrin is a synthetic insecticide belonging to the synthetic pyrethroid family and used particularly for dipteran flies and Mallophaga. It is the pure form (>99%) of one of eight possible diastereoisomers of α-cyano-3-phenoxybenzyl-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxylate. It is a neurotoxic agent that is widely

used in plant agriculture against insecticides. The ADI allocated by JMPR (1990) is 0 -10 µg/kg BW per day. It is authorised for veterinary use as an ecto-parasiticide in a number of countries. Withdrawal times vary between 0 and 10 days.

Dosage

Deltamethrin is prepared as a solution and used externally as a dip, spray or pour-on preparation for cattle, sheep, pigs, poultry and salmon.

PHARMACOKINETICS AND METABOLISM

General Comments on the Pharmacokinetics of Deltamethrin

The important aspect for laboratory animals is the pharmacokinetics following oral administration, because this route is to be compared with human consumption. The pharmacokinetics in the target animals also reviews the fate of the drug when applied externally to the animals, since this is the route of administration for the ecto-antiparasitic action of the drug. However, the target animals are also exposed to this compound as a contaminant present on or in plant foods. This aspect was covered by JMPR (1990).

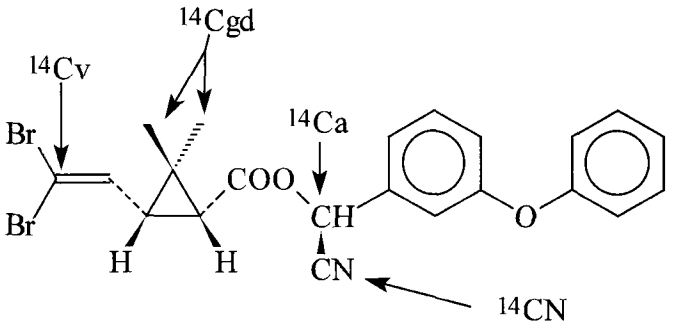
Pharmacokinetics in Laboratory Animals

Rats

The pharmacokinetics of deltamethrin following oral administration is reported in the open literature for both rats (Ruzo *et al.*, 1978) and mice (Ruzo *et al.*, 1979).

Male rats, 140 - 160 g, were dosed orally at 0.64 - 1.6 mg/kg BW with three differently labelled preparations of [^{14}C]-deltamethrin. The ^{14}C labels were placed at positions indicated in Figure 1 and each compound identified hereafter as ^{14}Cv, ^{14}Ca or ^{14}CN. Rats were also dosed with the 1RS-trans-^{14}Cv- isomer of deltamethrin. The excretion pattern was similar to that for the ^{14}Cv-deltamethrin.

Figure 1. Positions of the radiolabel in deltamethrin metabolite studies



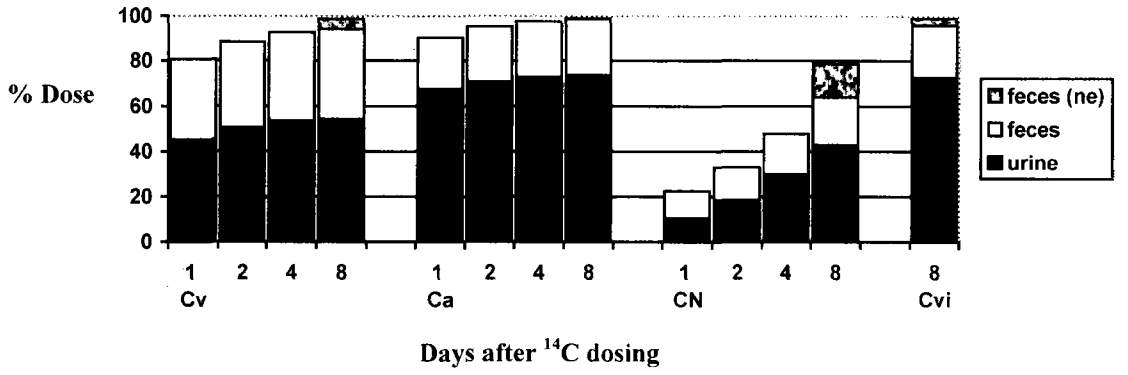
Urine, faeces and expired CO_2 were collected for 2 - 8 days. No radiolabelled CO_2 was expired and the cumulative totals for each labelled compound are shown in Figure 2. The excretion of radioactivity into the urine was greater than in the faeces and indicates that the drug was readily absorbed. The radiolabels at ^{14}Cv and ^{14}Ca were very rapidly excreted in the first day and almost completely excreted after 8 days. This contrasts with the excretion pattern for the ^{14}CN label where there was a more gradual excretion and <80% was excreted after 8 days. This difference is caused by the metabolism of deltamethrin and suggests that the metabolites containing the ^{14}CN label are incorporated into less readily excreted components. This was also supported by the distribution of the three different radiolabelled

deltamethrins in tissues collected at 8 days after dosing. The concentration of ^{14}C as deltamethrin equivalents was higher for the ^{14}CN label in most of the tissues and especially in bone, intestine, muscle, lung, heart, skin, spleen, stomach and testes. The differences were less marked in fat, blood, brain, kidney and liver.

Mice

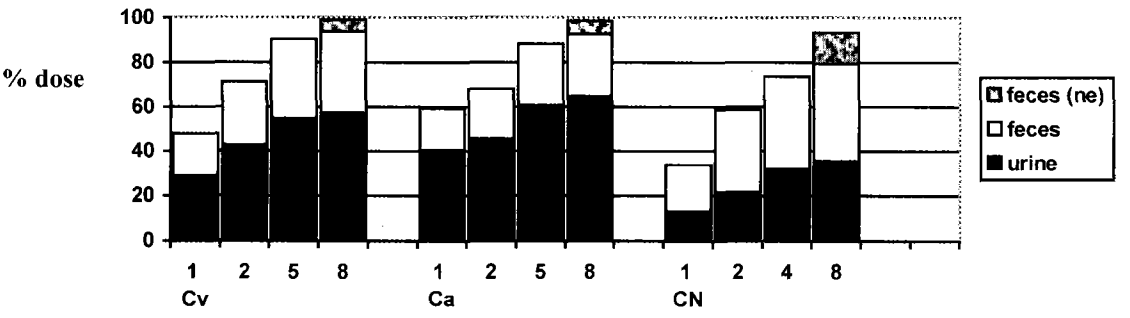
Male mice (18 - 20g) were orally dosed with the same three ^{14}C-radiolabeled deltamethrin compounds in a similar pharmacokinetics study to that employed for the rat studies discussed above (Ruzo *et al.*, 1979). The excretion of the same three specifically labelled compounds is shown in Figure 3.

Figure 2. Percent of radiolabelled dose excreted in rats.



Cv = ^{14}Cv –deltamethrin at 0.9 mg/kg BW; Ca = ^{14}Ca-deltamethrin at 1.6 mg/kg BW; CN = ^{14}CN-deltamethrin at 0.64 mg/kg BW; Cvi = 1RS-^{14}Cv-deltamethrin at 0.94 mg/kg BW; faeces (ne) is the total of non-extractable ^{14}C in the faeces over the 8-day period.

Figure 3. Percent of radiolabelled dose excreted in mice.



Cv = ^{14}Cv –deltamethrin at 4.4 mg/kg BW; Ca = ^{14}Ca-deltamethrin at 1.7 mg/kg BW; CN = ^{14}CN-deltamethrin at 2.2 mg/kg BW; faeces (ne) is the total of non-extractable ^{14}C in the faeces over the 8 day period.

The distribution of residues in the tissues was similar in both rats and mice for each of the three separately labelled deltamethrins.

No measurements were made of the bioavailability, absorption and blood pharmacokinetics in either rats or mice.

