	The animals were young healthy adult specific pathogen free mice of the [redacted] strain. At the beginning of the study the animals were aged between 4 and 7 weeks. The male animals weighed 26-34 g and the females weighed 23-29 g. Groups of five male and five female mice were used. Each animal was fasted for at least 3 hours immediately prior to being given a single dose of test substance in corn oil. Four dose levels were used, 1, 5, 25 and 100 mg/kg. A standard volume of 10 ml/kg bodyweight was dosed to each animal and differences in the dose-levels were achieved by altering the concentration of the dosed solution. The volume of the dose was calculated for each animal according to its weight at the time of dosing. Animals were observed for signs of systemic toxicity between 30 and 90 minutes and between 4 and 6 hours after dosing. Subsequent observations were made daily up to day 15. The animals were weighed at intervals throughout the study. Animals were given a post mortem examination for any macroscopic signs of abnormalities.	X2
Results:	None of the animals died following a dose of 1 or 5 mg/kg. All animals died following a dose of 100 mg/kg. A proportion of the animals died in the 25 mg/kg bw group. Deaths occurred up to day 5 of the study. Signs of toxicity were seen in animals at the higher dose levels; the most common effects were ataxia, upward curvature of the spine, urinary incontinence, piloerection, salivation. The clinical signs are consistent with pyrethroid toxicity. All surviving mice increased in bodyweight throughout the study and by day 8 all bodyweights were equal to or exceeded the initial bodyweight. No macroscopic signs of abnormalities were observed in any of the animals which were examined by necropsy.	
Conclusion:	The acute oral LD_{50} was 19.9 mg/kg to male and female mice (approximate 95% confidence limits 5, 100 mg/kg).	X3 X4

Reliability Indicator	1
Data Protection Claim	Yes

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.1.1 / 02	**Acute toxicity – Oral**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	August 2006
Materials and Methods	[redacted]

	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	6.1.2 / 01	Acute toxicity – Dermal	Official use only
91/414 Annex Point addressed	II 5.2.2	Acute toxicity - percutaneous	

Title:	„PP321: Acute Dermal Toxicity Study"	
Lab Report Number:	No. [redacted]/P/1149	
Authors:	[redacted]	
Test Substance:	Technical grade *lambda*-cyhalothrin (otherwise known as PP321). Purity [redacted] w/w.	X1
Species:	Rat	
Method:	OECD Guideline 402 "Acute dermal Toxicity"	
Date of Report:	1985	
Published:	No	
GLP:	Yes	
Reliability:	1	

Material and Methods:	The purpose of the study was to assess the acute toxicity of the test substance following administration of a single 24 hour dermal application. The animals were young healthy specific pathogen free	

[2] Finney, D.J. (1971). Probit Analysis, 3rd edition. Cambridge University Press, p43-44.

	(SPF) adult rats of the [redacted] strain. At the beginning of the study the males weighed 162-241 g and the females weighed 126-235 g. Groups of five male and/or five female rats were used. The hair was removed from an area approximately 10 cm x 5 cm on each rat. Five dose levels were used. Dose levels of 300, 600 and 900 mg/kg were administered to groups of male and female rats. A dose level of 750 mg/kg was administered to a group of male rats and a dose level of 1200 mg/kg was administered to a group of female rats. The appropriate amount of test material was weighed out onto a patch and then made into a paste with 0.5 ml of propylene glycol vehicle before being applied to the animal. The test material was applied under a semi-occlusive dressing for 24 hours. Animals were observed for signs of systemic toxicity between 2 and 4 hours after dosing. Subsequent observations of systemic toxicity and skin irritation were made once daily up to day 15. The animals were weighed at intervals throughout the study. Animals were given a post mortem examination for any macroscopic signs of abnormalities.	X2 X3
Results:	None of the animals died following a dose of 300 mg/kg. All males died following a dose of 900 mg/kg. In all other groups a proportion of the animals died. Signs of toxicity were seen in all animals; the most common effects were decreased activity, splayed gait, dehydration, upward curvature of the spine, urinary incontinence/signs of urinary incontinence, pilo-erection, salivation and pinched sides. The clinical signs seen are consistent with pyrethroid toxicity. All surviving rats increased in bodyweight throughout the study. No macroscopic signs of abnormalities were observed in any of the animals, all of which were examined by necropsy.	
Conclusion:	The acute dermal MLD value to male rats was 632 mg/kg (approximate 95% confidence limits 300, 900 mg/kg). The acute dermal MLD value to female rats was 696 mg/kg (95% confidence limits 309, 1169 mg/kg).	X4 X5

Reliability Indicator	1
Data Protection Claim	Yes

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.1.2 / 01	**Acute toxicity – Dermal**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	August 2006
Materials and Methods	[redacted]

Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
[redacted]	[redacted]

98/8 Doc IIIA section No.	**6.1.3 / 01**	**Acute toxicity – Inhalation**	**Official use only**
91/414 Annex Point addressed	**II 5.2.3**	Acute toxicity - inhalation	

Title:	„4 Hour Acute Inhalation Toxicity Study in the Rat"	
Lab Report Number:	No. [redacted]/P/1683	
Authors:	[redacted]	
Test Substance:	Technical grade *lambda*-cyhalothrin (otherwise known as PP321). Purity [redacted] w/w.	X1 X2
Species:	Rat	
Method:	OECD Guideline 403 "Acute Inhalation Toxicity"	
Date of Report:	1987	
Published:	No	
GLP:	Yes	

Material and Methods:	The objective of this study was to determine the 4-hour acute inhalation toxicity of the test substance in the rat. Specific pathogen free, Alpk:AP (Wistar-derived), albino	

[3] Finney, D. J (1971). Statistical Methods in Biological Assay, 3rd Ed, London Griffin Press.

	rats were used. The animals were acclimatised to the laboratory environment for 7 days prior to exposure. On arrival, animals were housed five to a cage (sexes separately). The room in which they were kept was maintained at a nominal temperature and relative humidity of 21 ± 2°C and 40-60% respectively. Daily measurements of both were made using wet and dry bulb hygrometers. Pelleted Porton Combined Diet (supplied by Special Diets Services Limited, Witham, Essex, UK) and water were provided ad libitum. Five days after arrival, rats were randomised using the Latin square method and allocated to four experimental groups, 5 males and 5 females per group. Animals were approximately 8 weeks old at the start of the study with bodyweight ranges on day 1 of males – 210 to 246 g and females 183 to 224 g. Groups of 5 males and 5 females were exposed, nose only, for a single four-hour period to atmospheres containing *lambda*-cyhalothrin at target concentrations of 0.010, 0.035 and 0.070 mg/L. A concurrent control group was similarly treated by exposed only to air. Atmospheres were generated using a Wrights dust feed and were carried to the exposure chamber by the addition of clean dry air. Particulate concentrations close to the animals' breathing zone were measured gravimetrically on filters at intervals during the exposure period and an assessment of the aerodynamic particle size made using a Marple cascade impactor. Trapped particulate on filters and on the cascade impactor stages were analysed for *lambda*-cyhalothrin using ultraviolet spectroscopy. All rats were examined pre-experimentally for clinical abnormalities, and were examined frequently, both during exposure and daily during the 14-day maintenance period. All rats were weighed on day -1 prior to exposure, on day 1 and then on days 2, 3, 8 and day 15. On day 15, surviving animals were killed by overexposure to halothane (FluothaneÔ, ICI Pharmaceuticals) vapour and exsanguinated by cardiac puncture. Rats were subjected to a macroscopic post mortem examination with particular attention given to the abdominal and thoracic viscera. Lungs and liver were excised and their weights recorded. The lungs (inflated with saline), liver and any abnormal tissue were preserved in 10% buffered formol saline. Animals killed in extremis were similarly examined as soon as possible after death.	

Borttaget: September

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Results:	The achieved particulate concentrations during the study were 0.015, 0.041 and 0.071 mg/l corresponding to analysed *lambda*-cyhalothrin concentrations of 0.014, 0.038 and 0.066 mg/l. There were no deaths and no significant changes in clinical condition in animals exposed to 0.015 mg/l *lambda*-cyhalothrin. One female exposed to 0.041 mg/l and three males and three females exposed to 0.071 mg/l were killed in extremis on day 2 with symptoms consistent with pyrethroid toxicity. Similar though less severe changes were seen in surviving animals, in addition to clinical changes associated with mild respiratory irritation. In general, most animals had recovered by day 5. There was a dose related bodyweight loss following exposure. Most animals had gained weight by day 8 and the subsequent day to day bodyweight gain of surviving animals was similar to controls. There was an apparent dose related increase in lung: bodyweight ratio in both sexes with females less affected than males. This finding correlated with post mortem findings and is considered to be attributable to mild pulmonary irritation. There were no other treatment related macroscopic findings at post mortem.	X5 X3 X4
Conclusion:	In conclusion, the four-hour LC_{50} of *lambda*-cyhalothrin in the rat is 0.06 mg/l.	X5

Reliability Indicator	1
Data Protection Claim	Yes

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	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.1.3 / 01	**Acute toxicity – Inhalation**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	August 2006
Materials and Methods	[redacted]
Results and discussion	[redacted]

[redacted]

Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	6.1.4 / 01	Acute toxicity – Skin and eye irritation	Official use only
91/414 Annex Point addressed	II 5.2.4	Acute toxicity - skin irritation	

Title:	„PP321 : Skin Irritation Study"	
Lab Report Number:	No. [redacted]/P/1139	
Authors:	[redacted]	
Test Substance:	Technical grade *lambda*-cyhalothrin (otherwise known as PP321). Purity [redacted]% w/w.	X1
Species:	Rabbit	
Method:	OECD Guideline 404 "Acute Dermal Irritation/Corrosion"	
Date of Report:	1985	
Published:	No	
GLP:	Yes	

Material and Methods:	The purpose of the study was to assess the skin irritation potential of the test substance following a single four hour application to rabbit skin. A group of six female New Zealand White albino rabbits was used for this test. The rabbits were supplied by [redacted] and were aged between 11 and 17 weeks (weighing 2.22-3.46 kg) at the beginning of the study. Approximately 24 hours before application of the test substance the hair was clipped from the flanks. The test substance (approximately 500 mg) was then moistened to a paste with a small amount (0.4 ml) of distilled water and applied to the test site. The treated area (25 mm x 25 mm) was covered with an occlusive dressing for four hours. The dressing was removed and the application site was decontaminated using swabs soaked in methylated spirit followed by clean warm water. Twenty hours after removal of the dressings, plastic collars were fitted. The Draize scale (as detailed in the report) was used to assess the degree of erythema at the application sites approximately 1, 20, 44 and 68 hours, 5, 7, 9 and 14 days after removal of the dressings. All animals were killed at the end of the study. Mean erythema scores were calculated. Individual erythema scores at 20, 44 and 68 hour readings were added together and the total divided by 18. Mean oedema scores were calculated in a similar manner.	X2 X3
Results:	No erythema was seen during the study and only very slight oedema was seen in four of the six animals one hour after decontamination. All signs of oedema had disappeared within twenty hours. The mean erythema and oedema scores were zero.	X4
Conclusion:	Lambda-cyhalothrin was classified as non-irritant, after a four-hour application to rabbit skin, according to Annex VI, Part IIB of the Sixth Amendment of Directive 67/548/EEC.	

