CYPERMETHRIN

First draft prepared by

Adriana Fernández Suárez, Buenos Aires, Argentina

Richard Ellis Washington, DC, United States

ADDENDUM

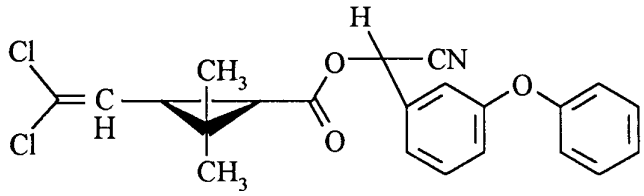
to the monograph prepared by the 47th meeting of the Committee and published in FAO Food and Nutrition Paper 41/9 and to addendum prepared by the 54th meeting published in FAO Food and Nutrition Paper 41/13

IDENTITY

Chemical Structure: (RS)-α-Cyano-3-phenoxybenzyl-(1 RS, 3 RS, l RS, 3 RS)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate (IUPAC name)

(RS)-Cyano-(3-phenoxypheny1)methyl (1 RS)--3-(2,2-dichloroetheny 1)-2.2-dimethylcyclopropane carboxylate (Chemical Abstracts name)

Structural formula: Cypermethrin is a mixture of a11 eight possible chiral isomers:



CAS No: 52315-07-8

Molecular Formula: $C_{22}H_{19}Cl_2NO_3$

Molecular Weight: 416.3

INTRODUCTION

General

Cypermethrin is a synthetic pyrethroid insecticide used for the control of ectoparasites such as ticks, fleas, lice and blowflies. It consists of a mixture of four cis- and four trans-isomers. The cis-isomers are considered to be more acutely toxic than the trans-isomers. It is applied to infested cattle, sheep, poultry and some companion animals. It is also considered to control sealice infestations in farmed fish.

Dosage

The commercial formulations are in the form of ear tags, sprays, dips and pour-on formulations.

Previous evaluation

Cypermethrin was first reviewed by the Joint Meeting on Pesticide Residues (JMPR) in 1979 and subsequently in 1981, 1986, 1988 and 1990. MRLs have been recommended for a wide range of crops, meat and milk products and feed commodities. Whereas cypermethrin has been used on horses, deer, goats and sheep, a 45:55 cis:trans cypermethrin was evaluated for use on cattle, sheep and poultry by the 47th meeting of JECFA. The Committee recommended temporary MRLs for cattle, sheep and poultry of 200 µg/kg in muscle, liver and kidney, 1000 µg/kg in fat, 50µg/kg for cattle whole milk and 100 µg/kg for eggs expressed as the parent drug. The Committee took the following factors into consideration:

- The ADI is 0-50 µg/kg bw, which is equivalent to a maximum ADI of 0-3000 µg for a 60-kg person. The ADI is the same as that established by the 1981 Joint FAO/WHO Meeting on Pesticide Residues.
- The parent drug is the marker residue.
- Fat is the target tissue, but muscle, liver and kidney should also be considered. Milk and eggs are also recommended for monitoring residues.
- The metabolism and residue-depletion studies using the radiolabelled drug were not adequate, and therefore very conservative estimates of the proportion of the total residues accounted for by the marker compound in all target species were proposed. The estimates were 30% for muscle, 10% for liver, 5% for kidney, 60% for fat, 80% for milk and 30% for eggs.
- There was adequate information on residues from the residue-depletion studies using the unlabelled drug in the recommended formulations.
- Analytical methods were available; however, evidence of adequate validation was needed.

The JMPR food consumption used approximately 300µg leaving 2700µg for veterinary use. The theoretical maximum daily intake of residues was 810 µg using the temporary MRLs noted above. The MRLs accommodate the ADI and the recommended use of this compound as veterinary drug and pesticide.

The 47th Committee required the following information to further elaborate MRLs:

1. The results of residue-depletion using the radiolabelled cypermethrin that extend beyond the recommended withdrawal times for the drug in its topical formulation. The depletion of the total residues and the parent drug should be determined.
2. Evidence that interconversion of isomeric forms does not occur during metabolism in the target species.
3. Further information on the validation of the analytical methods, particularly data on the derivation of the detection and quantification limits.