Pharmacokinetics in Food Animals

Cattle

Two studies, using the same cow for each study, was carried out to measure the pharmacokinetics parameters for both oral and dermal application of ^{14}Ca-deltamethrin [^{14}C-benzyl-deltamethrin, see Figure 2], (Dowling *et al.*, 1979). The radiochemical purity was ≤ 98.9%. A lactating cow weighing 350 kg was dosed intrarumenally with 0.27 g of ^{14}Ca - deltamethrin. Blood, milk, faeces and urine were collected over a 6 or 10 day period after dosing. Over a 6-day period 51% and 28% of the dose were excreted into the faeces and urine respectively. The concentration of radiolabel in the blood and whole milk were similar, reaching peak values within 24 hours and declining to < 1 µg/kg in 5 - 8 days with half lives of <1 day. The majority (95%) of the radioactivity in milk was in the fat phase, of which 89% was radiolabelled parent drug.

Forty-nine days after the intrarumenal administration, 0.21 g of ^{14}Ca-deltamethrin was applied topically to the cow. The dose was in a 1L solution and applied using a brush to paint the hair of the cow but not to the udder. Blood and milk were collected over a 10-day period and hair samples were taken for 45 days post-dosing. No measurements were made on excreta. The concentrations of radiolabel in the blood and whole milk were again similar, reaching peak values within 2.5 days and declining to < 1 µg/kg in about 9 weeks, with half lives in milk and butterfat of 4.3 and 4.4 days, respectively. The majority (95%) of the radiolabel in milk was contained in the fat phase. The radiolabel, probably as intact ^{14}Ca-deltamethrin, remained above 1mg/kg in the hair for approximately 75 days around the head and for about 100 days on the body hair. The mechanism of absorption of the drug from the coat was not clear but was most likely by ingestion through the cow licking herself.

A more recent study in two lactating cows provides more information on the absorption of the residue following a topical application in which the cows were not allowed to lick the application sites (Whalen, 1995). A 2.0% deltamethrin cattle pour-on formulation containing either ^{14}Ca-deltamethrin or ^{14}Cgd-deltamethrin (see Figure 1)) was administered topically to a dairy cow for three consecutive days. One cow received 1.47 mg/kg BW/d and 44.5 µCi/kg/d of ^{14}Ca-deltamethrin and the other cow received 1.50 mg/kg BW/d and 46.4 µCi/kg/d of ^{14}Cgd-deltamethrin. The radiochemical purity for both compounds was > 96%. The high dose level, about four times the recommended dose rate, was necessary to allow accurate evaluation of the extent of absorption and to facilitate metabolite identification. The doses were administered to the skin within an enclosure encircling the lumbar region of the back. The dose site was covered with a non-occlusive cover. Blood samples were collected pre-dose, at 1, 6, and 12 hours after the first dose, immediately before the 2nd and 3rd dose applications, and at sacrifice. Milk, urine, and faeces were collected twice daily (a.m. and p.m.). The animals were sacrificed approximately 24 hours after the last dose application and tissue samples were collected. Samples were analysed for radioactivity.

The total recovery of radioactivity from the cow treated with ^{14}Ca-deltamethrin was 80% that of the administered dose. A majority of the dose was recovered in the skin wash and wipe (48%) and in the dose enclosure (18.9%). The skin at the dose site contained 10.3% of the administered dose. Excretion of radioactivity in the faeces accounted for 0.6% of the administered dose and urine accounted for 0.3%. Less than 0.01% of the administered radioactive dose was recovered in the milk, bile, or tissues collected. The radioactivity was well contained within the dose site because only 0.51% was recovered in a wash of the area surrounding the dose application site, 1.95% in the non-occlusive cover and 0.06% in the stall wash and wipe.

For the cow treated with ^{14}Cgd-deltamethrin, the total recovery of radioactivity was 85% that of the administered dose. A majority of the dose was recovered in the skin wash and wipe (36%) and in the dose enclosure (37%). The skin at the dose site contained 10.1% of the administered dose. The excretion of radioactivity in faeces and urine accounted for 0.2% and 0.5% of the administered dose, respectively. Less than 0.01% of the administered dose was recovered in the milk or in the bile and tissues collected at sacrifice. The radioactivity was well contained within the dose site because only 0.5% was recovered in a wash of the skin surrounding the dose application site, 1.1% in the non-occlusive cover, and 0.1% in the stall wash and wipe.

The results were similar for both ^{14}Ca-deltamethrin and ^{14}Cgd-deltamethrin and indicate that at least 11% of the radioactive dose was absorbed and that about 70% of the administered dose remained at the dose application site. No metabolism of deltamethrin was observed in the skin at the dose site because essentially all radioactivity (greater than 95%) found in skin was unchanged ^{14}C-deltamethrin. Data for blood levels of radioactivity indicate that the radioactivity is rapidly absorbed and transported systemically. However, the blood concentrations remain low

throughout the study, with values of 1 and 4 µg/L for ^{14}Ca-deltamethrin and ^{14}Cgd-deltamethrin, respectively, at 1 hour post dose and less than 1 µg/L for either radiolabelled deltamethrin at 12 hours post dose.

Radioactive residues were low for all tissues analysed, ranging from 1 µg/kg in muscle to 13 µg/kg in liver. No radioactivity was detected in the blood collected at sacrifice. Whole milk contained up to 2 µg/L deltamethrin equivalents and the radioactivity was located in the cream and not in the skim milk.

Swine and Sheep

No pharmacokinetics studies were carried out.

Chickens

The fate of deltamethrin in laying hens, after both topical and oral dosing, has been determined in a study performed to GLP (Whittle, 1997). ^{14}Ca-deltamethrin and ^{14}Cgd-deltamethrin were administered, either topically or orally, to four individual groups of hens, six hens in each group, once daily for three consecutive days at a nominal dose level of 0.15 mg/kg BW. Birds were sacrificed approximately 23 hours after the final dose administration.

After topical application of ^{14}Cgd-deltamethrin, between 32% and 62% of the dose was recovered from the application site feathers and between 3.0% and 12.6% was found on the application site dressings. Radioactivity in the excreta accounted for between 1.2% and 3.7% that of the total applied dose. Concentrations of radiolabelled residues in eggs were below the LOD (1.0 µg/kg). Concentrations of radiolabelled residues in tissues remote from the application site were highest in the liver (5.0 - 17.5 µg/kg), followed by whole blood (1.1 - 3.5 µg/kg) and skin/fat (2.0 - 6.4 µg/kg), respectively. Residues in muscle samples were at or below the LOD while plasma concentrations were between 1.1 µg/kg and 3.5 µg/kg.

Similarly, for hens dosed topically with ^{14}Ca-deltamethrin, between 41% and 53% of the administered dose was found on the application site feathers and 1.9 - 8.3% found on the dressings. Radiolabelled residues in excreta accounted for between 1.0% and 2.5% of the total dose whereas levels of residues in eggs were below the LOD (1.0 µg/kg). Concentrations of radiolabelled residues in the tissues were highest in the liver (1.4 - 5.6 µg/kg), followed by whole blood (0.5 - 1.2 µg/kg) and skin/fat (1.0 - 19.7 µg/kg). Residues in muscle samples were at or below the LOD. Levels of radiolabelled residues in plasma were 0.5 - 1.4 µg/kg.

After oral administration of the labelled compounds, 73 - 99% of the total radioactivity was recovered, of which radioactivity in the excreta accounted for a mean of 95% of the administered ^{14}Cgd-deltamethrin and 84% of the administered ^{14}Ca- dm, respectively. Concentrations of radioactivity in eggs were below the LOD (3.8 µg/kg). Radiolabelled residues were present in the liver, whilst in the remaining tissues they were below the LOD. The concentration of radiolabelled residues in plasma were 0.6 - 15.3 µg/kg for ^{14}Cgd-deltamethrin but were <0.42 µg/kg (LOD) for the ^{14}Ca- deltamethrin.

Salmon

55 Atlantic salmon (140 ± 26 g), maintained at 12°C in sea water, were dipped for 30 min. in sea water containing 5 µg/L of a 1:1 mixture of ^{14}Cgd-deltamethrin and ^{14}Ca- deltamethrin. The fish were sampled between 1 hour and 10 days. In another study 13 salmon, similarly maintained, were administered the radiolabelled mixture as an intravascular dose of 0.25 mg/kg BW. The drug was absorbed after the dip treatment and residues were present in the tissues. The distribution of residues was followed after the parental administration and a tentative half-life of in blood was calculated as 54 hours (Horsberg and Ingebrigtsen, 1998).