KEY SCORES FOR LABELLING

Mean Scores for Days 1, 2 and 3

Animal numbers

	31	32	33	34	35	36
Mean erythema	0	0	0	0	0	0
Mean oedema	0	0	0	0	0	0

These data do not appear in the report but are derived from individual scores reported in [redacted]/P/1139.

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.1.4 / 01	Acute toxicity - skin irritation
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	August 2006
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	6.1.4 / 02	Acute toxicity – Skin and eye irritation	Official use only
91/414 Annex Point addressed	II 5.2.5	Acute toxicity – eye irritation	

Title:	„PP321 : Eye Irritation Study"	
Lab Report Number:	No. [redacted]/P/1207	
Authors:	[redacted]	
Test Substance:	Technical grade *lambda*-cyhalothrin (otherwise known as PP321). Purity [redacted] w/w.	X1
Species:	Rabbit	
Method:	OECD Guideline 405 "Acute Eye Irritation/Corrosion"	
Date of Report:	1985	
Published:	No	
GLP:	Yes	

Material and Methods:	The purpose of the study was to assess the eye irritation potential of the test substance following application to the rabbit eye. A group of 6 male New Zealand White albino rabbits was used for this test. The rabbits were aged between 11 and 17 weeks (weighing 2.59-3.65 kg) at the beginning of the study. The eyes were examined prior to the test and only rabbits without any apparent eye defects or ocular irritation were used. The test substance (approximately 100 mg) was applied into the conjunctival sac of the left eye. The other eye was untreated (control eye). Immediately after application, initial pain was assessed. Approximately 2 hours after application five drops of local anaesthetic (OphthaineÔ, 0.5% proparacaine hydrochloride solution) was instilled into the eyes of 2 of the rabbits over a period of 15 minutes to attempt to alleviate signs indicative of paraesthesia. The eyes were examined and the Draize scale (detailed in the report) was used to assess the grade of ocular reactions 1-2 hours, 1, 2, 3, 4, 7, 10 or 11 days (2 animals), 13 (1 animal) and 17 (1 animal) days after application of the test sample. The scheme used to interpret and classify the scores was detailed in the report. As an aid in the assessment of corneal damage, fluorescein staining was used at the 1, 2, 3, 4, 7, 13 and 17 day readings. At the end of the study all the animals were killed.	X2
Results:	Practically no or slight initial pain (class 1-2 on a 0-5 scale) was observed immediately after application of *lambda*-cyhalothrin into the eye. An hour after application, conjunctival effects were seen in all the animals which consisted of slight or moderate redness, slight or mild chemosis and slight or severe discharge. Two days after application slight or moderate redness, slight chemosis and slight discharge were present. Four of the animals had recovered after 4 days and the remaining 2 animals recovered after 10 days. During the first 24 hours of the study all animals showed signs of paraesthesia, which is a common finding in eye irritancy studies with pyrethroids. Administration of OphthaineÔ did not alleviate the signs.	X3
Conclusion:	Lambda-cyhalothrin was classified as a mild irritant (class 4 on a 1-8 point scale) to the rabbit eye.	

KEY SCORES FOR LABELLING

Mean Scores for Days 1, 2 and 3

Lesion Mean Draize Score (6 animals)

Animal Number	31	32	33	34	35	36
Corneal opacity	0	0	0	0	0	0
Iritis	0	0	0	0	0	0
Conjunctival redness	0.7	1.7	1.7	1.0	1.7	0.3
Chemosis	0.7	0.3	0	0.3	0.7	0.3

This table is not given in the report but the data are derived from individual scores reported in [redacted]/P/1207.

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.1.4/02	**Acute toxicity – eye irritation**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	August 2006
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	**6.1.5 / 01**	**Acute toxicity – Skin sensitisation**	Official use only
91/414 Annex Point addressed	**II 5.2.6**	Acute toxicity - skin sensitisation	

Title:	'PP321: Skin Sensitisation Study"	
Lab Report Number:	No. [redacted]/P/1054	

Authors:	[redacted]	
Test Substance:	Technical grade *lambda*-cyhalothrin (otherwise known as PP321). Purity [redacted]% w/w.	X1
Species:	Guinea Pigs	
Method:	OECD Guideline 406 "Skin Sensitization"	
Date of Report:	1984	
Published:	No	
GLP:	Yes	

Material and Methods:	The purpose of the study was to assess the skin sensitizing properties of the test substance. The animals were male Dunkin Hartley guinea pigs. At the beginning of the main study, the animals were aged between 4 and 7 weeks and they weighed between 315-455 g. Two main procedures were involved, the induction of an immune response and a challenge of that response. A group of thirty guinea pigs was used, twenty test and ten control animals. The first induction procedure consisted of three intradermal injections (0.1 ml each) each side of the mid-line on the scapular region. One week later a topical application (approximately 0.25 ml on filter paper) of the test substance was applied over the injection sites. The topical application site was occluded for 48 hours. Control animals received the bandage alone. <u>Intradermal Induction:</u> Test animals i) Freund's Complete Adjuvant plus corn oil in the ratio 1:1. ii) A 5% (w/v) solution of the test substance in corn oil. iii) A 5% (w/v) solution of the test substance in a 1:1 preparation of Freund's complete adjuvant plus corn oil. Control animals The intradermal induction procedure was identical to that used for the test animals, except that the test substance was not administered. <u>Topical Induction:</u> Test animals 1% w/v preparation of the test substance in corn oil. Control animals Corn oil only.	X2(iii) X3 X2(ii)

	Two weeks after the topical induction, all animals were challenged on the flanks (0.1 ml on filter paper). The challenge application site was occluded for 24 hours and examined for erythema 24 and 48 hours after the removal of the dressings. Challenge: Test and control animals - 1% (w/v) preparation of the test substance in corn oil. To classify the sensitisation response, the percentage of control animals that responded was subtracted from the percentage of test animals that responded. The report does not include information on a positive control study. However, a separately reported positive control study using the Magnusson and Kligman test procedure was performed at this time. In this study, guinea pigs were intradermally induced with a 0.1% preparation followed by a topical induction with a 40% preparation of formaldehyde in water. Challenge with a 50% preparation of formaldehyde in water elicited a moderate sensitisation response. This result confirmed the sensitivity of the test method and the responsiveness of the strain of guinea pig used ([redacted] 1987). The study details are provided below. The positive control study was conducted in a similar manner using a 40% w/v aqueous formaldehyde solution as the test substance and the following dose levels: Intradermal Induction: Test animals i) Freund's Complete Adjuvant plus deionised water in the ratio 1:1. ii) A 0.1% (w/v) solution of the test substance in deionised water. iii) A 0.1% (w/v) solution of the test substance in a 1:1 preparation of Freund's complete adjuvant plus deionised water. Control animals The intradermal induction procedure was identical to that used for the test animals, except that the test material was not administered. Topical Induction: Test animals 40% w/v preparation of the test substance in	X4

	deionised water. Control animals - deionised water only. Two weeks after the topical induction, all animals were challenged on the flanks (0.1 ml on filter paper). The challenge application site was occluded for 24 hours and examined for erythema 24 and 48 hours after the removal of the dressings. Challenge: Test and control animals 50% (w/v) preparation of the test substance in deionised water. To classify the sensitisation response, the percentage of control animals that responded was subtracted from the percentage of test animals that responded.	
Results:	Challenge concentration — No. of animals showing erythema: Test Animals / Control Challenge 1% (w/v) — 0/18 / 0/10 None of the previously induced guinea pigs showed an erythematous response when challenged with a 1% w/v preparation of *lambda*-cyhalothrin in corn oil. Lambda-cyhalothrin was therefore not a skin sensitiser under the conditions of the test.	X5 X6
Conclusion:	Based on the lack of positive responses to challenge in either the test or control group, *lambda*-cyhalothrin was not found to induce delayed contact hypersensitivity in this maximization test. The test substance does not require labelling as a skin sensitiser in accordance with EC classification directives.	

Reliability Indicator	1
Data Protection Claim	Yes

98/8 Doc IIIA section No. 6.1.5 / 01	**Acute toxicity – Skin sensitisation**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	August 2006
Materials and Methods	[redacted] approximately 24 hours before the topical application, be painted with 0.5ml of 10%

Borttaget: September

Borttaget: 0

	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

2. TOXICOKINETICS

98/8 Doc IIIA section No.	6.2 / 01	Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study	Official use only
91/414 Annex Point addressed	II 5.1.	Absorption, distribution and excretion in mammals	

Title:	cyhalothrin: The Disposition and Metabolism of 14C-ICI 146,814 in Rats Part I (report 6.2/01a): The Metabolism and Disposition ICI 146, 814 in Rats: Part II. Tissue Residues derived from [14C-benzyl] or [14C-cyclopropyl]-ICI 146, 814 after a single oral dose of 1 or 25 mg/kg (report 6.2/01b)	
Lab Report Number:	No. [redacted] C/1279A and [redacted]/C/1279B	
Authors:	[redacted] 1981	
Test Substance:	Technical cyhalothrin (otherwise known as PP563). Purity [redacted]% w/w.	X1
Species:	Rat	
Method:	OECD guideline reference 417	
Date of Report:	1981 and 1984	
Published:	No	
GLP:	No/Yes	X2

Material and Methods:	The objectives of these studies were to determine the absorption, metabolism, distribution and excretion of single doses of the cyclopropyl and benzyl-labelled forms of cyhalothrin at two dose levels. Other studies are presented to show equivalence of cyhalothrin and *lambda*-cyhalothrin (see IIIA 6.2/06). Young adult male and female rats (Alpk:ApfSD Wistar-derived strain) were used. The excretion and metabolism of both radiolabelled forms of cyhalothrin were studied in the following dosing groups: 1. Six male and six female rats were each given a single oral dose of 1 mg [14C-benzyl] cyhalothrin/kg; urine and faeces were collected for six days, expired air was collected over the first 24 hours. 2. Six male and six female rats were each given a single oral dose of 25 mg [14C-benzyl] cyhalothrin/kg; urine and faeces were collected for six days.	X4 X5

	3. Six male and six female rats were each given a single oral dose of 1 mg [14C-cyclopropyl] cyhalothrin/kg; urine and faeces were collected for seven days, expired air was collected for the first 24 hours. 4. Six male and six female rats were each given a single oral dose of 25 mg [14C-cyclopropyl] cyhalothrin/kg; urine and faeces were collected for six days. Concentrations of radioactivity in 12 tissues were analysed for groups 1-4 at termination. 5. Five male and six female rats were each given a subcutaneous dose of 1 mg [14C-benzyl] cyhalothrin/kg; urine and faeces were collected for six days, expired air was collected over the first 24 hours. 6. Three male and four female rats surgically equipped with a biliary fistula were each given a single oral dose of 1 mg [14C-benzyl] cyhalothrin/kg; urine and bile were collected for up to 96 hours. The experiment was repeated in four male rats supplied with replacement bile. Bile and urine samples were assayed for radioactive content. 7. Six male and six female rats were each given a single oral dose of 1 mg [14C-benzyl] cyhalothrin/kg; they were serially bled by tail vein at 8 intervals up to 48 hours. 8. Six male and six female rats were each given a single oral dose of 25 mg [14C-benzyl] cyhalothrin/kg; they were serially bled by tail vein at 8 intervals up to 48 hours. 9. Six male and six female rats were each given a subcutaneous dose of 1 mg [14C-benzyl] cyhalothrin/kg; they were serially bled by tail vein at 8 intervals up to 48 hours. 10. Six male and six female rats were each given a single oral dose of 1 mg [14C-cyclopropyl] cyhalothrin/kg; they were serially bled by tail vein at 8 intervals up to 48hours. Whole blood from groups 7-10 was analysed for radioactive content by liquid scintillation counting, and for cyhalothrin content by a gas chromatography method.	X6
Results:	The excretion profile for total radioactivity in 0-7 day excreta following a single oral dose of [14C]-cyhalothrin is tabulated below.	