In response to the first request, the Committee received at its 54th meeting a new study in sheep treated orally with radiolabelled cypermethrin with a cis:trans isomer ratio of 80:20, but not topically treated. No information was submitted to the second request. In answer to the third request, a suitable analytical method to measure the sum of isomers in mixtures of cypermethrin using a GC method was submitted. The Committee also noted that no information was made available for the toxicological evaluation of the 80:20 cis-trans cypermethrin. Therefore, the temporary MRLs were not extended.

The following data were submitted for evaluation at the 58th Committee to support the use of cypermethrin as an ovine ectoparasiticide:

1. A final report on the depletion study using the radiolabelled drug in sheep treated orally that had been evaluated previously at the 54th meeting
2. A study on the depletion rate and metabolic fate of ^{14}C-alpha-cypermethrin in sheep following topical application.
3. A new study on residues in sheep topically treated with non-radiolabelled cypermethrin.

RESIDUES IN FOOD AND THEIR EVALUATION[1]

Previous studies of the metabolism of cypermethrin

Studies on the metabolism of cypermethrin were carried out using equal mixtures of the cis:trans forms (45:55). ^{14}C-cypermethrin was labelled primarily in the rings of both acid and alcohol portions in the molecule (^{14}C-cyclopropyl and ^{14}C-benzyl, respectively).

Studies using radiolabelled drug

Rat

When the isomers of cypermethrin were dosed orally to rats, both were rapidly metabolised and eliminated **(**JECFA, 1997, p 42)**,** 98-101% of the radioactivity was recovered in 3 days (53-66% excreted in urine and 27-29% in faeces) (Crawford and Hutson, 1977a; Crawford and Hutson, 1977c). Tissue residues were low, apart from those in fat derived from the cis-isomers. The trans isomers were released from fat more quickly than the cis-isomers. (Crawford and Hutson, 1977a). The possibility that fat tissue contains an esterase that exhibit carboxylesterase activity and hydrolyse the trans-isomers 50 times faster than the cis-isomers was considered (Casilda et al., 1976). The majority of total

[1] The following abbreviations are used throughout: 3PBA, (3-phenoxybenzoic acid); 3-PBA-glut, (N-3-phenoxy-benzoyl-glutamic acid); 4-OH-3PBA, (3-(4-hydroxyphenoxy) benzoic acid; 3PBA-4-O-sulf, (4-hydroxyphenoxy-benzoyl-O-sulfate); 4-OH-cyper, (4-hydroxy-cypermethrin).

residues in the fat of rats after oral administration for 8 and 25 days was unchanged cypermethrin (Crawford and Hutson, 1978).

In another study, rats were administered 1-2 mg/kg BW of either cis- or trans-^{14}C-cypermethrin and the metabolites investigated. The major metabolites were in the cis form for the cis-isomers. Similar results were observed with the trans isomers.

Sheep

Two male sheep were topically treated (21.9 mg/kg BW) and a third was orally dosed (3.9 mg/kg BW) with ^{14}C-cypermethrin with a cis:trans ration of 45:55. (Crawford and Hutson, 1977b; JECFA, 1997, p 42**)**. When applied topically, cypermethrin was slowly absorbed and eliminated. Less than 0.5% of the dose was excreted in urine within 24 h and only 2% over a six day period. For faecal elimination, 0.5% of the dose was eliminated in six days. Approximately 30% of the dose was recovered from the application areas of both sheep treated. In the orally treated sheep, the elimination was rapid, 61% of the dose being eliminated 48 h after dosing (41% by urine and 20.5% by faeces). The metabolic profile was not determined, but the percent of total residues attributable to cypermethrin was measured in tissues. Results are summarized in Table 1. Tissues were extracted and analyzed using gas chromatography for cypermethrin. A summary of total residue values is provided in Table 2.