Metabolism in Toxicological Test Species

Rats

The metabolic pathway of deltamethrin in rats was based on identified metabolites with support, by analogy, with permethrin metabolism in rats (Gaughan et al., 1977a). The pathways involved in rat metabolism of the deltamethrin isomers are similar to those utilised for other pyrethroids in many segments of the ecosystem (Elliott, 1977; Gaughan *et al.,* 1977a, b; Miyamoto, 1976).

Male rats, 140 - 160g, were dosed orally at 0.64 - 1.6 mg/kg BW with three labelled ^{14}C-deltamethrins. Figure 1 shows the positions of the radiolabel in ^{14}Cv-, ^{14}Ca - or ^{14}CN-deltamethrins used in this study (Ruzo *et al.*, 1978). The metabolites were identified by a series of TLC separations, combined with autoradiography using authentic standards. A portion of an oral dose was excreted in the faeces without metabolism. Since there is no significant production of expired $^{14}CO_2$, the pathways did not include extensive fragmentation of the acid and alcohol moieties. The principal mechanisms of metabolism were ester cleavage and oxidation at the 4'-position of the *m*-phenoxyphenyl- moiety. Additional minor oxidation sites were at the 5 and 2' positions of the *m*-phenoxyphenyl moiety and on the methyl group *trans* to the carboxyl group of the acid moiety. The ester metabolites did not form conjugates but the corresponding acids underwent extensive conjugation at both the phenolic hydroxyl and carboxylic acid groups.

The acid moiety was rapidly excreted, principally as the glucuronide with smaller amounts free acid and the glycine conjugate. The *trans*-hydroxymethyl derivative was also excreted as free acid and as the glucuronide. All major metabolites of the aromatic portion of the alcohol moiety were rapidly excreted and probably arose from ester cleavage of deltamethrin or its ester metabolites, conversion of the released cyanohydrins to the aldehydes which rapidly gave the corresponding acids, and conjugates of these acids. 3-Phenoxybenzoic acid was excreted either unconjugated or as their glucuronide and glycine conjugates. The major metabolite, the sulfate of 4'-hydroxy-3-phenoxybenzoic acid, was probably formed by hydroxylation of the phenoxy group and ester cleavage, in an undetermined sequence, followed by oxidation to the benzoic acid and sulfate conjugation. Cleavage of the deltamethrin ester group led to release of cyanide which was converted mainly to thiocyanate and a small amount of 2-iminothiazolidine-4-carboxlylic acid, the latter via reaction with cystine and related substances (See Casida, et. al)

The slow release of thiocyanate from the body was due in part to selective tissue retention. The localisation pattern of ^{14}C from ^{14}CN-deltamethrin was probably a characteristic of thiocyanate localisation rather than an indication of the site of deltamethrin metabolism.

Mice

Male mice (18 - 20 g) were orally dosed (Ruzo *et al.*, 1978) with the same three ^{14}C-radiolabeled deltamethrin compounds in a similar pharmacokinetics study to that for rats (Ruzo *et al.*, 1979, *vide supra*). The identification of the metabolites was by methods similar to those used in the rat study. Two factors contributed to the rapid detoxification of deltamethrin in mice: the relevant esterases were present in many tissues and the oxidases in at least liver microsomes. Deltamethrin metabolism and the resulting detoxification in mice involved 4 sites of oxidative attack (trans methyl group of the acid moiety and 2', 4', and 5 positions of the *m*-phenoxyphenyl moiety), hydrolysis, and a variety of conjugation processes. Mice excreted less unmetabolised deltamethrin than rats (Ruzo *et al.*. 1978), suggesting a more efficient absorption and/or metabolism. Whereas rats hydroxylated deltamethrin predominantly at the 4' position, mice produced considerable amounts of the *trans*-2'- and 5-hydroxy derivatives. Portions of the deltamethrin and 4'-hydroxydeltamethrin were detected as the α-R-epimers probably due to an artefact resulting from isomerisation of the proton α- to the cyano-group (Ruzo *et al.*, 1977. 1978) during sample handling. The acid moiety was rapidly excreted as the glucuronide with smaller amounts of free and the glycine conjugate. The *trans* hydroxymethyl derivative was also excreted free, as well as the glucuronide and the sulfate conjugate. This sulfate conjugate was not detected in rats.

Deltamethrin hydrolysis yielded phenoxybenzylcyanohydrin (Shono *et al.*, 1979), which readily degraded to 3-phenoxybenzaldehyde and HCN (Ruzo *et al.*. 1977). The metabolites of the benzyl alcohol moiety formed from 3-phenoxybenzaldehyde generally follow the same pathways in mice as in rats (Ruzo *et al.*, 1978) with some important exceptions. Extensive conjugation of 3-phenoxybenzoic acid with taurine was found only in mice (Hutson and Casida, 1978) and only mice excreted glucuronides of 4'-hydroxyphenoxybenzyl alcohol and 5-hydroxy-3-phenoxybenzoic acid. Mouse excreta contained 3-phenoxybenzaldehyde and 3-phenoxybenzyl alcohol and its glucuronide, not present in the excreta of rats. Also, the aldehyde metabolite appeared to be less easily oxidized in mice than in rats, so that

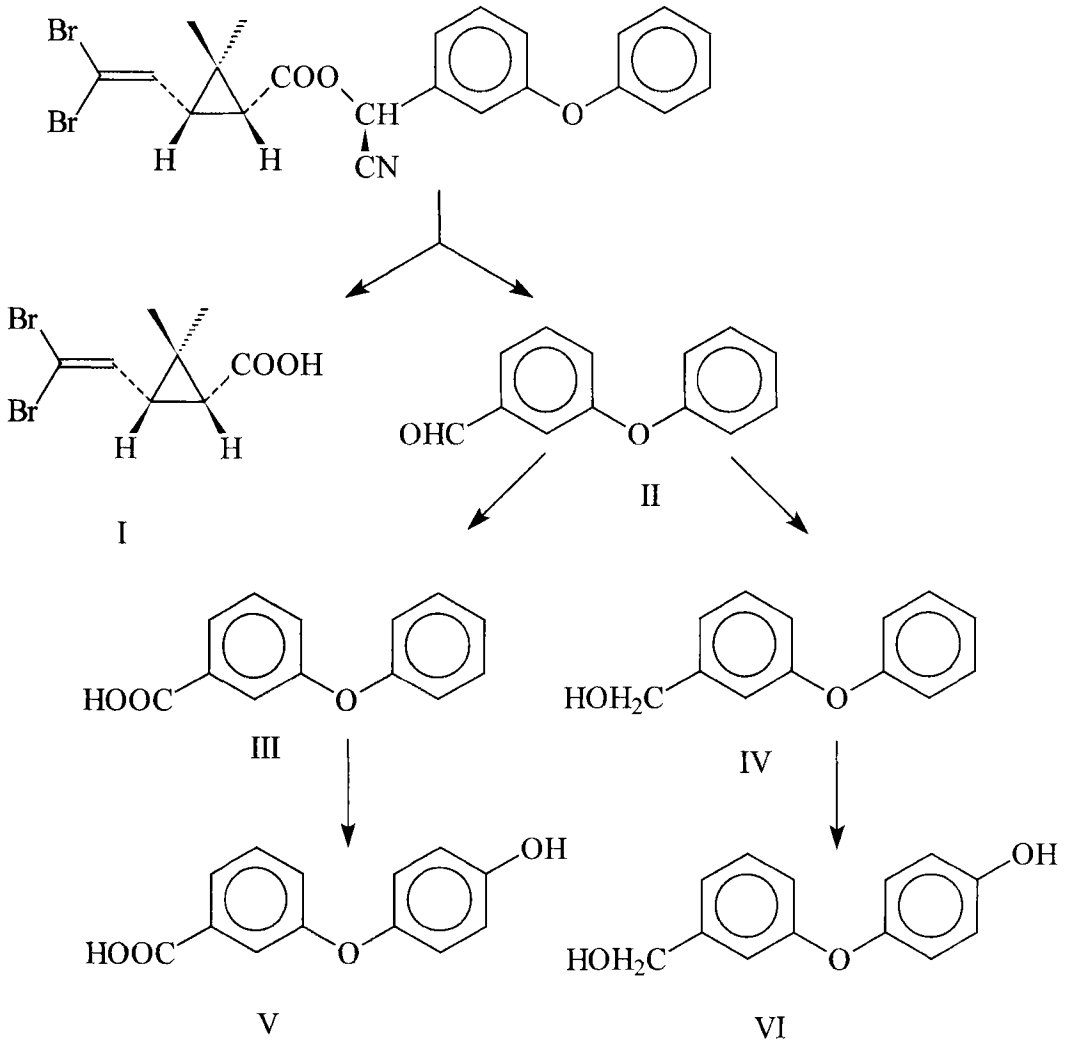
some was excreted *per se* and a portion was also reduced to the benzyl alcohol. Whereas rats converted HCN into thiocyanate and iminothiazolidine carboxylic acid, only thiocyanate was obtained by metabolism of HCN in mice.