Most of the radioactivity was rapidly eliminated in the first 24 hours after dosing; however a small proportion of the dose remained in the carcass at seven days accounting for 2-3% of the dose. X7 X8

Following oral administration of [14C]-cyhalothrin to rats at 1 mg/kg and 25 mg/kg, absorption was variable. The extent of absorption was estimated as approximately 55% of the administered dose, based on the ratio of urinary and faecal elimination following subcutaneous administration. X9

The proportions of absorbed dose on this basis were similar at both dose levels.

In bile duct cannulated rats, cyhalothrin was poorly absorbed (see table below), however when replacement bile was given the proportion of the dose excreted in urine and bile was approximately doubled.

The recovery of radioactivity in 0-4 day urine and bile following a single oral dose of 1 mg [^{14}C]-benzyl cyhalothrin/kg is tabulated below:

Dose	Sex	Urine	Bile	Total
1mg/kg	M	8.3± 0.5	4.8± 0.7	13.1± 0.3
[14C-benzyl]	M*	16.8+/-3.7	11.2+/-4.2	28.0+/-7.7
	F	7.2+/-3.0	8.9+/-4.0	16.1+/-6.5

* (received donor bile)

The [^{14}C] cyhalothrin absorbed after oral administration was completely metabolised and excreted primarily as conjugates, as judged by ß-glucuronidase hydrolysis experiments and TLC analysis of excreta before and after enzyme treatment. Metabolite patterns from each radiolabel form were completely different indicating extensive ester cleavage. The highest concentration of radioactivity was found in the fat (0.165-0.344 µg cyhalothrin equivalents/g) following a 1 mg/kg dose and (6.41-11.84 µg cyhalothrin equivalents/g) following a 25 mg/kg dose.

The blood radioactivity concentration time profile was very similar for male and female rats regardless of dose. The highest concentration of radioactivity in blood after a single oral dose of 1 mg [14C-benzyl] cyhalothrin/kg was 0.5-0.7 µg equivalents cyhalothrin/ml and occurred 4-7 hours after dosing. A similar blood concentration profile was found after a single oral dose of [14C]-cyclopropyl cyhalothrin. After a single oral dose of 25 mg [14C-benzyl] cyhalothrin/kg, peak blood levels were 5.9-6.4 µg X10 X11

	equivalents cyhalothrin/ml. The blood elimination half life for radioactivity was estimated as 11 hours. The maximum concentration of unchanged cyhalothrin in blood at the high dose was detected at 2 hours post dose, accounting for approximately 5% of the radioactivity present in blood.	
Conclusion:	cyhalothrin, labeled at either the benzyl or cyclopropyl part of the molecule, was incompletely absorbed following oral administration (approximately 55% of dose), irrespective of dose level. Radioactivity was eliminated rapidly in the first 24 hours after dosing, and after 7 days, 2-3% of dose remained in the carcass, mostly in white fat. The [14C] cyhalothrin absorbed after oral administration was completely metabolised and excreted primarily as conjugates, as judged by ß-glucuronidase hydrolysis experiments and TLC analysis of excreta before and after enzyme treatment. No parent material was detected in blood, urine or bile. Metabolite patterns from each radiolabel form were completely different indicating extensive ester cleavage. The blood radioactivity concentration time profile was very similar for male and female rats regardless of dose. . The blood elimination half life for radioactivity was estimated as 11 hours. The maximum concentration of unchanged cyhalothrin in blood at the high dose was detected at 2 hours post dose, accounting for approximately 5% of the radioactivity present in blood.	X12

Dose (Oral)	Sex	% Recovery of Administered Dose		
		Urine	Faeces	Total
1 mg/kg	M	**30.0+/-12.4**	**61.4+/-14.4**	**91.3+/-10.8**
[14C-benzyl]	F	**41.5+/-9.4**	**46.5+/-7.5**	**86.2+/-4.4**
25 mg/kg	M	**40.3+/-10.7**	**49.7+/-14.6**	**90.0+/-10.9**
[14C-benzyl]	F	**40.9+/-9.4**	**40.2+/-7.6**	**81.0+/-6.2**
1 mg/kg	M	**18.6+/-5.4**	**65.7± 4.3**	**84.3+/-3.2**
[14C-cyclopropyl]	F	**24.5+/-7.3**	**58.7+/-9.6**	**83.2+/-2.9**
25 mg/kg	M	**26.9+/-8.2**	**60.9+/-8.4**	**87.9+/-2.9**
[14C-cyclopropyl]	F	**39.3+/-7.0**	**45.9+/-7.9**	**85.2+/-1.9**

Reliability Indicator	1	
Data Protection Claim	Yes	

Evaluation by Competent Authorities	
98/8 Doc IIIA section No. 6.2 / 01	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**

Borttaget: September

Borttaget: 0

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	August 2006
Materials and Methods	[redacted]
Results and discussion	[redacted]

Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	**6.2 / 02**	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**	**Official use only**
91/414 Annex Point addressed	**II 5.1**	Absorption, distribution and excretion in mammals	

Title:	cyhalothrin: The Disposition and Metabolism of 14C-ICI 146,814 in Rats Part III: Studies to determine radioactive residues in the rat following 14 days repeated oral administration	X1
Lab Report Number:	No. [redacted]/C/1279C	
Authors:	[redacted] 1981	
Test Substance:	Technical cyhalothrin (otherwise known as PP563). Purity [redacted]2% w/w. 14C-benzyl cyhalothrin batch [redacted] (19.53 µCi/mg, radiochemical purity [redacted]% and 14C-cyclopropyl cyhalothrin batch [redacted]3 (10.49 µCi/mg, radiochemical purity >98.8%)	
Species:	Rat	
Method:	OECD guideline reference 417	
Date of Report:	1984	
Published:	No	
GLP:	No/Yes	

Material and Methods:	The objective of the study was to determine the excretion and tissue distribution of 13 repeat daily doses of 1 mg/kg bw/day cyhalothrin, followed by a single dose of the cyclopropyl and benzyl-labelled forms of cyhalothrin. Young adult male and female rats (Alpk:ApfSD Wistar-derived strain) were used. Test materials were dissolved in corn oil for oral administration. Urine and faeces samples were collected from the end of dosing every 24 hours up to 7 days after the final dose. Groups of two male and two	X2

	female animals were killed at 2, 5 and 7 days after the final dose and a range of tissues (heart, brain, lungs, liver, spleen, kidneys, gonads, brown fat, white fat, muscle, bone, blood, residual carcass) removed for measurement of radioactivity. Fat samples were analysed for unchanged cyhalothrin by HPLC.	
Results:	Approximately 91-94% of the cumulated dose was recovered in urine and faeces by 7 days after the last dose. The carcass residue at 7 days (approximately 4% of dose) was due almost entirely to residues in the fat. These fat residues were shown to be 79% unchanged cyhalothrin present at a concentration of 3.3 µg equivalents/g. Using the limited data points available, the elimination half life of cyhalothrin in fat was estimated as 23 days. Tissues such as heart, brain, spleen muscle and bone contained only trace amounts of radioactivity from 2-7 days.	X3
Conclusion:	Repeat oral administration of two radiolabelled forms of cyhalothrin showed rapid absorption and excretion, and tissue distribution similar to that found in animals which received single doses. Over 90% of the oral radioactivity was excreted, mostly in 24 hours, with approximately 4% retained by 7 days after dosing, mostly in white fat, and mostly as unchanged cyhalothrin. The half-life of excretion from white fat is approximately 23 days.	

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.2 / 02	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	August 2006
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

cyhalothrin are compared. However, some of the radioactivity in ovaries may be attributable to fat adherent to the tissue as it is difficult to remove.

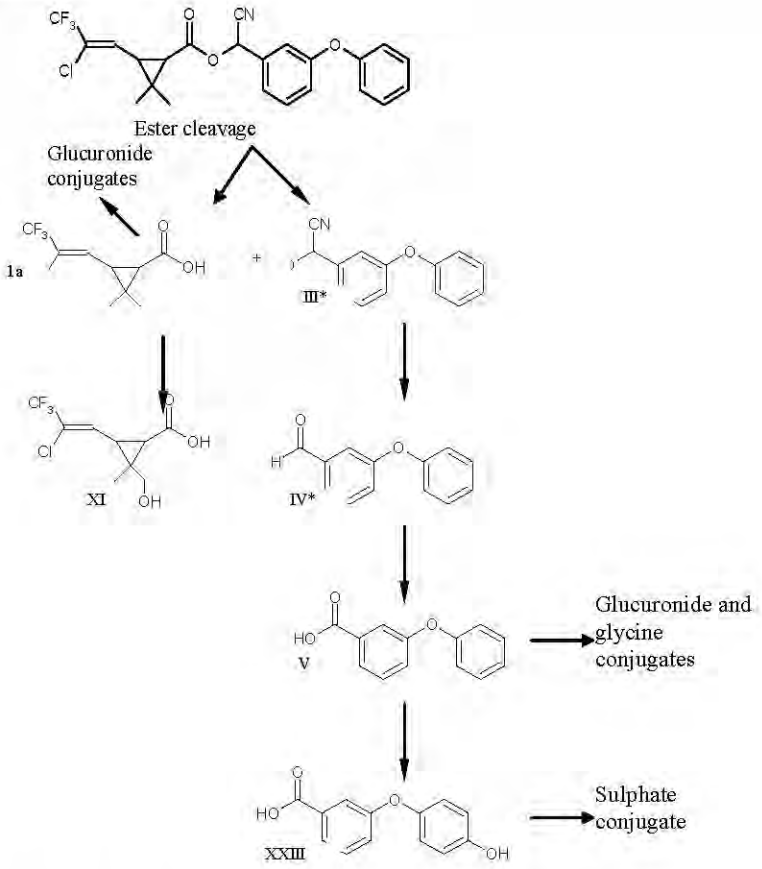
98/8 Doc IIIA section No.	**6.2 / 03**	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**	**Official use only**
91/414 Annex Point addressed	**II 5.1**	Absorption, distribution and excretion in mammals	