Table 1. Total residues as cypermethrin following treatment with ^{14}C-cypermethrin in sheep (in %)

Tissue	Topical (24 h)	Topical (6 d)	Oral (2 d)
Liver	13	17	8
Kidney	< 3	< 4	<1
Muscle	NQ	NQ	33
Renal fat	88	80	63
Subcutaneous fat	-	92	67

NQ = non quantifiable

Table 2. Total residues of ^{14}C-cypermethrin in sheep (in µg/kg)

Route	Time post treatment	Muscle	Liver	Kidney	Renal fat	Subcutaneous fat
Topical	1 day	30-40	100	140	170	100000*
	6 day	30-60	140	120	300	3300*
Oral	2 day	30-40	390	360	410	260

* at site of application

A study investigating the depletion of ^{14}C-cypermethrin with a cis:trans-ration of 80:20 after oral administration (1 mg/kg BW) to adult sheep was submitted at the 54th Committee though a topical study had been requested (JECFA, 2000, p. 19). Three groups of five sheep (two sexes) were slaughtered at 1, 3 and 5 days after dosing. Mean values of total radiolabelled residues (TRR) were three times higher in liver than kidney and approximately 1.3 times higher than in fat at day 5 (none detected in muscle). Both radiolabelled cis- and trans-cypermethrin were measured by radio-TLC only at day 1 due to small quantities at later times. No residues of trans-isomers were detected. Results are presented in table 3.

Table 3. Total residues and marker residue (in µg/kg) content in sheep tissues one day after oral treatment with ^{14}C-cypermethrin (1 mg/kg bw)

Tissue	TRR	cis-Cyp	trans-Cyp	Ratio (%) Cyp:TRR
Liver	334 ±23	13 ±5	0	4
Kidney	408 ±105	5 ±1	0	1.2
Muscle	13±3	3 ±2	0	22
Fat	50 ±13	43 ±17	0	86

Other residue depletion studies (with unlabelled drug)

Residue information was provided using dips and pour-on preparations (JECFA, 1997, p. 42). The main residue measured was the parent compound cypermethrin determined by GC-ECD with non-validated methods. In the dipped sheep, residues were close or below the LOQ in most cases for all tissues, residues were only found in perirenal and omental fat. In one of the pour-on studies, 20 sheep were treated with 0.375 g of cypermethrin and 20 sheep with 0.75g.

Residues of cypermethrin reached 40 µg/kg at 3-7 days after treatment, descending at 20 µg/kg at 28 days after treatment in both perirenal and omental fat. In the other study, 10 sheep were treated with 0.375 g of cypermethrin in two different pour-on formulations. Residues at 7 days post treatment were 18-35 µg/kg in omental fat and 4-10 µg/kg in perirenal fat (very low recoveries). Residues in subcutaneous fat were not measured.

Twenty-four wethers were dunked into a dip containing 0.01% cypermethrin (JECFA, 2000, p 23). Residues were detected in omental fat, perirenal fat and muscle at levels ranging from <10 µg/kg (0 day) up to 170 µg/kg in perirenal fat at day 14. Residues could not be detected in liver and kidney.

Merino ewes were treated using 2.5% cypermethrin pour-on at 15 ml (normal maximum dosage rate) and 30 ml (JECFA, 2000, p. 23). For the recommended maximum dose rate of 15 ml, residues in both omental and perirenal fats reached peak values of 40 µg/kg after seven days. Values for a double dose rate of 30 ml also peaked after seven days at 70 µg/kg for omental fat and 80 µg/kg for perirenal fat. For muscle, liver and kidney samples, results were all less than 20 µg/kg.

New studies on cypermethrin

The following data were submitted for evaluation at the 58th Committee to support the use of cypermethrin as an ovine ectoparasiticide:

1. A final report on the radiodepletion study in sheep treated orally that was evaluated at the previous 54th meeting
2. A study on the depletion rate and metabolic fate of ^{14}C-alpha-cypermethrin in sheep following topical application.
3. A new study on residues in sheep topically treated with non-radiolabelled cypermethrin.

Though mentioned, no validated analytical method was presented (method reference number MC/99/31).

A study submitted previously at the 54th meeting of the Committee using sheep treated orally with cypermethrin was provided, however, not topically treated using a 80:20 cis:trans isomer ratio as requested. As there was no response to the Committee's request from the 47th meeting, it was not evaluated.

The complete description and results of the study on the depletion rate and metabolic fate of ^{14}C-alpha-cypermethrin in sheep following topical application is described in the alpha-cypermethrin monograph.