Metabolism in Food Animals

Cattle

The metabolism of deltamethrin in farm animals is extensive and this, associated with the rapid degradation and clearance of the drug, presents a difficult challenge to identifying the biotransformations that do take place. Akhtar (1984) investigated the metabolism *in vitro* using bovine and chicken liver enzyme preparations incubated with either ^{14}Cgd-deltamethrin or ^{14}Ca-deltamethrin. Using chromatography and mass-spectrometry he was able to identify 3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxlyic acid (Br_2CA)(I), 3-phenoxybenzaldehyde (II), 3-phenoxybenzoic acid (III), 3-phenoxybenzyl alcohol (IV), 3-(4-hydroxyphenoxy)benzoic acid (V) and 3-(4'-hydroxyphenoxy)benzyl alcohol (VI). The metabolic pathway proposed for bovine and chicken liver metabolism is shown in Figure 4.

Figure 4. The biotransformation of Deltamethrin in *in vitro* liver preparations cattle and poultry.



A 2.0% deltamethrin cattle pour-on formulation, containing either ^{14}Ca or ^{14}Cgd-deltamethrin,, was administered topically to dairy cows for three consecutive days (Whalen, 1995) (see Pharmacokinetics section for detail). The liver, kidneys, renal fat and cream were analysed to determine the nature of the radioactive residues. No individual radioactive metabolites, extracts, or residual radioactivity accounted for more than 10 µg/kg deltamethrin equivalents. ^{14}C-Deltamethrin was the primary radioactive component in the renal fat and cream accounting for 48.4% (4 µg/kg) and 42.1 (4 µg/kg) % of total residues, respectively, for ^{14}Ca-deltamethrin and for 59.4% (7 µg/kg) and 54.7% (5 µg/kg) of total residues, respectively, for ^{14}Cgd-deltamethrin. Little, if any, ^{14}C-deltamethrin was found in the liver and kidney, indicating that considerable metabolism occurred in these tissues. Polar metabolites, including N-(3-phenoxybenzoyl)-L-glutamate, were found in the liver (31% of total residues) and kidney (33% of total residues) of the ^{14}Ca-deltamethrin treated cow, and up to seven metabolites (including trace amounts of Br_2CA) were found in the and kidney tissue from the ^{14}Cgd-deltamethrin treated cow. Residual radioactivity that remained in liver and kidney tissues after extraction with organic solvents, was released (solubilised) by hydrolysis of the residue with 3*N*-HCl. The percentage of deltamethrin of the total residues in the edible tissues is shown later in the discussion of Table 4.

Chickens

The metabolism of deltamethrin was studied in liver preparations by Akhtar (1984) and is similar to that for cattle (see above).

Excreta from birds dosed topically (with both ^{14}Ca-deltamethrin and ^{14}Cgd-deltamethrin), were extracted and analysed by HPLC and TLC (Whittle, 1997). The major metabolites identified were polar materials and deltamethrin accounting for ca 0.l% of the dose. Analysis of pooled excreta extracts from orally dosed birds showed deltamethrin to be the major component accounting for approximately 30% of the sample radioactivity in birds dosed with both labelled forms of deltamethrin. Other minor components were resolved but these accounted for 1% or less of the sample radioactivity and did not correspond to available reference compounds except for a metabolite (from ^{14}Cgd-deltamethrin-dosed birds) which was tentatively identified as Br_2CA (I in Figure 4).

Liver samples from each group of hens were pooled, extracted with organic solvent and the extracts analysed by both HPLC and TLC. For birds dosed with ^{14}Cgd-deltamethrin, the major components resolved were polar metabolites (18.5% total radioactivity (TR) in orally dosed hens and 1.8% TR in the topically dosed hens) and deltamethrin (1.6% TR in oral hens and 5.3% TR in topically dosed hens). A further metabolite was also detected in orally dosed hens but this did not correspond to available reference compounds. Similarly, for hens dosed with ^{14}Ca-deltamethrin, the major components resolved were polar material (5.7% TR for orally dosed hens and 5.4% TR for topically dosed hens) and deltamethrin (3.1% TR for orally dosed hens and 10.9% for topically dosed I hens). The remaining metabolites did not correspond with the available reference compounds. Extracts of the application site skin, feathers, occlusive cover and swabs from the topically dosed hens were analysed by HPLC and TLC. In all the samples the major component was unchanged deltamethrin and no other significant component was separated. The percentage of total deltamethrin radioactivity in the edible tissues and excreta is shown in Table 1.

Table 1. Percentage of total residues (TR) found as parent drug measured by HPLC and non-extractable residues in cows and hens following dermal application of ^{14}C-deltamethrin.

Tissue	% TR as deltamethrin (^{14}C-gem-dimethyl)		% TR as deltamethrin (^{14}C-benzyl)		% Non-extractable			
					^{14}C-gem-dimethyl		^{14}C-benzyl	
	Cow	Hen	Cow	Hen	Cow	Hen	Cow	Hen
Skin*	95	94.4	97.3	88.9	1.5		0.8	
Liver	3.9	5.3	ND	10.9	63.7	42.9	63.6	68.5
Kidney	3.1	nm	ND	nm	33.9	nm		nm
Fat	59.4	nm	48.4	nm	NA	nm	30.5	nm
Excreta	nm	32	nm	32	nm	6-10	0	3-6
Cream	54.7	NA	42.1	NA	0	NA	nm	NA

* skin at the application site nm = not measured; NA = not applicable.

Pigs and Sheep

No metabolism studies reported.

TISSUE RESIDUE DEPLETION STUDIES

Radiolabelled Residue Depletion Studies

The depletion of radiolabelled ^{14}C-deltamethrin following topical application as a veterinary drug was studied in cattle and chickens. Studies using orally administered drug have been reported and assessed by JMPR (1990) as part of the assessment as an agricultural pesticide. Successful long acting topical application necessitates a parasiticidal dose on the exterior of the treated animal for the duration of the claimed antiparasitic activity. Thus, typical of the characteristic residue pattern is the high and persistent residues of deltamethrin at the site of application. The relatively small percentage of the parent that is absorbed through the skin or by ingestion, enters the fat compartments or is rapidly metabolised.

Cattle

The depletion of ^{14}C-deltamethrin following topical application of a pour-on formulation of 2 mg/kg BW to three heifers (200 – 240 kg BW) has been reported (Dowling et al, 1981). Heifers were sacrificed at 3, 7 and 14 days after dosing and tissue samples collected for analysis of total residues and parent drug. The results are shown in Table 2. The residues in fat persisted over 14 days and were almost entirely deltamethrin. A significant proportion of the very low residues detected in muscle were also parent drug. Less than of the total residues in kidneys was deltamethrin, except in one heifer at 14 days, which is probably an erroneous result,. High residue levels persisted in liver. However, only less than <20% of these residues were extractable and residues of parent deltamethrin were too small to be measured.