Title:	cyhalothrin: The Metabolism and Disposition of [14C]-ICI 146,814 in Rats Part IV	
Lab Report Number:	[redacted]/C/1279D	
Authors:	[redacted] (1983)	
Test Substance:	[14C-cyclopropyl]-cyhalothrin (acid-labelled) was of [redacted] radiochemical purity. Purity [redacted] % w/w.	X1
Species:	Rat	
Method:	OECD guideline reference 417	
Date of Report:	1983	
Published:	No	
GLP:	Yes	

Material and Methods:	The objective of this study was to identify the major pathways of cyhalothrin metabolism in the rat. Young adult male and female (Alpk:APfSD Wistar-derived strain) rats were used. This report describes part of the work done to characterize and identify the major metabolites of cyhalothrin in the rat. The excretion and metabolism of cyhalothrin has been previously reported by [redacted] (1981a). In this study additional rats were dosed as follows to aid metabolite identification. 1. Six male and six female rats were given nominal oral doses of 12.5 mg/kg/day [14C-benzyl] cyhalothrin over a period of eight days until each rat had received approximately 25 mg cyhalothrin. Urine and faeces were collected daily, following dosing and for up to three days after the last dose. 2. Six male and six female rats were each given fourteen consecutive daily oral doses of 1 mg [14C-cyclopropyl] cyhalothrin/kg, and the urine was collected and combined.	X3 X4

	Metabolite profiles were determined by thin layer chromatography (TLC), both before and after enzymic hydrolyses using aryl sulphatase and ß-glucuronidase enzymes. Individual metabolites were purified by reverse phase HPLC prior to analysis by GC-MS, probe MS, FAB-MS and/or 13C-NMR.	
Results:	TLC analysis of urine from rats dosed with [14C-benzyl] cyhalothrin showed there to be one major component (approximately 75% of the radioactivity) and three minor metabolites. The major component in urine was identified following 13C-NMR and aryl sulphatase hydrolysis as the sulphate conjugate of 3-(4'-hydroxyphenoxy) benzoic acid (compound XXIII). The identity of this metabolite was confirmed by FAB mass spectrometry of the intact sulphate. The un-conjugated 3-(4'-hydroxy-phenoxy) benzoic acid was also identified as a minor metabolite. The least polar component co-chromatographed with 3-phenoxybenzoic acid (compound V), and its identity was confirmed by GC-MS analysis of the methylated metabolite. TLC analysis of urine from rats dosed with [14C-cyclopropyl] cyhalothrin showed there to be one major component (approximately 50% of the radioactivity) and at least four minor metabolites (total ca. 37%). The major component was completely hydrolysed following treatment with ß-glucuronidase to give an increased proportion of one of the minor metabolites. This metabolite was identified as 3(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (compound Ia) by co-chromatography and was confirmed by mass spectrometry. The identity of the major metabolite as the glucuronide conjugate of cyclopropane acid was confirmed by FAB mass spectrometry of the intact conjugate and by TLC analysis of excreta before and after enzyme treatment. One of the minor metabolites also appeared to be a glucuronide conjugate, which was tentatively identified as a hydroxylated analogue of cyclopropane acid (compound XI). Thus, the major pathways of cyhalothrin metabolism were elucidated and, as reported by [redacted] (1981a), these involved extensive ester cleavage and conjugation prior to urinary elimination. A pathway, illustrating the proposed biotransformation of cyhalothrin in the rat, is presented below.	X5

Proposed metabolic pathway:



* Metabolic intermediates which are too unstable to be detected in animals

Conclusion:	The metabolic pathway of cyhalothrin involved extensive ester cleavage and conjugation prior to urinary elimination.	
Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.2 / 03	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**
Date	EVALUATION BY RAPPORTEUR MEMBER STATE August 2006
Materials and Methods	[redacted]

Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	**6.2 / 04**	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**	**Official use only**
91/414 Annex Point addressed	**II 5.1**	Absorption, distribution and excretion in mammals	

Title:	cyhalothrin: Tissue Distribution and Elimination Following a Single Oral Dose (1 mg/kg) in the Rat.	
Lab Report Number:	[redacted]/P/2489	
Authors:	[redacted]	
Test Substance:	cyhalothrin (otherwise known as PP563). Purity [redacted]% w/w.	X1
Species:	Rat	
Method:	OECD guideline reference 417	
Date of Report:	1989	
Published:	No	
GLP:	Yes	

Material and Methods:	The objectives of this study were to determine the tissue distribution of radioactivity with time in rats following the single oral administration of a low dose level of [14C]-methine-labelled cyhalothrin (elsewhere referred to as benzyl or 3-phenoxybenzyl-label).	

	Fifteen male and fifteen female young adult rats (Alpk:ApfSD Wistar-derived strain) were used. Each rat was given a single oral dose of 1 mg [14C-methine] cyhalothrin/kg in corn oil (4 ml/kg). Three male and female rats were killed at intervals of 6.5, 11 (13 females), 24, 48 and 96 hours after dosing. Timepoints were chosen to cover the time of peak blood level and the timepoint corresponding to half maximal blood concentration. Samples of plasma, whole blood, liver, kidneys, lungs, spleen, bone, brain, heart, muscle, gonads, white and brown fat from each rat were analysed for radioactive content.	X2
Results:	The highest concentration of radioactivity in male and female rats was found in brown fat at 6.5 hours after dosing with concentrations of 0.89 and 1.45 µg cyhalothrin equivalents/g respectively. The concentration of radioactivity in brown fat declined relatively quickly from the peak during the course of the study. Whilst the concentration of radioactivity in white fat was generally lower than that of brown fat (peaks of ca. 0.35 µg cyhalothrin equivalents/g in both male and females) these concentrations did not decline from their peak to the same extent as brown fat. This result was consistent with previously determined half life of 30.5 days for cyhalothrin in fat [redacted], 1984). Of the other tissues analysed, liver had the highest peak concentration of radioactivity at 0.53 and 1.11 µg cyhalothrin equivalents/g in male and female rats respectively at times corresponding to peak blood levels. Progressively lower concentrations of radioactivity were found in the following tissues; lungs, blood, kidneys, heart and testes. Only low concentrations of radioactivity of approximately 0.1 µg cyhalothrin equivalents/g or less were detected in the remaining tissues; muscle, spleen, bone, and brain. No marked sex differences were noted in elimination profiles with the exception of the ovaries. However, as it is difficult to remove all of the (white) fat from the ovaries, some of the radioactivity associated with the ovaries may be attributable to traces of fat adherent to the organs.	X4 X5 X6 X7
Conclusion:	Excretion of methine-labelled cyhalothrin was similar to cyclopropyl -labelled form, with rapid elimination from most tissues, and a small proportion of the dose retained in fat.	X8

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.2 / 04	Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	August 2006
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]e
Remarks	[redacted]

98/8 Doc IIIA section No.	6.2 / 05	Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study	Official use only
91/414 Annex Point addressed	II 5.1	Absorption, distribution and excretion in mammals	

Title:	cyhalothrin: Tissue Distribution and Elimination Following a Single Oral Dose (25 mg/kg) in the Rat.	
Lab Report Number:	[redacted]/P/2490	
Authors:	[redacted]	
Test Substance:	cyhalothrin (otherwise known as PP563). Purity [redacted]% w/w.	X1

Species:	Rat	
Method:	OECD guideline reference 417	
Date of Report:	1989	
Published:	No	
GLP:	Yes	

Material and Methods:	The objectives of this study were to determine the tissue distribution of radioactivity with time in rats following the single oral administration of a high dose level of [14C]-methine-labelled cyhalothrin(elsewhere referred to as benzyl or 3-phenoxybenzyl-label). Fifteen male and fifteen female young adult rats (Alpk:ApfSD Wistar-derived strain) were used. Each rat was given a single oral dose of 25 mg [14C-methine] cyhalothrin/kg in corn oil (4 ml/kg). Three male and female rats were killed at timepoints chosen to cover the time of peak blood level (10 hours after dosing for males and 7 hours for females) and the timepoint corresponding to half maximal blood concentration (17 hours for males and 21 hours for females). Other intervals were 24 hours for males, 30 hours for females, and 48 and 96 hours for both sexes. Samples of plasma, whole blood, liver, kidneys, lungs, spleen, bone, brain, heart, muscle, gonads, white and brown fat from each rat were analysed for radioactive content.	
Results:	In both sexes, radioactivity was retained in fat, with the highest concentration present in brown fat, with peak values of 15.3 and 15.1 µg equivalents of cyhalothrin for males and females respectively. Half-life elimination from brown fat was 18 and 34 hours, for males and females respectively. Concentrations in peri-renal fat, although lower initially than brown fat, did not decline markedly from peak levels. This result was consistent with the low dose study 6.2/04. Of the other tissues analysed, liver had the highest peak concentration of radioactivity at 9.4 and 8.7 µg cyhalothrin equivalents/g in male and female rats respectively, corresponding to 1.6% and 1.3% of administered dose, at times corresponding to peak blood levels. Progressively lower concentrations of radioactivity were found in the following tissues; lungs, blood, kidneys, heart and gonads. Concentrations of radioactivity of approximately 1 µg cyhalothrin equivalents/g or less were detected in the remaining tissues; muscle, spleen, bone, and brain. No	X3

	marked sex differences were noted in elimination profiles. Half-lives of elimination from most tissues examined were between 6 and 14 hours, with the exception of fat and ovaries (the latter possibly confounded by the difficulty in trimming fat from the ovary). The elimination profiles for these other tissues were similar to that observed for plasma, with a rapid initial decline followed by a slower terminal phase, apparently corresponding to the release of radioactivity from fat depots back into systemic circulation. With the exception of fat, radioactivity concentrations in other tissues declined to the limit of detection by 96 hours.	
Conclusion:	Excretion of a higher dose of methine-labelled cyhalothrin was essentially similar to that of the low dose, with correspondingly (but not proportionally) higher values in tissues. Brown fat peaks at 25 mg/kg were 15.3 and 15.1µg cyhalothrin equivalents/g respectively in males and females, compared to 0.89 and 1.45 µg cyhalothrin equivalents/g respectively at 1 mg/kg bw. The slower terminal elimination phase at the high dose level was considered to be due to the release of radioactivity from fat depots, back into circulation for redistribution to tissues	

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.2 / 05	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	August 2006
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	**6.2 / 06**	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**	**Official use only**

91/414 Annex Point addressed	**II 5.1**	Absorption, distribution and excretion in mammals

Title:	PP321: Comparative Absorption Study in the Rat	
Lab Report Number:	[redacted]/P/1214.	
Authors:	[redacted]	
Test Substance:	cyhalothrin (otherwise known as PP563).Lambda-cyhalothrin (PP321) Purity [redacted]% w/w.	X1
Species:	Rat	
Method:	OECD guideline reference 417	
Date of Report:	1985	
Published:	No	
GLP:	Yes	