Alpha-cypermethrin, that consists of two of the four cis isomers present in cypermethrin, was formulated at a nominal concentration of 12.5 g/L and was topically administered to 12 animals (6 male and 6 female) at a mean dose level of 0.5 g per animal (15.02 mg/kg). In summary, mean TRR reached maximum values at day 4 for all tissues except muscle (2 days), then decaying with time. The cis-isomeric form of alpha-cypermethrin was the main metabolite in fat tissues and muscle (confirmed by MS analysis in a single fat and muscle sample but not in liver and kidney due to low amounts of residues). Extensive metabolism was shown in liver and kidney (up to 15 metabolites) with 4-OH-parent and 3-PBA-glut as main metabolites, respectively. The metabolites tentatively identified were: 3-PBA, 4-OH-3-PBA and 3-PBA-4-O-sulfate.

The ratio between parent drug (main metabolite) and total residues at different time points can be estimated from radiolabelled scintillation analysis: 85 ±5% for back fat, 83 ±17% for omental fat and 62 ±23% in muscle. On average, parent compound accounted for 84% of the TRR in fat. In contrast, parent drug accounted for 9 ±6% in liver and 6 ±8% in kidney. Thus, fat can be selected as the target tissue and the sum of isomers of parent compound is suitable as marker residue as there was no evidence of interconversion from the cis to the trans isomers.

The study to determine residues in sheep tissues after topical treatment was claimed to be conducted in accordance with GLP practice. Only a final draft summary report is presented. The study measured the residues of high-cis cypermethrin in sheep tissues after treatment with Crovect^{TM} (12.5 g high-cis cypermethrin/L; 75-85% cis-isomer).

Forty-two female Suffolk cross sheep (approximately 50-60 kg body weight and 9 months old) were treated with Crovect^{TM} at a rate of 1 ml/kg BW (12.5 mg/kg; mean dose level 0.72-0.75 g/animal). The drug was applied by pin-stream application to the backline, directly onto the skin of each sheep.

Groups of five sheep were sacrificed at 7, 14, 21, 28, 35 and 42 days. Duplicate samples of liver, muscle, kidney and subcutaneous fat were taken from each animal and analyzed for cis-cypermethrin using a GC-ECD method. The remaining two slaughter groups were not killed (not required for analysis). Analysis for muscle and kidney samples were stopped at 14 days post-treatment because residues were below the limit of quantitation or not detected in all samples at 7 and 14 days post treatment. Similarly, liver sample analysis was stopped at 21 days post treatment. Analysis of subcutaneous fat samples was stopped at 28 days post treatment. The limit of quantitation (LOQ) was 10 µg/kg and the limit of detection (LOD) was 4 µg/kg. To estimate mean values, analytical results below the LOQ and LOD were allocated half values. Results are presented in Table 5 based on the summaries in Table 4.

Table 4. Summary of residues of cypermethrin in sheep tissues

Post treatment (days)	Liver	Kidney	Muscle	Fat µg/kg
7	5 <LOD	2 <LOQ, 3 <LOD	3 <LOQ, 2 <LOD	33.9, 17.2, 25.8, 20.2, 36.2
14	3 <LOD, 2 <LOD	5 <LOD	5 <LOD	17.1, 17.9, 1 <LOQ, 2 <LOD
21	1 <LOD, 4 <LOD	NA	NA	5 <LOD
28	NA	NA	NA	5 <LOD

NA= samples not analyzed, previous analysis showed levels of BLQ or ND for two consecutive points in time.

Table 5. Estimated cis-cypermethrin residues (µg/kg) in sheep tissues after topical treatment (12.5 mg/kg)

Days		Liver	Kidney	Muscle	Subcutaneous Fat
7	Max	2.0	5.0	5.0	36.2
	Mean	2.0	3.2	3.8	26.66
	S.D.	2.0	1.64	1.64	8.30
14	Max	5.0	2.0	2.0	17.9
	Mean	3.8	2.0	2.0	8.80
	S.D.	1.64	0.00	0.00	8.04
21	Max	5.0	NA	NA	2.0
	Mean	2.6	NA	NA	2.0
	S.D.	1.34	NA	NA	0.0
28	Max	NA	NA	NA	2.0
	Mean	NA	NA	NA	2.0
	S.D.	NA	NA	NA	0.0

APPRAISAL

Based upon the sponsor's submission, only studies for sheep were considered. Though a radiodepletion study using the topical formulation of the drug had been requested, a study employing a pour-on formulation of non-radiolabelled cypermethrin (high cis cypermethrin, 75-85% cis-isomer) at 12.5 mg/kg, 0.72-0.75 g/animal was presented by the sponsors.