Table 2. Total residues and percentage as parent drug after a pour-on dose of 2 mg/kg BW of ^{14}C-deltamethrin to heifers

Tissue		3 days(µg/kg)	(%)	7 days(µg/kg)	(%)	14 days(µg/kg)	(%)
Muscle	Gluteous	6	33	8	75	6	33
	Psoas	12	58	7	57	7	67
Liver		214	16*	32	12*	309	6.7*
Kidney		81	7	79	8	48	60?
Fat	Renal	119	82	221	86	185	81
	Omental	69	96	121	92	129	99

- * = % of radioactivity which was extractable with organic solvents. ? = possibly an erroneous result

A 2.0% deltamethrin cattle pour-on formulation containing either ^{14}Ca-deltamethrin or ^{14}Cgd-deltamethrin was administered topically to dairy cows for three consecutive days (Whalen, 1995). One cow received ^{14}Ca- deltamethrin (1.47 mg/kg BW/day and 44.5 µCi/kg/day) and one cow received ^{14}Cgd-deltamethrin (1.50 mg/kg BW/day and 46.4 µCi/kg/day). The radiochemical purity for both compounds was > 96%. The dose level, was about 3 - 4 times the label dose rate. The animals were sacrificed 24 hours after the last dose. The liver, kidneys, renal fat, and cream (from the Day 4 a.m. milk collection) were analysed to determine the nature of the radioactive residues. The total residues in edible tissues and application site are shown in Table 3.

The liver, kidneys, renal fat and cream were analysed to determine the nature of the radioactive residues. No individual radioactive metabolites, extracts, or residual radioactivity accounted for more than 10 µg/kg deltamethrin equivalents. ^{14}C-Deltamethrin was the primary radioactive component in the renal fat (4 -7 µg/kg) and cream (4 - 5 µg/kg). Little, if any, ^{14}C-deltamethrin was found in the liver and kidney indicating that considerable metabolism occurred in these tissues. 3-Phenoxybenzoyl-L-glutamate was found in the liver and kidney of the ^{14}Ca-deltamethrin-treated cow and up

to six metabolites (including trace amounts of Br_2CA) were found in the liver and kidney tissues of the cow treated with ^{14}Cgd-deltamethrin-. The skin at the application site contained mostly unchanged deltamethrin.

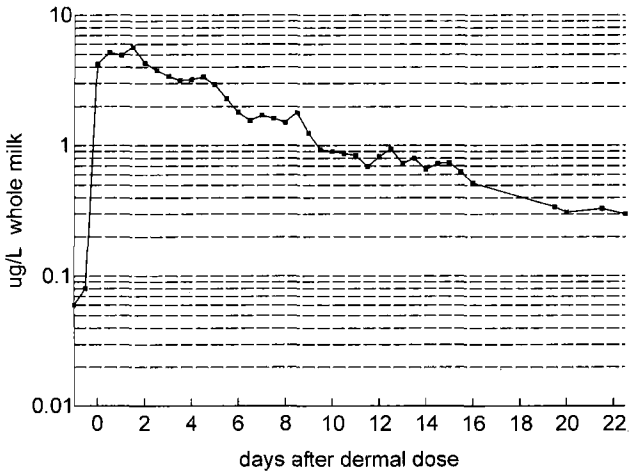
Table 3. Total residues and percentage as parent drug in cows 1 day after 3 daily topical doses of 1.47 mg/kg BW of ^{14}Ca-deltamethrin or 1.5 mg/kg BW of ^{14}Cgd-deltamethrin.

Tissue	^{14}Ca-deltamethrin		^{14}Cgd –deltamethrin	
	(µg/kg)	(%)	(µg/kg)	(%)
Muscle	2	-	1	-
Liver	13	-	9	3.9
Kidney	10	-	10	3.1
Fat omental	8	-	4	-
Renal	9	62.2	11	59.4
Skin (test site)	226	97.3	214	95.8
Cream (at sacrifice)	9	42.1	10	54.7
Milk (at sacrifice)	1		2	

Residue Depletion in Milk

A dairy cow was treated externally with 0.21 g (ca. 0.55 mg/kg BW) of ^{14}Cgd-deltamethrin ((Dowling *et al.*, 1979). Milk samples were collected twice daily and the radioactivity in the whole milk determined. The results are shown in Figure 5. The butter fat was rendered and the radioactivity measured. There was a consistent ratio of 20 between the concentration in the butterfat and the whole milk indicating that most of the residue was in the fat. The maximum level in whole milk was 5.7 µg/L, two and a half days after dosing. The terminal half-lives in milk and butter fat were about 4 days.

Figure 5. The depletion of radioactivity (as equivalents of ^{14}C-deltamethrin) in bovine milk after a topical application of 0.21g (ca. 0.55 mg/kg BW) ^{14}Cgd- deltamethrin.



Chickens

^{14}Ca-deltamethrin and ^{14}Cgd-deltamethrin were administered topically to individual groups of hens once daily for three consecutive days at a nominal dose level of 0.15 mg/kg BW. Birds were sacrificed approximately 23 hours after the

final dose administration. Radioactivity of the residues was measured in muscle, liver, skin/fat and eggs. The results are shown below in Table 4.

All residues in eggs and breast muscle and in some of the leg muscles were below the limits of detection of the analytical method. The dose applied to the hens is 10 times lower than that used in the cattle studies and thus it is not surprising that the residues are lower in hens than cattle

Table 4. Total residues in hens 23 hours after dermal dosing daily for three days with ^{14}C-deltamethrin at 0.15 mg/kg BW.

Tissue	^{14}Ca- deltamethrin		^{14}Cgd-deltamethrin	
	Range (µg/kg)	Mean + SD (µg/kg)	Range (µg/kg)	Mean + SD (µg/kg)
Muscle Leg	0.8 – 1.8	NA	<0.8 – 4.9	NA
Muscle Breast	<0.8	NA	<1.0	NA
Liver	1.4 – 5.6	3.85 ± 1.77 (21%)*	5.0 – 17.5	9.2 ± 4.9 (13%)*
Skin/Fat	1.0 – 19.7	5.53 ± 7.12	2.0 – 6.4	4.47 ± 1.91
Eggs	<1		<1	

The results are expressed as equivalents of ^{14}C-deltamethrin. There were six hens per group. * = percentage of total residues found as parent drug.

Pigs and Sheep

No radio-depletion studies were reported.

Salmon

55 Atlantic salmon (140 ± 26 g) were dipped for 30 minutes in sea water at 12°C containing 5 µg/L of a 1:1 mixture of ^{14}Cgd- deltamethrin and ^{14}Ca-deltamethrin. The fish were sampled between 1 hour and 10 days (Horsberg and Ingebrigtsen, 1998). The depletion of total residues in edible tissues is shown in Table 5.

Table 5. Total residues (µg/kg) of ^{14}C-deltamethrin in tissues of salmon maintained at 12°C.

Hours after treatment	Muscle	Liver	Kidney	Skin
1	1.57	95.4	40.7	11.4
4	3.83	82.3	18.9	12.9
8	2.88	25.3	9.61	10.6
12	2.59	18.0	8.00	8.37
24	3.6	9.80	7.02	5.93
48	5.29	6.53	4.52	4.82
72	8.52	4.80	2.15	4.64
96	2.46	2.70	2.49	4.55
168	1.02	2.50	1.95	3.92
240	1.00	2.96	2.28	3.31

Residue Depletion Studies with Unlabelled Drug

The residues of deltamethrin following topical and parental administration were fully reviewed by JMPR (1990). Since then only one new study is reported (McKinney and Crotts, 1995) in which two doses of a pour-on preparation were applied to lactating cattle. A summary of the highest residues found in the several species is shown in Table 6.

Table 6. Maximum residues (μg/kg) of Deltamethrin following topical administration.