Material and Methods:	The objective of this study was to establish whether *lambda*-cyhalothrin is metabolised in the same way as cyhalothrin. This experiment was designed to compare the metabolism of *lambda*-cyhalothrin (a partially resolved material containing one enantiomeric pair) with cyhalothrin (a mixture of 2 enantiomeric pairs), and thereby to test the validity of using toxicological data derived following administration of cyhalothrin to support the toxicological evaluation of *lambda*-cyhalothrin. Young adult male and female rats (Alpk:APfSD Wistar-derived strain) were obtained from the [redacted] The excretion and metabolism of both cyhalothrin and *lambda*-cyhalothrin were studied in the following dosing groups: 1. Four male and four female rats each given a single oral dose of 1 mg/kg [14C]-cyclopropyl labelled cyhalothrin ([14C]-cyhalothrin); urine and faeces collected for three days. 2. Four male and four female rats each given a single oral dose of 1 mg/kg [14C]-cyclopropyl labelled *lambda*-cyhalothrin ([14C]-*lambda*-cyhalothrin); urine and faeces collected for three days.	X2

	3. Four male and four female rats each given a single oral dose of 1 mg/kg [14C]-cyclopropyl labelled *lambda*-cyhalothrin and 1 mg/kg unlabelled R157836 ([14C]-*lambda*-cyhalothrin + R157836), urine and faeces collected for three days. Concentrations of radioactivity in blood, liver, kidneys and fat were analysed for groups 1-3 at termination.	
Results:	Following oral administration of [14C] cyhalothrin, [14C] *lambda*-cyhalothrin, or [14C] *lambda*-cyhalothrin + R157836 to rats at 1 mg/kg, approximately 65% of the administered dose was excreted in faeces and approximately 25% of the dose was excreted in the urine. There were no significant differences in the proportions of dose excreted by either route amongst the different groups. The metabolite profiles for each treatment group were very similar. The major urinary metabolite was tentatively identified as the glucuronide of 3(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethyl-cyclopropne-1-carboxylic acid (cyclopropane acid). Free cyclopropane acid was also identified as a significant urinary metabolite accounting for 3-9% of the urinary radioactivity. Unchanged parent compound was the major radioactive component present in faeces. Most of the radioactivity was rapidly eliminated in the first 24 hours after dosing; by 96 hours residues in blood, liver and kidney were low. Higher concentrations were found in the fat corresponding to 0.25-0.30 µg cyhalothrin equivalents/g. There were no significant differences in tissue residues between the treatment groups.	X3
Conclusion:	The metabolic fate of [14C]-*lambda*-cyhalothrin was the same as that of [14C]-cyhalothrin. Furthermore, the co-administration of equimolar amounts of R157836 (the other enantiomer pair from cyhalothrin) to rats dosed with [14C]-*lambda*-cyhalothrin did not alter the metabolism or disposition of [14C]-*lambda*-cyhalothrin. These findings suggest that it is valid to use toxicological data derived following administration of cyhalothrin to support the toxicological evaluation of *lambda*-cyhalothrin.	

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.2 / 06	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**
Date	**EVALUATION BY RAPPORTEUR MEMBER STATE** August 2006

Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	**6.2 / 07**	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**	**Official use only**
91/414 Annex Point addressed	**II 5.1**	Absorption, distribution and excretion in mammals	

Title:	The Metabolism and Pharmacokinetics of Lambda-cyhalothrin in Man following single oral administration	
Lab Report Number:	[redacted]/P/4208.	
Authors:	[redacted]	
Test Substance:	Lambda-cyhalothrin Purity [redacted]% w/w.	X1
Species:	Man	
Method:	There are no regulatory guidelines for this type of study which was designed specifically to investigate the metabolism and pharmacokinetics of *lambda*-cyhalothrin in man following single oral administration. The study was designed and performed according to the principles of the Declaration of Helsinki (1989 Hong Kong amendment)	
Date of Report:	1994	
Published:	No	
GLP:	Yes	

Material and Methods:	The objectives of this study were to investigate the metabolism and pharmacokinetics of *lambda*-cyhalothrin in man following single oral dosing. Occupational exposure studies have shown that three major metabolites are excreted in urine. One aim of this study was to relate amounts of these metabolites to the amount of parent material administered. Another phase of the study investigated urinary excretion following dermal administration of a formulation. The metabolism and pharmacokinetics of *lambda*-cyhalothrin were studied in the following group of adult male human volunteers: Six volunteers were each given a single oral dose of 5 mg of the test substance as a corn oil solution (25 mg/g) in a gelatin capsule, followed by 150 ml of water. Blood samples were taken from an in-dwelling cannula before dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours post dosing and by venepuncture at approximately 24, 31 and 48 hours. Complete urine collections were made at 2 hourly intervals up to 14 hours then, 14-24 hours followed by 12 hourly periods up to 120 hours. Faeces were collected daily for three days. Blood and excreta samples, including hydrolysed samples were extracted with solvent, which was analysed for the test substance and for 3 specific metabolites. These were 3-(2-chloro-3,3,3,-trifluoropropenyl)-2,2-dimethylcyclopropan-1-carboxylic acid (TFMCVA), 3-phenoxybenzoic acid (3PBA) and 3-(4-hydroxyphenoxy) benzoic acid (4-OH-3PBA). These metabolites were analysed as pentafluoropropionyl derivatives by gas chromatography-mass spectrometry. For the dermal administration phase, 20 mg of *lambda*-cyhalothrin in formulation were applied to an 800 cm^2 area of skin on the backs of 8 volunteers. The dose was dried using a hairdryer, and volunteers were given a loose-fitting T-shirt to wear for 8 hours, after which the test site was washed using a cotton swab moistened with a mild detergent solution. Subjects were given two more T-shirts, for the 8-24 and 24-48 hour periods. Blood, urine and faeces samples were taken as for oral administration.	X2 X3
Results:	Following the administration of a single oral dose of 5 mg test substance, approximately equal amounts of 3-(2-chloro-3,3,3,-trifluoropropenyl)-2,2-dimethylcyclopropa n-1-carboxylic acid (TFMCVA), and 3-phenoxybenzoic acid (3PBA) + 3-(4-hydroxyphenoxy) benzoic acid (4-OH-3PBA) were excreted in urine, with peak excretion rates	X4

	typically in the first 4 hours after dosing. No parent compound was detected in urine. Based upon TFMCVA measurements in urine, the estimated amount of test substance absorbed ranged from 50-64% (average 59%). The mean half lives of elimination for the 3 analysed urinary metabolites ranged from 14 to 17 hours. The presence of intact test substance in plasma showed that the test substance can be absorbed unchanged; however, the observation that the highest plasma concentrations of TFMCVA and 3PBA occurred soon after dosing indicates possible pre-systemic hydrolysis and/or rapid hydrolysis of the test substance in the liver and blood. Unabsorbed test substance and TFMCVA were detected in faeces, but, with the exception of one subject (showing 9% of dose excretion in faeces) accounted for less than 1.5% of the dose. The average amount of test substance accounted for by analyses of the test substance and its metabolites in all excreta samples was 62% of the administered dose. The results expressed as group means are presented in the table below. The variability between subjects in the metabolism and pharmacokinetics of this test substance was quite small. Summary of the recoveries of administered dose Test Substance TFMCVA 3-PBA 4-OH-3-PBA 5 mg Oral Dose Urine + faeces 2.19 56.71 25.12 25.23 Results are expressed as percentages of administered dose and represent group means. The amount of each metabolite was converted to equivalents of the test substance to derive a percentage of dose result. Recovery estimates are based on TFMCVA and PBA parts of the molecule and are independent and therefore are not additive. Following dermal administration of a formulation, and average of 50% (range 38-60%) of dose was recovered from the skin using a mild detergent wash after 8 hours. An average of 24% and 4% were recovered in T-shirts worn between 8-24 and 24-48 hours respectively. A total of 78% of dose was recovered by these procedures. Note that the T-shirt worn for the 8 hours was apparently not analysed, which would account for the missing 22% of dose. The average total amount of metabolites recovered from urine	X5

	represented 0.1% of applied dose (range 0.04 – 0.19%). The low recovery is typical for this type of study. The report quotes similar absorption of cypermethrin of between 0.3 and 0.1%. The amounts of metabolites recovered were too low to permit accurate estimation of urinary elimination half-lives, and in view of this blood and faecal samples were not analysed.	
Conclusion:	Oral and dermal administration of *lambda*-cyhalothrin to man resulted in detection of three metabolites in the urine: approximately equal amounts of 3-(2-chloro-3,3,3,-trifluoropropenyl)-2,2-dimethylcyclopropa n-1-carboxylic acid (TFMCVA), and 3-phenoxybenzoic acid (3PBA) + 3-(4-hydroxyphenoxy) benzoic acid (4-OH-3PBA). Peak excretion rates were typically in the first 4 hours after dosing and half-lives were 14-17 hours following oral administration. No parent compound was detected in urine. Absorption following oral administration was on average 59%, and following dermal administration a maximum of 0.2%. Determination of half-lives following dermal administration was not possible because of the small amounts present in urine.	X6 X7

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.2 / 07	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	August 2006
Materials and Methods	[redacted]
Results and discussion	[redacted]

Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	6.2 / 08	Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study	Official use only
91/414 Annex Point addressed	II 5.1	Absorption, distribution and excretion in mammals	

Title:	cyhalothrin: The Metabolism and Disposition of [14C]-ICI 146,814 in dogs	
Lab Report Number:	[redacted]/C/1277	
Authors:	[redacted]	
Test Substance:	[14C-cyclopropyl]-cyhalothrin batch[redacted] and [14C-benzyl]-cyhalothrin batch[redacted] both of[redacted] radiochemical purity. Non-radiolabelled material used to dilute radiolabel: purity [redacted]% pure cis Z.	X1
Species:	Dog	
Method:	OECD guideline reference 417	
Date of Report:	1984	
Published:	No	
GLP:	Yes	

