Section A 6.2 (01) Toxicokinetics/Metabolism

Annex Point IIA VI.6.2

ADE study in the rat

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted]; [^{14}C]-Cypermethrin-cis:trans 40:60:- Absorption, Distribution and Excretion in the Rat; [redacted].	
		Dates of experimental work: 14 April 2005 – 23 January 2006	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Chimac-Agriphar S.A.	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes, OECD Guideline 417, OPPTS 870.7485 (1998)	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	X
		3 MATERIALS AND METHODS	
3.1	**Test material**	Cypermethrin cis:trans/40:60	
3.1.1	Lot/Batch numbers	AS 175COV/05 (Cis Cypermethrin, non-radiolabelled)	
		AS 176COV/05 (Trans Cypermethrin, non-radiolabelled)	
3.1.2	Specification	Deviating from the specification given in section 2 as follows	

Section A 6.2 (01) Toxicokinetics/Metabolism

Annex Point IIA VI.6.2

ADE study in the rat

3.1.2.1	Description	-
3.1.2.2	Purity	98.4 % w/w (Cis Cypermethrin, non-radiolabelled) 98.9 % w/w (Trans Cypermethrin, non-radiolabelled)
3.1.2.3	Stability	Stable
3.1.2.4	Radiolabelling	Radiolabelled cypermethrin was supplied as separate cis- and trans-cypermethrin labelled in either the cyclopropyl or phenyl ring: *Cis* [^{14}C-cyclopropyl]-cypermethrin Study number 04 BLY 115b Specific radioactivity 53 mCi/mmol (4.7 MBq/mg) Radiochemical purity 100%. *Trans* [^{14}C-cyclopropyl]-cypermethrin Study number 04 BLY 115b Specific radioactivity 53 mCi/mmol (4.7 MBq/mg) Radiochemical purity 100%. *Cis* [^{14}C-phenyl]-cypermethrin Study number 04 BLY 115b Specific radioactivity 55.4 mCi/mmol (4.9 MBq/mg) Radiochemical purity 100%. *Trans* [^{14}C-phenyl]-cypermethrin Study number 04 BLY 115b Specific radioactivity 55.4 mCi/mmol (4.9 MBq/mg) Radiochemical purity 100%.
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Sprague Dawley (Crl:CD®(SD) IGSBR)
3.2.3	Source	[redacted]
3.2.4	Sex	Males and Females
3.2.5	Age/weight at study initiation	Males: 188 – 301 g Females: 180 – 247 g
3.2.6	Number of animals per group	4 males, 4 females (excretion balance studies) 12 males, 12 females (tissue distribution study) See Table A6.2_01-1
3.2.7	Control animals	No
3.3	**Administration/ Exposure**	Oral
3.3.1	Type	Gavage
3.3.2	Concentration of test substance	See Table A6.2_01-1