Species	No	Treatment	No	Dose	M	L	K	F	S	E	Mk	Reference
Cow	12	Bath	1	62 mg/L	<2	<2	<2	70				HIDH 80-1
Cow	9	Bath	27	50 mg/L				148				HIBH 82-5
Cow	17	Bath	57	18-52 mg/L				130				HIDH 81-1
Calf	9	Pour-on	1	0.5 mg/kg BW				180				HCAH 83-5
Cow	6	Pour-on	1	0.25 mg/kg BW							9	HIBH 83-5
Cow	3	Pour-on	4 + 1	0.66 mg/kg BW 1 mg/kg BW							11	CIBH 85-C1
Cow	12	Pour-on	4 + 1	0.66 mg/kg BW 1 mg/kg BW				155				CIBH 85-C2
Cow	2 2	Pour-on Pour-on	1 1	0.2 mg/kg BW 2 mg/kg BW							16 53	VENANT et al, 19??
Cow	6	Pour-on	6	0.75 mg/kg BW							11	E 236
Calf	24	Pour-on	1	0.75 mg/kg BW	30	5	34	220				E 249
Cow	24	Pour-on	1	0.75 mg/kg BW	14	<2.5	20	370				E 316
Cow	6	Spray	1	1 mg/kg BW							7	E 224
Cow	6	Spray	1	1 mg/kg BW							11	E 240
Calf	24	Spray	1	1 mg/kg BW	14	<2.5	13	361				E 248
Sheep	10	Bath	1	15 mg/L				430				HIBH 81-1
Sheep	12	Bath	1	15 mg/L				500				AITH 81-3
Sheep	12	Bath	1	11 mg/L	32	<5	<5	19				HIBH 83-2
Sheep	9	Pour-on	1	2.5 mg/kg BW				42				CIBH 85-C2
Sheep	9	Pour-on	1	4 mg/kg BW				60				HITH 80-1
Sheep	11	Pour-on	1	4 mg/kg BW	<30	<30	<30	80				HITH 80-2
Pig	9	Pour-on	1	1 mg/kg BW	<10	11	<10	201	3243[a]			HIBH 84-1
Pig	9	Pour-on	1	0.75 mg/kg BW	<7	<10	<7	<7				Scheid 1986
Hen	75	Spray	1	50 g/L	<12	<7	<8	<13		<15		Ansoborlo

[a] skin from site of administration 3 days after dosing, highest residue in skin at non-application site was 40
M = muscle, L = liver, K = kidney, F = fat, S = skin, E = eggs, Mk = milk

Cattle

Six lactating cows were dosed with a pour-on formulation of deltamethrin at 0.4 mg/kg BW, followed by a repeat dose 7 days later. A further group of twelve lactating cows were similarly treated but dosed with 1.6 mg/kg BW. Cows were milked twice daily until slaughter on days, 3, 7 or 14 after the second treatment. Samples of edible tissues were taken for residue analysis for total deltamethrin (the sum of α–R, *cis*- and *trans*- deltamethrin) using gas chromatography with electron capture (GC-ECD) (McKinney and Clayton, 1995). The results for the residues are shown in Table 7.

Table.7. Concentration range of residues of deltamethrin after treatment with pour-on preparations to lactating cattle (McKinney and Clayton, 1995).

Tissue	Dose	LOQ (µg/kg)	1 day (µg/kg)	3 days (µg/kg)	7 days (µg/kg)	14 days (µg/kg)
Muscle	Low	15	<LOQ	NA	<LOQ	NA
	High		<LOQ	<LOQ	<LOQ	<LOQ
Liver	Low	15	Nm	NA	Nm	NA
	High		<LOQ	<LOQ	<LOQ	<LOQ
Kidney	Low	15	Nm	NA	Nm	NA
	High		<LOQ	<LOQ	<LOQ	<LOQ
SC. fat	Low	45	<LOQ – 106	<LOQ	<LOQ	<LOQ
	High		<LOQ - 48	<LOQ	<LOQ	<LOQ
Renal fat	Low	45	<LOQ	NA	Nm	NA
	High		64 – 67	46 – 90	46 – 74	58 – 70
Milk	Low	15	Nm	Nm	Nm	Nm
	High		<LOQ	<LOQ	<LOQ	<LOQ
Milk fat	Low	75	<LOQ – 95	<LOQ – 80	Nm	Nm
	High		111 - 531	119 – 282	100 – 113	<LOQ

Nm = not measured because values predicted <LOQ. NA = not applicable because no low dose animals were slaughtered on days 3 and 14. The values for the tissues are the ranges for 3 animals. All animals not sacrificed were used for the milk measurements. The low dose = 0.4 mg/kg BW and the high dose = 1.6 mg/kg BW.

In an Australian study, cattle were dipped, in a bath containing 62 mg/kg deltamethrin and 320 mg/kg ethion. The animals were slaughtered 1, 3, 6 or 10 days after treatment and edible tissues sampled for residue analysis. Residue levels peaked at 6 days, the maximum residue being 70 µg/kg in perirenal fat. Most residues were 30 µg/kg or lower and residues in samples of liver, kidney and neck muscle did not exceed 2 µg/kg (Dowling *et al.*, 1980a).

In a South African study, cattle were dipped approximately weekly in a bath containing 0.0018 to 0.0057% deltamethrin, slaughtered, and omental and renal fat analysed for residues. For a group of cattle dipped 57 times and slaughtered 14 days after the last dipping, mean residue levels were 30 and 40 µg/kg deltamethrin in omental and renal fat, respectively. For cattle dipped only 3 times and slaughtered 4 days after the last dipping, the corresponding levels were 100 and 110 µg/kg in omental and renal fat, respectively. This latter group were smaller animals and in poorer general condition (Dowling *et al.*, 1980b).

Cattle were treated, in another South African study, by dipping on 27 occasions, at weekly intervals, in a bath that contained a nominal concentration of 50 mg/kg deltamethrin. Selected samples of body fat were removed from animals slaughtered at 1, 4 and 7 days after the last dipping. The highest mean levels of deltamethrin residues detected were 120 µg/kg and 11 µg/kg in omental and perirenal fat, respectively (HIBH 82-5, 1982).

Nine calves were treated with 10 mL of 1% deltamethrin in Miclycol 812 and slaughtered in groups of 3 at intervals of 3, 7 and 14 days after treatment. A further group of 3 animals served as controls. Samples of omental and perirenal fat were analysed for residues. One animal, slaughtered after 3 days, had residues of 175 µg/kg and 99 µg/kg in perirenal and omental fat, respectively. All other samples contained less than 60 µg/kg deltamethrin (HCAH 83-5, 1984).

Six lactating cows were each treated topically with 10 mL of a 1% deltamethrin in Miglycol 812 formulation. The cows were milked twice daily and milk from each cow was retained once or twice daily for 10 days and processed into rendered butterfat, which was analysed for residues of deltamethrin. The highest residue found was 150 µg/kg in butterfat from the milk of one cow collected 2 days (fourth milking) after treatment. It was calculated that this corresponded to a residue of 9 µg/kg in whole milk (HIBH 83-5, 1984).

Three cows were treated with a 1% pour on preparation weekly for 4 weeks with 0.66 mg deltamethrin per kg BW and milk samples were collected. Seven days after the last treatment, the cows were given a single pour on treatment of 1 mg/kg BW and milk samples again collected. The milk samples were processed to rendered butterfat. The highest level of residues was equivalent to 10 µg/kg in whole milk, after treatment with 1 mg/kg deltamethrin (CIBH 85-Cl, 1985).

Four groups, each comprising 3 animals, were dosed weekly at 0.66 mg/kg BW with a 1% w/v deltamethrin pour-on for 6 months. Three groups were killed at 1, 7 or 14 days after the last treatment. The fourth group was treated with a further dose of 1 mg/kg BW and killed 7 days later. There were less than 200 µg/kg deltamethrin residues in all analytical samples of perirenal and omental fat obtained from slaughtered animals (CIBH 85-C5, 1987).

In a study to determine the metabolic fate of deltamethrin in lactating cows, two cows were treated with 0.1 g and two others with 1 g of deltamethrin by pour-on application. Samples of urine, faeces, milk and blood, collected during 8 days, were analysed. About 95% of the total eliminated deltamethrin was excreted in the faeces, with less than 1% excreted in both urine and milk. The maximum residue levels of 16 µg/kg (low dose) and 53 µg/kg (high dose) in milk were observed after 2 days. Residues in milk were 1 µg/L after 8 days (Venant *et al.*, undated).