Cypermethrin is a synthetic pyrethroid insecticide which is applied topically for the control of ectoparasites such as ticks, fleas, lice and blowflies. It consists of a mixture of 4 cis- and 4 trans-isomers. High-cis cypermethrin consists of more than 80% of the 4 cis-isomers.

After oral treatments, total residues are higher in liver and kidney than after dermal (dip and pour-on) treatments. After oral treatment using ^{14}C-cypermethrin with a cis:trans-ration of 45:55 (3.9 mg/kg BW), TRR residues reached 390, 360 and 410 µg/kg in liver, kidney and renal fat, respectively, at day 2 after treatment. With cypermethrin cis:trans 80:20 (1 mg/kg BW) TRR reached 334, 408 and 50 µg/kg in liver, kidney and fat, respectively, at day 1 after treatment. Percent of total residues attributable to cypermethrin was 65%, 8%, <1% and 33% in fat, liver, kidney and muscle, respectively, for the first treatment mentioned and 86%, 4%, 1.2% and 22% in the same tissues for the second treatment.

In dermal treatments, cypermethrin was slowly absorbed and eliminated. In pour-on treatments using ^{14}C-cypermethrin with a cis:trans-ration of 45:55 (21.9 mg /kg BW, approximately 1g/animal), parent molecule is the main metabolite representing 80-92% of fat residues, 13-17% of liver residues and <4% in kidney residues in sheep. In muscle, cypermethrin was not quantifiable. Residues were higher in fat tissues: 170-300 µg/kg and up to 3300-100000 µg/kg in subcutaneous fat at the site of application. Residues in liver, kidney and muscle were respectively 100-140 µg/kg, 140-120 µg/kg and 30-60 µg/kg between 1 and 6 days post treatment.

In pour-on non radiolabel studies, considerable minor values of cypermethrin have been found (up to 80 µg/kg in fats 7 days post treatment). Doses applied were similar: approximately 1g/animal in the pour-on radiolabel study and up to 0.75 g/animal (double normal maximum dose) in the non-radiolabel study. For muscle, liver and kidney samples, residues were non detected or less than 20 µg/kg.

Results obtained in dip studies are in accord with those obtained in pour-on applications. Residues are only detected in fats up to a maximum of 170 µg/kg at 14 days post treatment.

Metabolism are similar in all species and involved cleavage of the ester bond to form phenobenzoic acid and a cyclopropanecarboxilic acid derivative which are excreted as conjugates.

In answer to the second request about the lack of interconversion of isomeric forms, the sponsor presented a complete study on metabolism of alpha-cypermethrin. Extensive metabolism was found in liver and kidney, but no interconversion from cis- to trans-form was observed. Previous studies performed in rats indicated no interconversion between the cis- and trans-isomers of cypermethrin and a rapid elimination of the trans-isomers.

In the new study (conducted according to GLP) female Suffolk cross sheep of approximately 50-60 kg body weight were treated with a 75-85% cis-isomer formulation of cypermethrin at a rate of 1 ml/kg body weight, equivalent to 12.5 mg/kg body weight. The drug was applied by pin-stream application to the backline, directly onto the skin of each sheep. Samples of muscle, liver, kidney and subcutaneous fat were collected at 7, 14, 21 and 28 days post treatment. Residues of cypermethrin were found in fat at 7 and 14 days post treatment. They were measured using a GC-ECD method. The highest residue found in fat was 34 µg/kg at 7 days post treatment. Residues were below the LOQ (10 µg/kg) at 21 and 28 days post treatment in fat. Residues at 7 days and at any point thereafter in liver, muscle and kidney were below the LOQ.

At the 47th meeting of the committee only considered the 45:55 cis:trans cypermethrin and the recommended use of cypermethrin as an ectoparasiticide. No toxicological evaluation has been performed for the 80:20 isomeric mixture. Because alpha-cypermethrin contains only cis isomers, the Committee agreed to use the ADI for alpha-cypermethrin of 0-20µg/kg of body weight established at the 47th meeting of the Committee.