Section A 6.2 (01) Toxicokinetics/Metabolism

Annex Point IIA VI.6.2

ADE study in the rat

3.3.3	Preparation of test substance	Appropriate amounts of the non-radiolabelled *cis* and *trans* isomers were weighed into a formulation vessel. Appropriate volumes of the *cis* and *trans* isomers of [^{14}C]-cypermethrin were then transferred to the same formulation vessel which was agitated to co-dissolve the non-radiolabelled test substance. The solvent was removed under a stream of nitrogen and an appropriate volume of corn oil was then added to the test substances, which were dissolved using sonication or mixing.
3.3.4	Dose volume	5 ml/kg
3.3.5	Dose administration	Single doses were administered in the balance study. In the distribution study, doses were administered daily for up to 9 days
3.3.6	Sampling time	See Table A6.2_01-1 At each collection timepoint, cage debris was removed and the cages washed with water and then a methanol wash. Cage debris and washings were pooled separately for each animal
3.3.7	Tissue analysis	<u>Balance studies</u> Following the final sample collection, the animals were exsanguinated by cardiac puncture under anaesthesia and weighed blood samples taken into two heparin-lined tubes, one of which was used to prepare plasma. The following tissues were also taken and the residual carcasses retained for analysis: Adrenals, bone, brain, fat, GI tract (+ contents) heart, kidneys, liver, lungs, muscle (quadriceps), ovaries and uterus (females only), skin, spleen, testis (males only). <u>Distribution study</u> Animals were killed by cold shock in a mixture of hexane and solid carbon dioxide following deep anaesthesia. Carcasses were retained in the freezing mixture for at least 30 mins and were then stored frozen (-20ºC) before being prepared for QWBA. Blood samples were also taken prior to terminal sacrifice in order to prepare plasma.
3.3.8	Treatment of samples	Carcasses were digested in potassium hydroxide (40% solution in methanol) under reflux. Digests were neutralised prior to LSC analysis. Blood samples were incubated with solubilising agent. Liquid scintillant was then added and the samples left to dark-adapt prior to LSC analysis. Faeces, cage debris and tissues were similarly treated with solubilising agent and left to incubate before the addition of liquid scintillant. <u>Quantitative Whole body Autoradiograpy (QWBA)</u> Legs, whiskers and tail were trimmed off and each frozen carcass was set in a block of aqueous 2% (w/v) carboxymethylcellulose. Sagittal sections (nominal thickness 30 µm) were obtained at a minimum of 5 levels through the carcass using a cryomicrotome. These levels included, but were not limited to, the following tissues: exorbital lachrymal gland (males) or ovary (females), intra-orbital lachrymal gland, Harderian gland, adrenal gland, thyroid, brain and spinal cord. The sections were mounted, freeze-dried and placed in contact with FUJI imaging plates. [^{14}C]-Blood standards of appropriate activity (also sectioned at a nominal thickness of 30 µm) were placed in contact with all imaging plates and exposed for 7 days in a copper lined lead exposure box. After exposure, the imaging plates were processed using a FUJI FLA 5000

Section A 6.2 (01) Toxicokinetics/Metabolism

Annex Point IIA VI.6.2

ADE study in the rat

radioluminography system. The carbon-14 blood standards included with each autoradiogram were used to construct calibration lines over a range of radioactivity concentrations.

4 RESULTS AND DISCUSSION

4.1 Excretion Balance study

Low Dose (3mg/kg bw)

The rats of Group A received a single oral dose of [^{14}C-cyclopropyl]-cypermethrin at a mean level of 3.417 mg/kg bodyweight. Analysis of the levels of radioactivity in the urine and faeces showed that the excretion was virtually complete by 72 h after dosing. The mean overall recovery was 102.9 ± 2.6% of the dose. The excretion of radioactivity was split equally between the urine (47.8% of the dose in males, 52.9% in females) and faeces (50.2% in males and 43.4% in females). There was no significant elimination of [^{14}C]-carbon dioxide in the expired air (<0.3% of the dose). The minimum absorption, as measured by the radioactivity excreted in the urine plus cage washes and debris, was 52.8% of the dose in the males and 57.6% in the females. The residual carcass contained <0.7% of the dose showing that elimination of the radioactive dose was complete.

The rats of Group C received a single oral dose of [^{14}C-phenyl]-cypermethrin at a mean level of 3.051 mg/kg bodyweight. As with the [^{14}C-cyclopropyl]-cypermethrin, analysis of the levels of radioactivity in the urine and faeces showed that the excretion was virtually complete by 72 h after dosing. The mean overall recovery of radioactivity was 101.4 ± 5.3%. The main route of excretion was *via* the faeces (48.5 and 59.8% of the dosed radioactivity in males and females respectively) with the urine containing a further 47.5% of the dose in the males and 40.8% in the females, though there was significant inter-individual variation. There was no significant elimination of [^{14}C]-carbon dioxide in the expired air (below the LOQ). The minimum absorption, as measured by the radioactivity excreted in the urine plus cage washes and debris, was 51.3% of the dose in the males and 43.6% in the females. The residual carcass contained 0.4 - 0.6% of the dose showing that elimination of the radioactive dose was essentially complete.