Material and Methods:	The objectives of this study were to investigate the pharmacokinetics of the test substance in the dog and to identify the major pathways of metabolism of the test substance in the dog following oral and intravenous administration of two radiolabelled forms. Three male and three female beagle dogs of nominal bodyweight 15 kg were used. The disposition and metabolism of cyhalothrin was studied in this group of six dogs. The same group was used for all studies, however at least three weeks were allowed to elapse between each dosing. The dogs were given a single oral dose of 1 and 10 mg [14C] cyhalothrin/kg, and a single intravenous dose of 0.1 mg [14C] cyhalothrin/kg. The compound was administered twice at each dose level; once with each radiolabel form. The experiments were done in the following order: 1 mg/kg oral, 10 mg/kg oral, 0.1 mg/kg intravenous - the benzyl labeled form was dosed first in the oral studies and the cyclopropyl labelled form first in the intravenous studies. Urine and faeces were collected daily, following dosing, for seven days after dosing. Blood samples were taken pre-dose and at 1, 2, 3, 4, 6, 12, 24 and every 24 hours for the next six days post-dose. For the intravenous dosing experiments an additional sample was taken at 0.5 hours post-dose. Metabolite profiles were determined by TLC, both before and after enzymic hydrolyses using aryl sulphatase and ß-glucuronidase enzymes. Individual metabolites were purified by reverse phase HPLC prior to analysis by GC-MS, probe MS, FAB-MS and or 13C-NMR.	X2 X4 X5 X6
Results:	No significant differences were noted between data from male and female dogs. The pattern of excretion of radioactivity after administration of [14C-benzyl] cyhalothrin at 1 and 10 mg/kg following an oral dose or 0.1 mg/kg following an intravenous dose was found to be similar: 29.5%, 32.4%, and 36.7% was recovered in urine and 54.2%, 46.9%, and 54.2% was recovered in faeces. The pattern of excretion of radioactivity after administration of [14C-cyclopropyl] cyhalothrin at 1 and 10 mg/kg following an oral dose was found to be similar: 19% and 19.4% was recovered in urine and 67.8% and 67.6% was recovered in faeces. After intravenous dosing of [14C-cyclopropyl] cyhalothrin at 0.1 mg/kg, 40% of the dose was recovered in urine and 41.5% in faeces. The presence of nearly half the administered dose in the	X7 X8

	faeces following intravenous dosing for both radiolabel forms confirms that biliary excretion is an important route of elimination for cyhalothrin in the dog. The extent of absorption of an oral dose was variable but was estimated to be in the range 48-80%. The absorbed dose was extensively metabolized and eliminated in bile and urine. The main route of metabolism was via cleavage of the ester bond, although there may have been intact ester metabolites present in the faeces. The metabolite profile following intravenous dosing was very similar to that seen in the oral dosing experiments. No unchanged cyhalothrin was found in urine; however, at the 10 mg/kg dose level unchanged compound was found to account for approximately 80% of the radioactivity present in faeces. Metabolites identified for the[14C-benzyl] label included 3-phenoxy benzoic acid (compound V) mainly as its glucuronide conjugate, but also as a glycine conjugate and 3-('4-hydroxyphenoxy) benzoic acid (compound XXIII) mainly as the sulphate conjugate. These metabolites accounted for just over 60% of the radioactivity in the 0-24 hour urine. Analysis of urine from dogs dosed with [14C-cyclopropyl] cyhalothrin identified 3(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethyl-cyclopropane1-carboxylic acid (compound 1a) (accounting for up to 23% of the dose) and the corresponding glucuronide (up to 45% of dose). Radiolabel present in plasma was found to account for most of the radiolabel present in blood. The mean concentration of radioactivity in plasma rose steadily after oral administration of [14C-benzyl] cyhalothrin to reach peak levels of 1.34 µg equivalents cyhalothrin/ml between 2 and 12 hours post dose (1 mg/kg) and 3.19 µg equivalents cyhalothrin/ml between 1 and 4 hours post dose (10 mg/kg). Secondary peaks of radioactivity were seen at 12 hours for some animals following both treatments. After this time concentrations in plasma steadily declined. Following a single intravenous administration of [14C-benzyl] cyhalothrin (0.1 mg/kg) concentrations of radioactivity declined initially from 0 to 4 hours before peaking again at 12 hours post dose. After this time concentrations in plasma steadily declined with an estimated half-life of 33.6 hours. The mean concentration of radioactivity in plasma rose steadily after oral administration of [14C]-cyclopropyl labelled cyhalothrin to reach peak levels of 0.689 µg equivalents cyhalothrin/ml after 4 hours (1 mg/kg) and 2.72 µg equivalents cyhalothrin/ml after 12 hours (10 mg/kg). After these times, concentrations in plasma fell rapidly initially, and later more slowly.	X9 X10

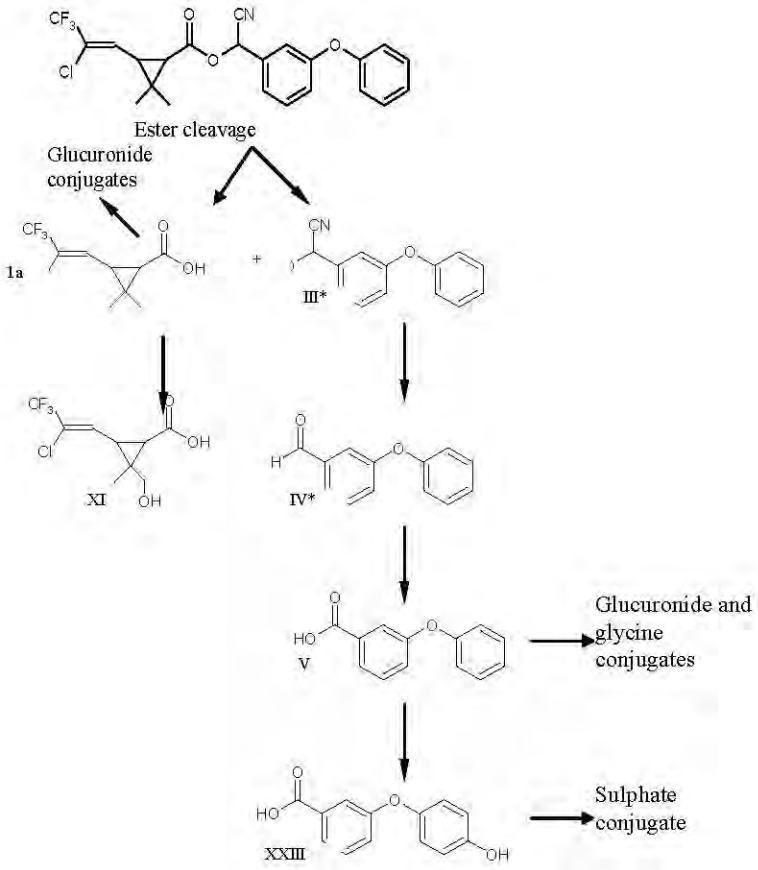
Conclusion:	Absorption varied from 48-80% following oral dose (variation attributed to inter-animal variation, rather than dose level). Excretion was rapid, following both oral and intravenous administration, with the majority of dose excreted in 48 hours. However, excretion was incomplete after 7 days, with total excreted dose ranging from 82 to 93%. Major metabolism was ester cleavage, followed by conjugation and excretion in urine and bile.	X11

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.2 / 08	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	August 2006
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]

Remarks	Tissue distribution was not studied thus it does not cover all parts of a full ADME study by itself.

Proposed metabolic pathway:



* Metabolic intermediates which are too unstable to be detected in animals

98/8 Doc IIIA section No.	**6.2 / 09**	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**	**Official use only**
91/414 Annex Point addressed	**II 5.1**	Absorption, distribution and excretion in mammals	

Title:	cyhalothrin: Bioaccumulation in the rat	

Lab Report Number:	[redacted]/P/1014	
Authors:	[redacted]	
Test Substance:	cyhalothrin, purity [redacted]%, and [14C-cyclopropyl]-cyhalothrin radiochemical purity [redacted]%	X1
Species:	Rat	
Method:	OECD guideline reference 417	
Date of Report:	1989	X2
Published:	No	
GLP:	Yes	

Material and Methods:	Groups of male Alpk/AP rats were each given up to 119 consecutive daily oral doses of 1 mg/kg bw/day [^{14}C]-cyclopropyl labelled cyhalothrin in corn oil (equivalent to 20 ppm in the diet). Control animals received corn oil alone Groups of 3 test and one control rats were killed at intervals (weekly to day 63, then at days 77, 91, 105 and 119) and radioactivity in the liver, fat and blood were determined. After the last dose on day 119, groups of animals were retained and killed 8, 22, 36, 50 64 and 85 days after the last dose. At sacrifice, blood was taken by cardiac puncture, and the liver, kidneys and samples of abdominal fat were dissected free and weighed. Radioactivity was assessed by combustion and scintillation counting. Dosing solutions and fat were analysed for cyhalothrin by HPLC.	X4
Results:	Residues in fat were predominantly cyhalothrin. The concentration of cyhalothrin in fat increased throughout the dosing period to a maximum of approximately 10 µg/g cyhalothrin equivalents at 119 days, whereas those in liver and kidneys appeared to reach a plateau after 70 days and were significantly lower (liver 2.5 µg/g, kidney 1.2 µg/g cyhalothrin equivalents). Blood levels of radioactivity remained constant at approximately 0.2 µg/g cyhalothrin equivalents. On cessation of dosing the radioactive residues in tissues other than fat declined rapidly indicating rapid elimination, although after an initially rapid decline in liver residues, further elimination from this organ appeared similar to that of fat. Levels in blood and kidney had declined to at or below limit of detection by day 36 post dose. The concentration of radioactivity in fat declined more slowly with a half life of 30.5 days. The ratio of the two enantiomeric pairs of cyhalothrin in fat was essentially the same as in the dosing solution.	

Conclusion:	Daily administration of 1 mg/kg bw/day cyhalothrin in corn oil to rats was associated with a gradual increase in cyhalothrin levels in fat to 10 µg/g cyhalothrin equivalents at 119 days. After the end of dosing, the concentration of radioactivity in fat declined slowly with a half life of 30.5 days. The residue in fat was cyhalothrin, and the ratio of the two enantiomeric pairs of cyhalothrin in fat was essentially the same as in the dosing solution. Blood levels during dosing remained constant at approximately 0.2 µg/g cyhalothrin equivalents, and declined rapidly when dosing ceased. Liver and kidney levels rose to a plateau at day 70, and declined rapidly when dosing ceased. Liver levels subsequently reflected those in fat, as depuration took place.	

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.2 / 09	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2007
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

3. SHORT-TERM REPEATED DOSE TOXICITY

ORAL 28-DAY STUDY

98/8 Doc IIIA section No.	6.3.1 / 01	Short Term Repeated Dose Toxicity - Oral	Official use only
91/414 Annex Point addressed	II 5.3.1	Oral 28-day study	

Title:	cyhalothrin induced liver changes: reversibility study in male rats	
Lab Report Number:	[redacted]/P/668	
Authors:	[redacted]	
Test Substance:	Stated to contain [redacted]% w/w cyhalothrin.	X1
Species:	Rat	
Method:	Non-standard study	X2
Date of Report:	1982	
Published:	No	
GLP:	Yes	

Material and Methods:	Studies in rats have shown that rats given cyhalothrin showed proliferation of the hepatic smooth endoplasmic reticulum and elevated hepatic aminopyrine-N-demethylase activity. This study was intended to demonstrate what happened to these changes if treatment ceased. Two groups of 32 male Wistar-derived rats of [redacted] strain were fed either control diet or diet containing 250 ppm cyhalothrin for 28 days. Eight rats per group were killed and examined. The remaining rats were fed control diet for 7, 14 or 28 days and a further 8 rats per group were killed and examined at each interval. Animals were killed by halothane overdose and exsanguinated by cardiac puncture. All animals were subject to gross necropsy. The livers were weighed. Subsequent analysis included electron microscopy and presence/absence and quantitation of smooth endoplasmic reticulum. Sections were also preserved for light microscopy and the remainder of the liver analysed for APDM activity	
Results:	Rats receiving 250 ppm cyhalothrin showed reduced bodyweight gain, which persisted during the 28 day recovery period. There was also a slight reduction in absolute liver weight compared to controls, but after adjustment for bodyweight, liver weights of the treated group were comparable to the control group at all time	X3

	periods. The majority of treated rats showed proliferation of the hepatic smooth endoplasmic reticulum and elevated hepatic aminopyrine-N-demethylase activity. These changes had reversed 7 days after treatment ceased, and were considered to be an adaptive response to increased liver workload, rather than a toxic effect. However, the bodyweight effect persisted after the end of treatment, and the report considers this a toxic effect.	
Conclusion:	Administration of 250 ppm cyhalothrin for 28 days to male rats was associated with reduced bodyweight gain, increase in smooth endoplasmic reticulum and elevated hepatic aminopyrine-N-demethylase activity. After 7 days of a 28-day treatment-free „recovery"period, there was no smooth endoplasmic reticulum proliferation, and hepatic aminopyrine-N-demethylase activity had returned to normal. These responses were considered to be an adaptive response to increased liver workload, rather than a toxic effect. However, the bodyweight effect persisted after the end of treatment, and the report considers this a toxic effect.	