RECOMMENDED MAXIMUM RESIDUE LIMITS

The Committee considered the following factors in recommending maximum residue limits for cypermethrin:

- An ADI of 0-50 µg/kg bw, equivalent to 0-3000 µg for a 60-kg person, has been established for 45:55 cis:trans cypermethrin with a cis:trans-ratio. The ADI of 0-20 µg/kg bw established for α-cypermethrin can be used in setting MRLs for cypermethrin, as α-cypermethrin consists entirely of the more toxicologically significant cis isomer of cypermethrin. No studies have been provided on the toxicity of 80:20 cis:trans cypermethrin.
- Cypermethrin can be used as a pesticide or as a veterinary drug.
- The parent drug cypermethrin is the only appropriate marker residue in tissues.
- The concentration of cypermethrin is highest in fat, which is a suitable marker tissue.
- No new residue depletion studies have been provided, and the estimates of marker compound are those used by the Committee at its 47th meeting. These are: muscle, 30%; liver, 10%, kidney, 5% and fat, 80%.
- The metabolism of cypermethrin and α-cypermethrin is similar.
- No conversion of cis to trans isomers has been demonstrated for α-cypermethrin, and a similar situation is expected to exist for cypermethrin, because: the metabolic fate of cypermethrins is similar and there is no evidence of interconversion; in laboratory animals (rats), the major metabolites correspond to the isomeric form administered; and trans isomers, even when formed in small quantities, are more quickly metabolized and depleted from animals and are not detectable.
- Validated methods were not described for cypermethrin, although methods have been described for α-cypermethrin.
- The MRLs for fat are based on the studies with a pour-on formulation reviewed by the Committee at its 54th meeting.
- MRLs for muscle, liver and kidney are recommended on the basis of the limit of quantification (10 µg/kg), as the concentrations 7 days after treatment were above the limit of quantification only in fat tissue

The recommendation for MRLs in sheep, measured as cypermethrin are: 20 µg/kg for muscle, liver and kidney, and 200 µg/kg for fat.

The theoretical maximum residue intake is 73 µg per day. The TMDI accounts for 6 percent of the alpha-cypermethrin ADI.

Table 6. Estimated theoretical maximum daily intake of cypermethrin residues

Tissue	Recommended MRL (µg/kg)	Ratio Cyp:TRR	Cyp. Equivalents	Food factor (kg)	Intake of residues (µg/kg)
Muscle	20	0.3	66.7	0.3	20
Liver	20	0.1	200	0.1	20
Kidney	20	0.05	400	0.05	20
Fat	200	0.8	250	0.05	12.5
Total residues					72.5

REFERENCES

Beyerbach, A.(2000). ^{14}C-Cypermethrin: Absorption, distribution, metabolism and excretion in sheep. Covance Laboratories, Report No. 1412/021-D1141, Sponsor submitted.

Casilda J.E., Ueda, K., Gaughan, L.,C., Jao, L.T. and Sutherland, D.M. (1976). Structure-biodegradability relationships in pyrethroid insecticides, Arch. Environ. Contam. Tox., 3, 491-500.

Crawford, M. and Hutson, D.H. (1977a). The metabolic fate of WL43467 (cypermethrin). Metabolism and elimination of ^{14}C-aryl-labelled cis and trans isomers in rats. TLGR 0131.77

Crawford, M. and Hutson, D.H. (1977b). TLRG.0098.77. The elimination and retention of WL 43467 when administered dermally or orally to sheep.

Crawford, M. and Hutson, D.H. (1977c). The metabolic fate of WL43467 (cypermethrin) in mammals. The fate of a single oral dose of ^{14}C-cyclopropyl WL 43467in the rat. Group Research Report. TLGR 0004.77

Crawford, M. and Hutson, D.H. (1978). TLRG.0078.78. The elimination of residues from the fat of rats following the oral administration of [^{14}C-benzyl] WL 43481 (cis-WL 43467)

Crovect (pour-on residue study in sheep).2001. Inveresk Research Report 20933., Sponsor submitted.

CVMP (1998). Cypermethrin, Summary Report. EME/MRL/403/98. Committee for Veterinary Medicinal Products (European Agency for the Evaluation of Medicinal Products).

JECFA (1997). Residues of some veterinary drugs in animals and foods. FAO Food and Nutrition Paper 41/9.

JECFA (2000). Residues of some veterinary drugs in animals and foods. FAO Food and Nutrition Paper 41/13.

Phillips, M., McLean, C.L. (2000). RENEGADE alpha-cypermethrin (CL 900049): The depletion rate and metabolic fate of [^{14}C] CL 900049 in sheep. Inveresk Research Report 18093., Sponsor submitted.