High Dose (50mg/kg bw)

The rats of Group B received a single oral dose of [^{14}C-cyclopropyl]-cypermethrin at a mean level of 50.186 mg/kg bodyweight. As with the lower dose, analysis of the levels of radioactivity in the urine and faeces showed that the excretion was virtually complete by 72 hours after dosing. The mean overall recovery was 106.0 ± 5.7% of the dose. The mean recovery values showed a slight sex difference in the excretion of the radioactivity with more of the dose being excreted in the urine of the females, though, there were significant inter-individual variations in the route of excretion. However, the main route of excretion was *via* the faeces (78.6 and 60.7% of the dosed radioactivity in males and females respectively), the urine contained a further 27.2% of the dose in the males and 36.9% in the females. There was no significant elimination of [^{14}C]-carbon dioxide in the expired air (<0.2% of the dose). The minimum absorption, as measured by the radioactivity excreted in the urine plus cage washes and debris, had fallen at the high dose to 28.7% of the dose in the males and 42.5% in the females. The

Section A 6.2 (01) Toxicokinetics/Metabolism

Annex Point IIA VI.6.2

ADE study in the rat

residual carcass contained approximately 0.4% of the dose showing that elimination of the radioactive dose was complete.

The rats of Group D received a single oral dose of [^{14}C-phenyl]-cypermethrin at a mean level of 48.749 mg/kg bodyweight. Analysis of the levels of radioactivity in the urine and faeces showed that the excretion was virtually complete by 72 h after dosing . The mean overall recovery was 109.7 ± 4.9% of the dose. The main route of excretion was *via* the faeces (80.0 and 68.3% of the dosed radioactivity in males and females respectively), with the urine containing a further 29.1% of the dose in the males and 34.8% in the females. There was no significant elimination of [^{14}C]-carbon dioxide in the expired air (below the limit of quantification). The minimum absorption, as measured by the radioactivity excreted in the urine plus cage washes and debris, was 31.5% of the dose in the males and 38.4% in the females. The residual carcass contained 0.5% of the dose showing that elimination of the radioactive dose was essentially complete.

See Table A6_2_01-2

4.2 Radioactivity in blood samples

At necropsy, 144 h after dosing, the mean concentration of radioactivity in the plasma of the low dose group animals was 2.56 ng equivalents/g for males and 0.81 ng equivalents/g for the females dosed with the cyclopropyl label, and below the limit of quantification in males and females dosed with the phenyl label.

In the high dose group, the mean concentration of radioactivity in the plasma was 12.6 and 11.0 ng equivalents/g in males and females dosed with the cyclopropyl label and was below the limit of quantification in all animals dosed with the phenyl label.

See Table A6_2_01-3

4.3 Radioactivity in tissue samples

The levels of radioactivity measured in the tissues generally reflected the lipophilic nature of cypermethrin with the highest levels being found in the fat in all dose groups. These levels were approximately 6 times higher than any other tissue in the case of the male rats. In female rats, the ovaries generally contained the next highest concentrations of radioactivity, though these were approximately 3 times lower than concentrations in the fat.

The high dose rate was 15-17 times greater than the low dose, and the concentration of radioactivity in the tissues did not automatically increase in direct proportion to the dose level. The concentration of radioactivity in the tissues in rats receiving [^{14}C-cyclopropyl]-cypermethrin, were 7-9 times greater at the high dose than at the low dose for the fat, liver and kidneys and 23 times greater for the adrenals. In the females, the concentrations of radioactivity in the tissues were 6-10 times greater at the high dose for the liver and adrenals, and 14-17 times for the fat, kidney, and ovaries.

When the rats were dosed with [^{14}C-phenyl]-cypermethrin, the concentration in the tissues of male animals were 9-14 times higher for the fat, liver and kidney, and 20 times higher for the adrenal. In the

Section A 6.2 (01) Toxicokinetics/Metabolism

Annex Point IIA VI.6.2

ADE study in the rat

females, the concentrations of radioactivity was 15 times higher for the liver, 6 times higher for the adrenal, and 15-21 times higher for the kidney, fat and ovaries.

4.4 QWBA – Tissue distribution study

The highest levels of radioactivity were found in the fat (peri-renal, inguinal and subcutaneous) at all timepoints. Residues were rapidly cleared from the body once dosing had ceased.