Cattle were dipped, in a bath containing 62 mg/kg deltamethrin and 320 mg/kg ethion in an Australian study. The animals were slaughtered 1, 3, 6 or 10 days after treatment and edible tissues sampled for residue analysis. Residue levels peaked at 6 days, the maximum being 70 µg/kg in perirenal fat. Most residues were 30 µg/kg or lower. Residues in samples of liver, kidney and neck muscle did not exceed 2 µg/kg. (HIDH 80-1, 1980)

Cattle dipped approximately weekly, in a South African study, in a bath containing 0.0018 to 0.0057% deltamethrin were slaughtered, and omental and renal fat analysed for residues. For a group of cattle dipped 57 times and slaughtered 14 days after the last dipping, mean residue levels were 30 and 40 µg/kg deltamethrin in omental and renal fat, respectively. For cattle dipped only 3 times and slaughtered 4 days after the last dipping, the corresponding levels were 100 and 110 µg/kg. This latter group were smaller animals and in poorer general condition (HIDH 81-1, 1981).

In a South African study, cattle were treated by dipping at weekly intervals for 27 weeks, in a bath containing a nominal concentration of 50 mg/kg. Selected samples of body fat were removed from animals slaughtered at 1, 4 and 7 days after the last dipping. The highest mean level of deltamethrin residues was 120 µg/kg and 11 µg/kg in omental and perirenal fat respectively (HIBH 82-5, 1982).

Nine calves were treated with 10 ml of 1% deltamethrin in Miclycol 812 and slaughtered in groups of 3 at intervals of 3, 7 and 14 days after treatment. A further group of 3 animals served as controls. Samples of omental and perirenal fat were analyzed for residues. One animal, slaughtered after 3 days, had residues of 18 µg/kg and 10 µg/kg in perirenal and omental fat respectively. All other samples contained less than 60 µg/kg deltamethrin (HCAH 83-5, 1984).

Six lactating cows each were treated topically with 10 ml of a 1% deltamethrin in Miglycol 812 formulation. The cows were milked twice daily and milk from each cow was retained once or twice daily for 10 days and processed into rendered butterfat, which was analysed for residues of deltamethrin. The highest residue found was 15 µg/kg in butterfat from the milk of one cow collected 2 days (fourth milking) after treatment. It was calculated that this corresponded to a residue of 9 µg/kg in whole milk (HIBH 83-5, 1984).

Six lactating cows were treated with deltamethrin pour-on at 0.75 mg/kg BW weight and the residues of deltamethrin determined in the butterfat from the milk of each cow, up to the 10th milking after application. Some variations between animals were observed but the results generally confirm other studies. The highest residue in the milk of an individual cow was 10 µg/kg after 2 days, and the highest mean residue was 4 µg/kg after 3 days (E 236, 1985).

Twenty-four calves, 12 male and 12 female, were divided into four groups of 3 males and 3 females each and treated with deltamethrin pour-on at 0.75 mg/kg BW. The groups of animals were slaughtered after 12 hours, 24 hours, 3 days and 5 days, and samples of muscle, liver, kidney and fat taken for analysis. In muscle and liver, traces did not reach the LOQ, 3 µg/kg for muscle and 5 µg/kg for liver. In kidney, the maximum concentration was 34 µg/kg. The maximum concentration in fat was 220 µg/kg reached on day 3 after treatment (E249. 1986).

Six cows were treated with a deltamethrin 50g/L formulation, sprayed on after dilution to a 50 mg/L solution. The dose per animal was ca 1 mg/kg BW. Samples of milk were taken from the 10 milkings after treatment, and butterfat was extracted and analysed. The maximum level of 0.007 mg/kg deltamethrin was observed in whole milk at the 7th milking

on day 3. (Report E224, 1986). A second study using a formulation of 12.5 g/L but the same dose rate showed a maximum level of 10 μg/kg in whole milk (E 240, 1986).

Twenty-four calves were treated with a 12.5 g/L formulation of deltamethrin at 1 mg/kg BW by spraying. Four groups, each of 3 males and 3 females were used and the groups were slaughtered 12 h, 24 h, 3 days and 5 days after treatment and samples of muscle, liver, kidney and fat taken for analysis. Levels were below the limit of determination in liver. Maximum levels in kidney were 13 μg/kg, in muscle 14 μg/kg and in fat 360 μg/kg (at 3 days after application) (Report E 248. 1986).

Sheep

In an Australian study, ten sheep were treated by dipping in a bath with a nominal concentration of 15 mg/L deltamethrin. Omental and perirenal fat, gluteus muscle, kidney and liver collected from animals slaughtered after 1, 3 and 7 days were analysed. The maximum residue of deltamethrin in muscle was 2 μg/kg, 1 day after treatment. One sample of perirenal fat taken at 1 day contained 430 μg/kg deltamethrin; all other fat samples contained less than 200 μg/kg deltamethrin (HIBH 81-1, 1981).

Twelve sheep, nine dipped in a solution of 15 mg/L deltamethrin and three used as untreated controls, were slaughtered in groups of three (controls slaughtered at day 1) at 1, 3 and 7 days after treatment. At slaughter, samples of perirenal and omental fat, liver, kidney and neck muscle were taken for analysis. The maximum individual residue in omental fat was 35 μg/kg at 1 day; the maximum individual residue in perirenal fat was 470 mg/kg, again at 1 day. However, the highest mean residues of 14 μg/kg and 80 μg/kg occurred on day 3 for omental fat and on day 1 for perirenal fat, respectively (AITH 81-3, 1981).

Twelve sheep were dipped in a bath containing 100 mg/L deltamethrin and slaughtered in groups of three at 3, 7, 14 and 21 days after treatment. A further group of three sheep served as controls. Samples of fat, muscle, kidney and liver were taken for analysis. Residues of deltamethrin in muscle, kidney and liver were all below 5 μg/kg with the exception of one muscle sample with a residue level of 32 μg/kg at 7 days. Residues at 3 days were 36 μg/kg in one sample of omental fat and 15 μg/kg in perirenal fat; residues in fat samples at 7, 14 and 21 days were less than 5 μg/kg with one exception, which had a deltamethrin residue of 6 μg/kg (HIBH 83-2, 1983).

Nine sheep were treated topically with 10 mL of a 1% deltamethrin pour-on formulation and subsequently slaughtered at 3, 7 and 14 days. A further group of three sheep served as controls. At slaughter, omental and renal fat were excised, rendered and the rendered fat was analysed for deltamethrin. All samples contained < 50 μg/ kg (CIBH 85-C2, 1985).

Nine sheep were treated topically with a 4 mg/kg BW dose of a deltamethrin pour-on formulation and subsequently slaughtered at 3 and 7 days. At slaughter, muscle, liver, kidney, omental and renal fat were excised and analysed for deltamethrin. All fat samples contained between 0 and 80 μg/ kg (HITH 80/1, HITH 80/2), and all residues were <LOQ (<30 μg/kg) in muscle, liver and kidney (HITH 80/2, 1980).

Hens

Laying hens and their enclosures were sprayed with either a 25 mg/kg or a 50 mg/kg solution of deltamethrin in water. Eggs were collected daily and the hens slaughtered at 1, 2, 3, 4 and 8 days after treatment. Tissue samples were collected and analysed for residues of deltamethrin. All residues were < LOQ and the results are shown in Table 6. (Ansoborlo, 1988).

Animal feeding studies.

Three trials, one with pigs, one with chickens and one with laying hens were carried out to determine the residues generated by feeding a diet containing deltamethrin equivalent to the maximum residue in cereals. The maximum residues in the pig study were in fat (40 μg/kg) and in muscle (3 μg/kg). In liver and kidney, residues were below the limit of determination of 1 μg/kg (E.3O7, 1989). The maximum residues in the chicken studies were 3 μg/kg in fat and 10 μg/kg in skin. Muscle, liver and eggs, residues were below the limit of quantification of 1 μg/kg for muscle and liver and 2 μg/kg for eggs (E.3O8, 1988; Mougon and Protais, 1989).