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.3.1 / 01	**Short Term Repeated Dose Toxicity - Oral**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2007
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]

Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]).

98/8 Doc IIIA section No.	6.3.1 / 02	Short Term Repeated Dose Toxicity -Oral	Official use only
91/414 Annex Point addressed	II 5.3.1	Repeated Dose Toxicity – Oral Short term toxicity (6 weeks)	

Title:	Lambda cyhalothrin: 6 Week oral toxicity study in dogs	
Lab Report Number:	[redacted]/P/5256	
Authors:	[redacted]	
Test Substance:	Lambda-cyhalothrin	X1
Species:	Dog	
Method:	Non-guideline in-house study design, generally following EEC B.7 (Directive 96/54/EC), extended from 28 to 42 days.	X2
Date of Report:	1996	
Published:	No	
GLP:	Yes	

Material and Methods:	Groups of one male and one female beagle dog (strain [redacted] Beagle) were dosed with 0.75, 1.5, 3.0 or 4.0 mg *lambda*-cyhalothrin/kg/day in corn oil in gelatine capsules for 6 weeks. A control group was dosed with capsules containing corn oil only. During the in-life phase of the study, all procedures were conducted "blind" (technician unaware of the dose level each animal received). Clinical signs, including faecal consistency, and food consumption were recorded daily throughout the study. Body weights were recorded weekly. Detailed clinical examinations were made pre-experimentally and at termination, which included cardiac and pulmonary auscultation and indirect ophthalmoscopy. Blood samples were collected from all dogs pre-experimentally and during weeks 1, 3 and 6 (prior to termination), for haematological and blood biochemistry analyses. At termination, all animals were given a full macroscopic examination *post mortem*, selected organs were removed and	

	weighed and a full range of tissues was taken for subsequent histopathological examination.	
Results:	Both dogs receiving 4.0 mg *lambda*-cyhalothrin/kg/day were killed for humane reasons on day 15, following inappetence and bodyweight loss from the start of dosing. Prior to this, occasional clinical signs of slightly decreased activity and thin appearance, and a low incidence of fluid faeces and regurgitation/vomiting, had been seen for these dogs. The dogs given 1.5 or 3.0 mg/kg/day occasionally showed transient, treatment-related clinical signs (including decreased activity, slight tremors, unsteady gait and/or salivation, predominantly at dosing). However, as these clinical signs were of mild severity, and were not associated with any adverse effects on bodyweight or food consumption, they are considered to be of no toxicological importance. An increased incidence of fluid faeces was seen, after dosing, for the male receiving 3.0 mg/kg/day throughout most of the study, although this was not present in the female at this level. A low incidence of fluid faeces was also seen for animals from all groups receiving *lambda*-cyhalothrin. In the absence of any adverse effects in animals receiving 0.75, 1.5 or 3.0 mg/kg/day, the increased incidence of fluid faeces seen was considered to be of no toxicological importance. There were no changes in any of the haematological parameters examined, at any level, which could be associated with treatment with *lambda*-cyhalothrin. Slightly reduced plasma alkaline phosphatase (ALP) activity and phosphorus levels were seen in both dogs receiving 4.0 mg/kg/day prior to termination in week 3. Slightly increased plasma cholesterol was also seen in the male at this dose level in weeks 1 and 3. There were no treatment-related changes seen in any of the blood clinical chemistry parameters examined at the other dose levels. No treatment-related effects were seen in organ weights and there were no treatment-related macroscopic or microscopic findings.	X3
Conclusion:	In conclusion, administration of *lambda*-cyhalothrin to beagle dogs at a dose level of 4.0 mg/kg/day produced adverse effects on bodyweight and food consumption, which required these animals to be killed for humane reasons on day 15. No other toxicologically significant changes were observed in these animals. Administration of dose levels of 0.75, 1.5 or 3.0 mg *lambda*-cyhalothrin/kg/day to beagle dogs for 6 weeks produced mild clinical signs and/or a slightly increased incidence of fluid faeces, which were considered to be of no toxicological importance.	

	A dose level of 3.0 mg/kg/day is considered to be the toxicological NOEL in this study.	

Table : Intergroup Comparison Of Bodyweight (Kg) - Selected Timepoints

Week	Dose level of *Lambda*-cyhalothrin (mg/kg/day) Males					Females				
	0	0.75	1.5	3.0	4.0	0	0.75	1.5	3.0	4.0
-1	10.3	10.0	11.3	12.2	12.3	8.8	9.1	7.8	11.4	7.8
1	10.5	10.0	11.5	12.3	12.4	8.9	9.2	8.0	11.4	8.1
3	10.7	10.4	12.0	12.5	11.0	9.0	9.4	8.2	11.8	7.2
5	11.2	10.7	12.2	12.7		9.2	9.7	8.2	12.0	
7	11.4	10.9	12.4	12.7		9.4	9.8	8.3	12.4	

Table : Intergroup Comparison Of Food Consumption (G/Dog/Day) - Selected Timepoints

Week	Dose level of *Lambda*-cyhalothrin (mg/kg/day) Males					Females				
	0	0.75	1.5	3.0	4.0	0	0.75	1.5	3.0	4.0
-1	400	400	392.9	400	400	350	350	316.4	350	287.9
1	400	400	400	400	285.7	350	350	330	350	175.7
2	400	400	400	400	134.3	350	341.4	305	350	82.1

Table : Intergroup Comparison of Blood Clinical Chemistry - Selected Parameters and Timepoints

Parameter		Dose level of *Lambda*-cyhalothrin (mg/kg/day) Males					Females				
		0	0.75	1.5	3.0	4.0	0	0.75	1.5	3.0	4.0
ALP	week 3	367	362	260	294	171	245	220	224	238	206
Phosphorus	week 3	2.26	1.98	2.20	1.98	1.78	2.32	1.99	1.79	2.08	1.39
Cholesterol	week 1	3.2	2.0	3.6	3.6	5.0	2.8	3.6	3.1	4.2	3.7
	week 3	3.6	1.8	4.3	3.2	5.6	2.8	3.1	2.9	4.1	3.3

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.3.1 / 02	Short Term Repeated Dose Toxicity - Oral
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2007
Materials and Methods	[redacted]

Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**6.3.2 / 01**	**Short Term Repeated Dose Toxicity -Dermal**	**Official use only**
91/414 Annex Point addressed	**II 5.3.3**	Other routes	

Title:	Lambda-cyhalothrin: 21-day dermal toxicity to the rat	
Lab Report Number:	[redacted]/P/2532	
Authors:	[redacted]	
Test Substance:	*Lambda*-cyhalothrin, purity [redacted]% w/w, reference [redacted]	X1
Species:	Rat	
Method:	Guideline not stated, but follows US Guidelines for 21-day dermal study.	X2

Date of Report:	1989	
Published:	No	
GLP:	Yes	

Material and Methods:	Groups of five male and five female Wistar-derived Alpk:APSD rats were given 6-hour applications of 1, 10 or 100 mg/kg bw/day of *lambda*-cyhalothrin in olive oil, for twenty-one consecutive days. Dose level of 100 mg/kg bw/day was reduced to 50 after two or three applications. A control group of five males and five females was treated with olive oil only. Animals were dosed at 2 ml/kg bw, or 1 ml/kg at the high dose group. Test preparations were held in place for 6 hours/day using occlusive dressings. After 6 hours, the dressings were removed and the skin cleaned using cotton wool soaked in warm water, and dried with tissue paper. During the remaining 18 hours per day, the animals wore a plastic collar to prevent oral contamination. Animals were observed twice per day, prior to dosing and at dressing removal, for signs of gross toxicity and for signs of irritation at the application site. Food intake was estimated for a 24-hour period between days -1 – 1, 6-7, 13-14 and 20-21. At termination, blood samples were taken by cardiac puncture immediately after death for routine clinical chemistry and haematology. Gross necropsy was performed and the adrenals, brain, kidneys, liver, ovaries/testes dissected free and weighed for each animal. A full list of tissues, including treated and untreated skin, were taken and preserved. Skin, liver, kidney, adrenal, brain, heart, sciatic nerve, spinal cord and spleen from all animals in all groups were examined by light microscopy.	X3 X4
Results:	Dose formulations were analysed and shown to be homogenous and formulated within 10% of nominal. High and low dose formulations were shown to be stable for up to 13 days (fresh preparations were made every 7 days). Two males were found dead after 3 applications at 100 mg/kg bw/day. There were no indications of an adverse effect of treatment, either from clinical signs prior to death, at necropsy or histopathology, but it was thought that the likely cause was pyrethroid toxicity. As a precaution against further mortality, the decision was taken to reduce the top dose to 50 mg/kg bw/day for the rest of the study. There were no further deaths. Animals at 50 mg/kg w/day showed slight general toxicity including bizarre behaviour, reduced (postural) stability, and splay reflex. There were no signs of skin irritation at any dose level. Males showed reduced bodyweight gain and food intake. There were no haematological, clinical chemistry, organ weight or histopathology changes attributable to treatment.	X5 X6 X7

Conclusion:	The NOEL was 10 mg/kg bw/day.	