In males, the levels in the plasma 24 h after nine doses (565.5 ng equivalents/g) were twice those seen 24 h after a single oral dose. The highest increases (>10-fold) in the concentration of radioactivity were measured in the inguinal and peri-renal fat. In these tissues, the concentrations of residues rose from 91.8 to 1009 ng equivalents/g in the case of the inguinal fat and from 197.5 to 1966 ng equivalents/g in the case of the peri-renal fat. The lowest levels of radioactivity were seen in the brain (<9 ng equivalents/g) and spinal cord (<36 ng equivalents/g).

In female rats, the levels of radioactivity in the plasma were approximately 20% higher on Day 10 (698.2 ng equivalents/g) than on Day 2 (579.5 ng equivalents/g). The levels in the inguinal and peri-renal fat rose by 6-7 times those seen on Day 2, the concentrations of residues rising from 204 to 1196 ng equivalents/g in the case of the inguinal fat and from 295 to 2179 ng equivalents/g in the case of the peri-renal fat. The lowest levels of radioactivity were seen in the brain and spinal cord (<21 ng equivalents/g).

The radioactivity in the tissues was rapidly cleared, and by Day 16, 7 days after the last dose, many of the tissues contained levels of radioactivity that had fallen below the limit of detection. The concentrations of radioactivity in the fats had fallen by 2-6 times when compared to the levels on Day 10 whilst the levels in the plasma had fallen by approximately 30 times.

See Tables A6_2_01-4 and A6_2_01-5

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The absorption, distribution and excretion of cypermethrin was investigated according to OECD guideline 417. Male and female rats (Sprague Dawley (Crl:CD ® (SD) IGSBR) strain) were given a single oral dose of 3 or 50 mg [^{14}C]-cypermethrin labelled in either the cyclopropyl or phenyl ring and the rates and routes of excretion of the radioactivity were determined. A separate group of rats received up to 9 daily oral doses of 3 mg [^{14}C-phenyl]-cypermethrin/kg bodyweight and the concentration of radioactivity was determined in the tissues at 24 h after 1, 7 and 9 doses and at 7 days after 9 doses.

5.2 Results and discussion

At the higher dose level, faecal excretion was the major route of elimination accounting for 79 and 61% when [^{14}C-cyclopropyl]-cypermethrin was dosed and 80 and 68% when [^{14}C-phenyl]-cypermethrin was dosed. In each case, the higher excretion level was seen in the male rats. The observed increase in faecal elimination suggests that the absorption process was being saturated at

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Section A 6.2 (01) Toxicokinetics/Metabolism

Annex Point IIA VI.6.2

ADE study in the rat

the higher dose level.

At the low dose, a minimum of 43.6 to 57.6% of the dose was absorbed by the rats, as measured by the total radioactivity in urine and cage washes. At the high dose, a minimum of 28.7 to 31.5% of the dose was absorbed by the male rats and 38.4 to 42.5% in the case of the females.

Only trace amounts of radioactivity were measured in the expired carbon dioxide confirming that the positions of radiolabel were metabolically stable in the rat.

At necropsy, 144 h after dosing, the levels of radioactivity measured in the tissues generally reflected the lipophilic nature of cypermethrin with the highest levels being found in the fat in all dose groups. These levels were approximately 6 times higher than any other tissue in the case of the male rats. In female rats, the ovaries generally contained the next highest concentrations of radioactivity, approximately 3 times lower than those seen in the fat.

The high dose rate was 15-17 times greater than the low dose, and the concentration of radioactivity in the tissues did not automatically increase in direct proportion to the dose level. The concentration of radioactivity in the tissues in rats receiving [^{14}C-cyclopropyl] -cypermethrin, were 7-9 times greater at the high dose than at the low dose for the fat, liver and kidneys and 23 times greater for the adrenals. In the females, the concentrations of radioactivity in the tissues was 6-10 times greater at the high dose for the liver and adrenals, and 14-17 times for the fat, kidney, and ovaries.

When the rats were dosed with [^{14}C-phenyl]-cypermethrin, the concentration in the tissues of male animals were 9-14 times higher for the fat, liver and kidney, and 20 times higher for the adrenal. In the females, the concentrations of radioactivity was 15 times higher for the liver, 6 times higher for theadrenal, and 15-21 times higher for the kidney, fat and ovaries.