Bound Residues/Bioavailability

There were <10% bound residues in fat, milk and muscle. The extensive metabolism in the liver of all species resulted in low molecular weight substances, which are either bound or incorporated into the cellular components. The non-extractable residues in bovine liver and kidney were ca. 64% and 32% respectively. In hens the bound residues were 43-68% in liver. The nature of the bound residues is not known but the radioactivity could be released (extracted) after hydrolysis with 3*N*-HCl.

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

The JMPR considered the analytical methods for deltamethrin in 1990. Some of the analytical methods used to determine the concentrations of deltamethrin in tissues claimed limits of quantification (LOQs) lower than those in the latest method (see below). For example, in cattle, LOQs were claimed to be as low as 2 µg/kg for muscle, liver and kidney and 5 µg/kg for fat (HIDH 80-1).

Since then, the sponsor has provided full details of separate methods, in ISO78/2 format, developed under GLP and dated 1997, for both bovine and chicken, muscle, liver, kidney and fat; for bovine milk and chicken's eggs (Sponsor volume 18, reports 1 - 10). The methods are modifications of those of EN-CAS (1994). The methods are suitable for cattle and chickens but have not been validated for sheep. A method for residues in salmon tissues is also provided (Alpharma, 1997).

The method provided by the sponsor consists of the following steps: Alpha-R-deltamethrin, cis-deltamethrin, trans-deltamethrin and tralomethrin are extracted from tissues, milk and eggs with hexane/acetone. Partition and filtration steps are used where needed to remove particulate matter. The extract is taken through gel-permeation chromatography followed by clean up with alumina column chromatography using hexane - dichloromethane as eluents. The eluate is dried and reconstituted in hexane prior to analysis by gas chromatography with electron-capture detection. The principal characteristics of the methods are summarised in Table 8.

Table 8. Performance characteristics of analytical methods (Sponsor vol 18 & 19)

Species	Tissue	LOQ (µg/kg)	Sample Size (g)	Recovery (%) Mean ± SD (n)	Repeatability CV%	Reproducibilty CV%
Cattle	Muscle	15	10	91 ± 7.5 (8)[P]		
	Liver	15	10	104 ± 8 (12)[P]		
	Kidney	15	10	92 ± 13 (13)[P]		
	Fat	45	2	90 ± 12 (20)[P]		
	Whole Milk	15	10	101 ± 13 (70)[P]		
	Milk Cream/fat	15	10	95 ± 11 (49)[P]		
Chicken	Muscle	15	10	89 ± 10 (6)[M]		
	Liver	15	10	93 ± 4.3 (6)[M]		
	Fat	45	2	93 ± 8.6 (7)[M]		
	Eggs	15	10	92 ± 13 9 (8)[M]		
Salmon	Muscle	2	15	82[A] 79[B]	<17[A] <5[B]	<23[A] <9[B]
	Liver	2	8	73[C] 46[D] 65[E]	<16[C] <2[E]	<23[C] <17[E]
	Skin	2	3	80[C] 57[D] 71[E]	<8[C] <5[E]	<10[C] <15[E]

The GC - ECD range for the calibration curve was 0.015 –15 ng; $r^2 = 0.997$

[A] is at 25 µg/kg [B] is at 250 µg/kg [C] is at 20 µg/kg [D] is at 50 µg/kg [E] is at 500 µg/kg

P = the procedural recovery samples across all batch analyses. M = method validation recovery results.

CONCLUSION

Deltamethrin is widely used as an agricultural pesticide and is also licensed in many countries as an ectotopic parasiticide. In 1990 JMPR established an ADI and recommended MRLs to also cover the veterinary usage. These MRLs would appear to be for all species and, in addition, there are values specific for poultry. The sponsors have submitted the same data as to JMPR and also provided some new information; in particular, the analytical method for use with cattle and poultry food products is well documented. The method was applied to a new study to determine the cold residues in cattle given a pour-on preparation.

There are some deficiencies in the data package; namely:-

1. The expert reports are old and too brief to be of much value.
2. There are no pharmacokinetics, metabolism or radio depletion studies for pigs and sheep.
3. The marker compound, parent drug, may only be suitable for fat and milk and maybe muscle.
4. It is not possible to estimate the total unlabelled residues using the residue data in liver, kidney or eggs. This will depend on the Committee allotting a toxic activity to the other residues. The drug is extensively metabolised in the liver and much of the total residues in cattle and poultry liver is in the bound form.
5. The residues at the site of application may not be a problem in animals where the skin is removed but residues are very high on the skin of pigs.

APPRAISAL

The JMPR established an ADI of 0 – 10 µg/kg BW (0 - 600 µg / 60 kg person) for both veterinary and pesticide uses. The JMPR recommended MRL for Deltamethrin as a pesticide taking into account its use as a veterinary drug: namely; Meat (fat), 500 µg/kg; Poultry meat, 10 µg/kg: Offal, 50 µg/kg; Poultry offal, 10 µg/kg; Eggs, 10 µg/kg; Milk 20 µg/kg. Note that the definition of species for meat and offal is not clarified.

In evaluating MRLs using the JECFA procedures the following factors are considered;

1. The ADI and MRL set by JMPR.
2. The radiodepletion studies, metabolism and analytical methods are only provided for cattle and poultry.
3. There are unlabelled drug residue depletion studies for pigs and sheep.
4. The route of administration is ectodermal.
5. The parent drug is absorbed and residues as parent drug are predominantly distributed in the body fat and milk fat.
6. There is extensive metabolism of the parent drug by the liver (and kidney?) with rapid excretion of the products.
7. The parent drug is the proposed marker residue and is a good indicator of residues in body fat, milk fat and at the site of application. Because of the extensive metabolism it is extremely difficult to monitor the total residues in liver and kidney. Residues of marker compound in muscle are very low and the LOQ of the analytical method will be a determining factor.
8. The LOQ of the methods for cattle and poultry tissues are 15µg/kg for muscle, liver, kidney, eggs, milk and milk fat and 45 µg/kg for body fat.
9. The maximum total residues in cattle and poultry using ^{14}C-Deltamethrin are shown in Table 9. They are <7% of the ADI.

Table 9. Theoretical total residues of ^{14}C-Deltamethrin in "food basket" for cattle and poultry.

Tissue	Cattle (µg)		Poultry (µg)	Maximum for both (µg)
	(µg)	MR as % TR		
Muscle (300g)	3.6	(58%)	1.5	3.6
Liver (100g)	21.4 *	(16%)	1.8	21.4
Kidney (50g)	4.1	(7%)	Nm	4.1
Fat (50g)	6.0	(82%)	0.5	6.0
Milk (1500g)	3	(55 - 89%)		3.0
Eggs			<0.2	0.2
Total	38.1		4.0	38.3

10. The toxicological activity of the residues other than parent drug may be assumed not to have the neuronal and toxicological activities of a pesticide/parasiticide. Much of the residues in liver and kidney are the products of extensive metabolism and a large percentage of those in liver are non-extractable, i.e. bound residues.

The Committee took account of the MRLs recommended by JMPR and recommended the same MRLs for liver, kidney and fat. The Committee noted that the concentrations of residues in muscle, milk and eggs are less than twice the limit of quantification of the analytical methods used and, therefore, recommended MRLs based on the sensitivity of the method. These values are "guidance MRLs" and should not be used to calculate the theoretical maximum daily intake of deltamethrin residues. The MRLs for cattle and chicken tissues were extended to sheep for muscle, liver, kidney and fat and salmon muscle tissue. The MRL for muscle tissue, milk and eggs is 30µg/kg; for liver and kidney, 50 µg/kg; and for fat, 500µg/kg.

Based on the daily intake of 300g muscle, 100g liver, 50 g kidney and fat, 1.5 kg milk and 100g eggs, and considering the MRL in muscle, milk and eggs set at two times the limit of quantification of the method; that the marker residue accounted of 4-20% of the total residues in liver, 3% of the total residues in kidney and 60% of the total residues in fat, the theoretical maximum daily intake of residues from veterinary drug use would be 150-250µg as deltamethrin equivalents.

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