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.3.2 / 01	**Short Term Repeated Dose Toxicity -Dermal**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2006
Materials and Methods	[redacted]
Results and discussion	[redacted]

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[redacted]

[redacted]

Conclusion

Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	6.3.3	Short Term Repeated Dose Toxicity - Inhalation	Official use only

Section 6.3.3 Annex Point IIA 6.3.3	Repeat dose inhalation	Official use only
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	
Other existing data [ ]	Technically not feasible [ ] Scientifically unjustified [X]	
Limited exposure [ ]	Other justification [ ]	
Detailed justification:	[redacted]	

Section 6.3.3 Annex Point IIA 6.3.3	**Repeat dose inhalation**	Official use only
	[redacted]	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No.6.3.3	Short Term Repeated Dose Toxicity - Inhalation
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2007
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	[redacted]
RMS June 2010	[redacted]

4. SUBCHRONIC TOXICITY

98/8 Doc IIIA section No.	6.4.1 / 01	Subchronic toxicity - Oral	Official use only
91/414 Annex Point addressed	II 5.3.2	Oral 90-day study	

Title:	PP321: 90 day feeding study in rats	
Lab Report Number:	[redacted]/P/1045	
Authors:	[redacted]	
Test Substance:	*lambda*-cyhalothrin (otherwise known as PP321), purity [redacted]%, batch [redacted].	XI
Species:	Rat	
Method:	OECD Guideline 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"	
Date of Report:	1985	
Published:	No	
GLP:	Yes	

Material and Methods:	The purpose of the study was to establish no-effect and effect levels of the test substance when administered in the diet to rats, for a period of 90 days. The study also allows comparison with study on the unresolved form (6.4.1/02). Twenty-one day old rats of the Wistar-derived [redacted] strain were delivered to [redacted] the females arriving one week after the males. There were four groups of animals, 3 test and 1 control, each comprising of 20 rats of each sex. The study duration was 90 days. The treated groups received *lambda*-cyhalothrin at dietary concentrations of 10, 50 or 250 ppm*. The control group was treated in an identical manner to the treated groups except that their diet did not contain *lambda*-cyhalothrin. Samples were analysed for concentration, homogeneity and stability of *lambda*-cyhalothrin in powdered diet. The rats were housed five/sex/cage. The animals were housed in one room in a barriered limited access rodent facility with a controlled environment, the temperature being within the range of 19-27°C and relative humidity ranging between 38-77%. There were twelve hour alternating periods of light and darkness.	X3

	During the study all animals were examined daily for clinical abnormalities. Prior to feeding experimental diets and then weekly thereafter for the next 90 days, the animals were weighed. Food consumption for each cage of rats was recorded weekly. Blood for haematological analyses was collected from a pre-designated ten male and ten female rats per group, just prior to being fed experimental diets, after 4 weeks and at termination. The pre-dose and 4-week samples were collected from the tail vein and the terminal sample via cardiac puncture. The following parameters were determined at 4 and 13 weeks: haemoglobin; haematocrit; total white cell count; red cell count; mean cell volume; mean cell haemoglobin; mean cell haemoglobin concentration; platelet count and differential white cell count. After 13 weeks kaolin-cephalin and prothrombin times were also measured. At necropsy, bone marrow smears were prepared from these animals but were not examined. A different group of ten animals per sex from each treatment group was selected to provide blood and urine samples for clinical chemistry. The schedule followed was the same as that as for the haematology analyses. Blood as collected from the tail vein on all three occasions. The parameters measured were as follows: Blood:plasma alkaline phosphatase, alanine transaminase and aspartate transaminase activities; cholesterol; albumin; total protein; urea; glucose and triglycerides. Urine:volume; pH; specific gravity; quantitative glucose; quantitative protein; ketones and urobilinogen. The eyes of all animals from the control and top dose groups were examined during the week prior to termination. All rats, including any found dead/killed prior to scheduled termination were subjected to a full post mortem examination. The following tissues were preserved: adrenals; aorta; urinary bladder; bone marrow (left femur including knee joint); brain; caecum; cervix; colon; duodenum; epididymides; eyes and Harderian glands; heart; ileum; jejunum; kidneys; liver; lung; lymph nodes (cervical, mesenteric); mammary gland (from females only); oesophagus; ovaries; pancreas; pituitary; prostate; salivary glands; sciatic nerves; seminal vesicles; skin; spinal cord; spleen; testes; thymus; thyroid and	

	parathyroids; trachea; uterus; voluntary muscle, and any abnormalities. All tissues from the control and 250 ppm *lambda*-cyhalothrin groups and the liver, kidneys and lungs from the 10 ppm and 50 ppm *lambda*-cyhalothrin groups and any abnormal tissues were examined by light microscopy. The weights of the gonads, spleen, kidneys, adrenals, liver, heart, lungs and brain were recorded. Fresh liver samples were taken from the survivors of a designated 6 males and 6 females per group. These were submitted for hepatic aminopyrine-N-demethylase (APDM) activity determination.	X4
Results:	All diets gave concentration values within ± 10% of nominal. Homogeneity was satisfactory. Lambda-cyhalothrin was stable in the diet for up to 3 months of preparation. There were no deaths, nor were there any signs of compound-related clinical abnormalities or ocular changes. There was a decrease in bodyweight gain for both sexes fed 250 ppm *lambda*-cyhalothrin. Weight gain was also slightly reduced for the 10 and 50 ppm males for the first week of treatment. Food consumption was reduced for both sexes at 250 ppm throughout the study, and for males fed 50 ppm in week 1. There were also marginal effects on food intake and bodyweight gain in females at 10 ppm, but as there were no effects at 50 ppm, the effects at 10 ppm were considered unrelated to treatment. There a small effect on food utilisation in females fed 250 ppm for weeks 1 to 4. Test article intake (in terms of mg/kg bw/day) was not reported in this study, but the same age and strain of rats were used in the study on the unresolved form, and weight gains were similar in the present study, so it is not unreasonable to assign similar intake values i.e. for 10, 50 and 250 ppm, in males 0.61, 2.8 and 13.67, and in females 0.65, 3.56 and 15.4 mg/kg bw/day. Occasional differences from controls were seen in some haematology parameters, but they were of no toxicological significance. Decreased plasma triglyceride levels were seen in males at 50 ppm and 250 ppm *lambda*-cyhalothrin at 4 and 13 weeks. Similar findings were recorded in the 90-day rat study with the unresolved form, and it was probable that this was a pharmacological effect. Other differences	X5 X6 X7 X8 X9

	between test and control groups were minor and not dose-related and therefore not of toxicological significance. Plasma alkaline phosphatase and alanine transaminase activities were reduced in males at 250 ppm in weeks 13 and 4 respectively. Increased urine volumes were recorded for males at 250 ppm at week 4. Adaptive elevated hepatic aminopyrine-N-demethylase activity was seen at 50 ppm and 250 ppm *lambda*-cyhalothrin in males and at 250 ppm in females. After adjustment for bodyweight, liver weight was increased in both sexes at 250 ppm and in males at 50 ppm. No toxicologically significant treatment-related changes were seen at gross post mortem examination or at histopathological examination.	X10 X11 X12 X13
Conclusion:	Treatment was associated with reduced bodyweight gains, increased relative liver weight and elevated hepatic aminopyrine-N-demethylase activity, in both sexes at 250 ppm and in males at 50 ppm. These findings are similar to those in the study with the unresolved form cyhalothrin (6.4.1/02), which were shown to be reversible on withdrawal of the test material (6.3.1/01). It is therefore considered that these effects on the liver represent adaptive responses to increased physiological workload, rather than a true toxic effect. The reduction in plasma triglycerides seen in males at 250 and 50 ppm was considered unlikely to be toxicologically significant in the absences of elevated plasma ALT or AST levels, or liver histopathology. The bodyweight effects are considered true toxic effects and the NOAEL for the study is 50 ppm (approximately 3 mg/kg bw/day).	

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
98/8 Doc IIIA section No. 6.4.1 / 01	**Subchronic toxicity - Oral**
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2007
Materials and Methods	[redacted]

Borttaget: September

Borttaget: 0

Results and discussion	[redacted] e. [redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

	results of the follow-up study support the conclusion that effects represent adaptive and reversible changes.

98/8 Doc IIIA section No.	**6.4.1/ 02**	**Subchronic toxicity - Oral**	**Official use only**
91/414 Annex Point addressed	**II 5.3.2**	Oral 90-day study	

Title:	Cyhalothrin: 90 Day Feeding Study in Rats	
Lab Report Number:	No [redacted]/P/629	
Authors:	[redacted]	
Test Substance:	Technical cyhalothrin (otherwise known as PP563). Purity [redacted]% w/w.	X1
Species:	Rat	
Method:	OECD Guideline 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"	
Date of Report:	1981	
Published:	No	
GLP:	Yes	

Material and Methods:	The purpose of the study was to establish no-effect and effect levels of the test substance when administered in the diet to rats, for a period of 90 days. Twenty-one day old rats of the Wistar-derived [redacted] strain were delivered to the Specific Pathogen Free unit at the [redacted], the females arriving one week after the males. There were four groups of animals, 3 test and 1 control, each comprising of 20 rats of each sex. The study duration was 90 days. The treated groups received cyhalothrin at dietary concentrations of 10, 50 or 250 ppm*. The control group was treated in an identical manner to the treated groups except that their diet did not contain cyhalothrin. One batch of each test diet was prepared from a single premix. Samples were analysed for concentration, homogeneity and stability of cyhalothrin in powdered diet, while premixes were analysed for concentration. The rats were housed five/sex/cage. The animals were housed in one room in a barriered limited access rodent	

	facility with a controlled environment, the temperature being within the range of 19-27°C and relative humidity ranging between 38-77%. There were twelve hour alternating periods of light and darkness. During the study all animals were examined daily for clinical abnormalities. Prior to feeding experimental diets and then weekly thereafter for the next 90 days, the animals were weighed. Food consumption for each cage of rats was recorded weekly. Blood for haematological analyses was collected from a pre-designated ten male and ten female rats per group, one day prior to being fed experimental diets, after 4 weeks and at termination. The following parameters were determined at 4 and 13 weeks: haemoglobin; haematocrit; total white cell count; red cell count; mean cell volume; mean cell haemoglobin; mean cell haemoglobin concentration; platelet count and differential white cell count. After 13 weeks kaolin-cephalin and prothrombin times were also measured. At necropsy, bone marrow smears were prepared from these animals for cytological examination. A different group of ten animals per sex from each treatment group was selected to provide blood and urine samples for clinical chemistry. The schedule followed was the same as that as for the haematology analyses. The parameters measured were as follows: Blood:plasma alkaline phosphatase, alanine transaminase and aspartate transaminase activities; cholesterol; albumin; total protein; urea; glucose and triglycerides. Urine:volume; pH; specific gravity; quantitative glucose; quantitative protein; ketones and urobilinogen. The eyes of ten animals per sex from the control and top dose groups were examined during the week prior to termination. All rats, including any found dead/killed prior to scheduled termination were subjected to a full post mortem examination. The following tissues were preserved: adrenals; aorta; bone marrow (from costo-chondral junction or sternum); brain; caecum; cervix; colon; duodenum; epididymides; eyes and Harderian glands; heart; ileum; jejunum; kidneys; larynx; liver; lung; lymph nodes (cervical, mesenteric and thymic); mammary gland (from females only); oesophagus; ovaries; pancreas; pituitary; prostate; salivary gland; sciatic nerves; seminal vesicles; skin; spinal cord; spleen; testes; thymus; trachea; uterus; voluntary	X2(i) X2(ii)