Following repeated daily oral administration of [^{14}C-phenyl]-cypermethrin at a dose level of 3 mg/kg for up to 9 days, the levels of radioactivity in the tissues increased with the number of doses received. In males, the levels in the plasma 24 h after 9 doses were twice those seen 24 h after a single oral dose. The highest increase in the concentration of radioactivity were measured in the inguinal and peri-renal fat, and the spleen (>10-fold). In female rats, the levels of radioactivity in the plasma were approximately 20% higher on Day 10 than on Day 2 and the levels in the inguinal and peri-renal fat rose by 6-7 times those seen on Day 2.

Following the cessation of daily dosing, the radioactivity in the tissues was rapidly cleared, and by Day 16, 7 days after the last dose, many of the tissues contained levels of radioactivity that had fallen below the limit of quantification. The concentrations of radioactivity in the fat had fallen by 2-7 times when compared to the levels on Day 10 whilst the levels in the plasma had fallen by approximately 30 times.

5.3 Conclusion

Excretion of radioactivity was virtually complete by 72 h following a single oral dose of [^{14}C-cyclopropyl]- or [^{14}C-phenyl]-cypermethrin at a

Section A 6.2 (01) Toxicokinetics/Metabolism

Annex Point IIA VI.6.2

ADE study in the rat

dose rate of 3 or 50 mg/kg bodyweight. Urinary and faecal excretion were similar at the low dose for both radiolabels, but at the higher dose level faecal excretion predominated, especially in the males. This suggests that the absorption of cypermethrin was being saturated at the high dose rate. As minimum of 43.6-57.6% of the dose was absorbed at the low dose level. At the high dose level, a minimum of 28.7 to 31.5% of the dose was adsorbed in male rats and 38.4 to 42.7% in the case of the females. At 144 h after dosing, the highest residues were found in the fat for all dose groups.

Following repeated daily oral dosing of 3 mg [^{14}C-phenyl]-cypermethrin, the levels of radioactivity rose by 6-7 times in the female rats, and by >10 times in the males. The lowest levels of radioactivity were seen in the brain and spinal cord. The tissue residues were rapidly cleared following the cessation of dosing, with the levels of radioactivity in the plasma falling by approximately 30 times over a 7 day period, and the levels in the fat falling by 2-7 times.

5.3.1 Reliability 1

5.3.2 Deficiencies None

Evaluation by Competent Authorities

Use separate "evaluation boxes" to provide transparency as to the comments and views submitted

EVALUATION BY RAPPORTEUR MEMBER STATE

Date March, 2007.

Materials and Methods The applicant's version is acceptable with the following amendments:

Deviations protocol:

Because of the nature of the formulation, a solution of cypermethrin in corn oil, a trial formulation to assess homogenicity, stability, and radioactivity concentration was not performed prior to the preparation of the formulations for dose administration. The formulation prepared for dose group A was subsequently used to determine homogeniceity and stability at 4 and 11 days after preparation.

A number of rats were above the weight range (180-220g).

The number, quantity and identity of radiolabelled metabolites in urine, faeces, and bile and a proposed metabolic pathway were not determined in the study.

Results and discussion The applicant's version is acceptable with the following amendments:

Following a single oral dose of either 3 or 50 mg cypermethrin/kg bw to the rat, the excretion of radioactivity was virtually complete within 72h. There was little difference between the rates and routes of excretion of either of the radiolabelled forms of cypermethrin though there was significant inter-individual variations in the data. At the low dose urinary and faecal excretion were comparable when [^{14}C-cyclopropyl]-cypermethrin was dosed, but slightly higher urinary excretion was seen in the females dosed with [^{14}C-phenyl]-cypermethrin.

Added in table A6_2_01-1: actual dose rates

Conclusion The applicant's version is adopted.

Reliability 1

Section A 6.2 (01) Toxicokinetics/Metabolism

Annex Point IIA VI.6.2

ADE study in the rat

Acceptability Acceptable

Remarks -

COMMENTS FROM ...

Date

Materials and Methods

Results and discussion

Conclusion

Reliability

Acceptability

Remarks

Table A6_2_01-1: Treatment schedule and dose rates

Dose Group	Frequency of dose	Label	Study type	Dose level		Act. dose rate mg/kg	Number of animals		Sampling (hours after dose administration
				mg/kg	MBq/kg		M	F	
A	Single	cyclopropyl	Ex Bal	3	5	3.42	4	4	Urine: 6, 12, 24, 48, 72, 96, 120, 144 Faeces: 24, 48, 72, 96, 120, 144 Expired air: 24, 48
B	Single	cyclopropyl	Ex Bal	50	5	50.19	4	4	Urine: 6, 12, 24, 48, 72, 96, 120, 144 Faeces: 24, 48, 72, 96, 120, 144 Expired air: 24, 48
C	Single	phenyl	Ex Bal	3	2	3.05	4	4	Urine: 6, 12, 24, 48, 72, 96, 120, 144 Faeces: 24, 48, 72, 96, 120, 144 Expired air: 24, 48
D	Single	phenyl	Ex Bal	50	2	48.75	4	4	Urine: 6, 12, 24, 48, 72, 96, 120, 144 Faeces: 24, 48, 72, 96, 120, 144 Expired air: 24, 48
E	Repeated	phenyl	TD	3	2	3.01	12	12	3 M + 3 F sacreficed 24 h after 1, 7 and 9 doses and 7 days after the last dose.

Ex. Bal - Excretion balance study
TD - Tissue distribution study

Table A6_2_01-2: Overall recovery (mean % of administered dose)– Ex. Bal. study

Excreta	Time-point (h)	Low Dose (3 mg/kg bw)				High Dose (50 mg/kg bw)			
		[^{14}C]-cyclopropyl (Group A)		[^{14}C]-phenyl (Group C)		[^{14}C]-cyclopropyl (Group B)		[^{14}C]-phenyl (group D)	
		Males	Females	Males	Females	Males	Females	Males	Females
Urine	6	1.163	2.676	5.686	4.203	3.242	1.071	5.265	3.873
Urine	12	15.640	23.301	15.771	14.768	5.415	0.152	8.983	9.404
Urine	24	18.396	18.897	20.444	14.215	10.641	0.112	11.306	14.554
Urine	48	9.674	5.807	4.474	6.623	5.731	0.836	2.818	6.079
Urine	72	1.894	0.983	0.685	0.581	1.393	1.023	0.393	0.494
Urine	96	0.675	0.850	0.242	0.220	0.468	0.283	0.183	0.215
Urine	120	0.281	0.293	0.131	0.134	0.162	0.209	0.105	0.121
Urine	144	0.125	0.130	0.108	0.077	0.100	0.108	0.064	0.079
	Subtotal	47.846	52.935	47.541	40.822	27.150	36.883	29.115	34.816

Faeces	24	41.522	39.353	39.000	46.737	72.486	51.200	72.090	62.094
Faeces	48	7.135	3.305	6.269	9.980	4.849	7.366	6.354	5.808
Faeces	72	1.019	0.444	1.789	2.218	0.803	1.071	1.380	0.225
Faeces	96	0.318	0.154	1.312	0.161	0.291	0.152	0.241	0.094
Faeces	120	0.148	0.085	0.101	0.694	0.130	0.112	0.044	0.045
Faeces	144	0.095	0.050	0.042	0.016	0.070	0.836	0.020	0.011
	Subtotal	50.236	43.389	48.512	59.869	78.629	60.737	80.127	68.275
Cage Wash + Debris		4.992	4.624	3.717	2.773	1.591	5.660	2.352	3.582
CO2 Traps		0.255	0.151	BLQ	BLQ	0.121	0.164	BLQ	BLQ
Carcass	144	0.680	0.523	0.584	0.338	0.462	0.410	0.469	0.417
G.I. Tract +Contents	144	0.133	0.115	0.027	BLQ	0.068	0.056	0.083	0.110
	Subtotal	0.813	0.637	0.611	0.338	0.530	0.466	0.553	0.527
Overall recovery		104.143	101.735	100.381	102.487	108.023	103.91	112.145	107.198

BLQ = Below Limit of Quantification (DPM in sample below twice background)

Table A6_2_01-3: Mean concentration of radioactivity in tissues (ng equivalents/g tissue) – Ex. Bal

Tissue Sample	**Low Dose (3 mg/kg bw)**				**High Dose (50 mg/kg bw)**			
	[^{14}C]-cyclopropyl (Group A)		**[^{14}C]-phenyl (Group C)**		**[^{14}C]-cyclopropyl (Group B)**		**[^{14}C]-phenyl (Group D)**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Carcass	26.146	21.010	19.626	12.971	266.745	253.66	265.985	255.750
Skin	41.127	29.800	BLQ	BLQ	BLQ	315.963	329.725	BLQ
Plasma	2.564	0.808	BLQ	BLQ	12.597	10.961	BLQ	BLQ
Blood	2.392	1.500	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
Brain	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
Fat	321.490	227.665	254.38	232.78	2331.9	3184.1	3129.0	4895.35
Heart	2.207	1.640	BLQ	BLQ	15.314	BLQ	BLQ	BLQ
Lung	10.700	11.271	BLQ	BLQ	106.492	99.992	BLQ	BLQ
Spleen	5.115	6.092	BLQ	BLQ	23.323	45.895	BLQ	BLQ
Liver	48.021	21.856	14.411	11.651	408.84	226.81	126.660	170.515
Kidney	15.422	13.134	17.900	20.547	135.68	220.55	243.56	385.50
Testes	3.649	-	3.316	-	BLQ	-	BLQ	-
Ovaries	-	69.490	-	66.516	-	1178.1	-	1388.3
Adrenals	16.713	47.593	16.343	32.668	388.205	292.010	321.045	185.730
uterus	-	18.579	-	40.122	-	364.535	-	1024.5
Muscle (Quadriceps)	6.545	1.247	BLQ	1.931	17.505	20.613	BLQ	BLQ
Bone	5.450	3.760	1.455	BLQ	53.250	69.641	46.660	BLQ

BLQ = Below Limit of Quantification (DPM in sample below twice background)

Table A6_2_01-4: Mean concentration of radioactivity in tissues -Repeated dose study, male rats

	Mean Concentration of [^{14}C]-Cypermethrin residues (ng equivalents/g tissue)			
Number of doses given	**1**	**7**	**9**	**9**
Kill time	**Day 2**	**Day 8**	**Day 10**	**Day 16**
Plasma	292.9	432.5	565.5	17.90
Blood	182.2	241.7	315.4	BLQ
Aorta	193.7	292.7	540.6	BLQ
Mandibular lymph nodes	53.57	131.6	323.6	91.97
Kidney cortex	231.4	545.9	652.5	78.71
Kidney medulla	137.6	361.0	430.3	BLQ
Liver	180.7	455.8	693.9	88.29
Brain	BLQ	7.05	8.18	BLQ
Pineal body	92.67	BLQ	167.16	BLQ
Spinal cord	BLQ	21.04	35.83	BLQ
Adrenal	129.7	753.1	686.7	291.0
Pituitary	BLQ	293.2	58.83	BLQ
Thymus	23.50	38.56	48.11	BLQ
Thyroid	104.2	184.4	427.2	45.10
Exorbital lachrymal gland	45.51	80.49	109.1	BLQ
Harderian gland	93.52	255.3	224.2	10.31
Intra-orbital lachrymal gland	40.75	149.2	157.2	53.49
Salivary glands	35.73	62.17	100.3	19.42
Brown fat	568.8	1565	1936	321.1
Inguinal fat	91.81	953.4	1009	581.0
Peri-renal fat	197.5	1319	1966	717.7
Subcutaneous fat	86.63	381.9	351.6	73.48
Bulbo-urethral gland	43.18	73.71	116.10	BLQ
Epididymis	43.05	209.5	102.2	193.8
Preputial gland	82.20	431.8	635.4	367.4
Prostate	56.29	119.3	170.2	190.4
Seminal vesicles	48.82	31.99	366.6	204.3
Testis	41.87	59.87	65.82	8.18
Muscle	21.42	30.50	36.82	BLQ
Myocardium	59.39	102.0	127.5	BLQ
Tongue	53.84	81.50	128.7	BLQ
Skin	79.05	224.5	208.7	99.74
Uveal tract	76.22	76.27	132.9	BLQ
Bone marrow	32.79	76.27	62.71	29.98
Lung	136.4	195.4	260.0	7.82
Pancreas	43.21	98.76	72.81	20.56
Spleen	36.80	66.18	369.2	12.43
Tooth pulp	51.06	91.33	164.1	BLQ
Nasal mucosa	104.3	141.8	201.2	28.12
Oesaphagus wall	71.57	170.7	130.1	BLQ
Stomach mucosa	52.77	130.3	184.6	BLQ
Small intestine mucosa	270.8	650.6	471.5	BLQ
Caecum mucosa	167.8	321.3	1232	126.8
Large intestine mucosa	488.2	1202	2490	52.51
Rectum mucosa	111.4	599.8	584.6	BLQ
Limit of Quantification	23.50	22.11	21.75	22.01

BLQ - Tissue measurement below lower limit of quantification

NA - Not Available

Table A6_2_01-5: Mean concentration of radioactivity in tissues -Repeated dose study, female rats

	Mean Concentration of [^{14}C]-Cypermethrin residues (ng equivalents/g tissue)			
Number of doses given	**1**	**7**	**9**	**9**
Kill time	**Day 2**	**Day 8**	**Day 10**	**Day 16**
Plasma	579.5	548.4	698.2	24.40
Blood	381.1	344.0	452.9	22.41
Aorta	416.7	462.3	493.5	BLQ
Mandibular lymph nodes	117.3	145.2	154.8	52.88
Kidney cortex	439.6	656.4	926.1	127.2
Kidney medulla	276.9	167.7	238.5	26.22
Liver	651.6	882.9	991.8	103.3
Brain	7.744	9.187	15.54	BLQ
Pineal body	131.5	127.1	96.67	BLQ
Spinal cord	8.279	8.706	20.14	BLQ
Adrenal	220.3	342.9	784.1	358.9
Pituitary	78.67	NA	77.07	19.12
Thymus	36.21	37.97	384.3	BLQ
Thyroid	149.1	139.9	285.2	7.424
Harderian gland	78.99	138.1	193.9	23.93
Intra-orbital lachrymal gland	107.1	127.1	189.3	57.42
Salivary glands	72.32	91.06	152.6	8.599
Brown fat	882.9	1176	1831	280.9
Inguinal fat	203.7	1032	1196	347.2
Peri-renal fat	294.6	1250	2179	705.5
Subcutaneous fat	156.4	385.6	385.1	151.4
Clitoris	140.0	242.7	346.1	64.89
Ovary	247.8	837.5	1042*	715.2*
Uterus	233.1	549.7	943.8	BLQ
Muscle	26.44	23.39	34.66	BLQ
Myocardium	121.2	102.6	161.4	8.439
Tongue	102.5	109.4	150.3	BLQ
Skin	145.5	626.5	619.6	339.7
Uveal tract	166.2	166.6	229.1	BLQ
Bone marrow	92.24	212.0	198.6	111.9
Lung	255.3	258.0	322.1*	30.60
Pancreas	81.24	88.45	201.3	15.65
Spleen	48.60	NA	100.6	BLQ
Tooth pulp	163.2	148.1	236.6	BLQ
Nasal mucosa	168.5	127.9	370.9	51.75
Oesaphagus wall	103.3	210.8	275.4	BLQ
Stomach mucosa	209.4	157.3	341.3	BLQ
Small intestine mucosa	197.1	190.6	1473	BLQ
Caecum mucosa	556.0	562.9	591.8	BLQ
Large intestine mucosa	731.2	733.3	1344	BLQ
Rectum mucosa	1056	195.5	1764	BLQ
Limit of Quantification	23.23	25.96	22.11	22.11

BLQ – Tissue measurement below lower limit of quantification

NA – Not Available

* - Measurement affected by high levels of radioactivity in surrounding fat or tissue