Table A6.1.5- 2: Result of the skin sensitisation test.

	Number of animals with signs of allergic reactions/ number of animals in group	
	Negative Control	**Test group**
Scored after 24 h	0/5	0/10
Scored after 48 hours	0/5	0/10

Section A6.1.5 **Skin sensitisation**
Annex Point IIA6.1.5 **(Guinea pig maximisation test)**

Official use only

1 REFERENCE

1.1	**Reference**	**A6.1.5/02:** [redacted] (2005): BAS 310 I (alpha-Cypermethrin) – Maximization Test in Guinea pigs. [redacted]; Report no. 30H0563/042243, July 01, 2005 (unpublished), BASF Doc-ID: 2005/1011572.
1.2	**Data protection**	Yes
1.2.1	Data owner	BASF
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I.

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes OECD 406 (1992) EC method B.6 (1996) OPPTS 870.2600 (2003) MAFF (Japan, 2000)
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	BAS 310 I (alpha-Cypermethrin)
3.1.1	Lot/Batch number	COD-000166
3.1.2	Specification	As given in Section A2.
3.1.3	Purity	Solid white powder
3.1.4	Description	99.3%
3.1.5	Stability	The stability under storage conditions over the study period was guaranteed.
3.1.6	Preparation of test substance for application	For induction and for challenge: homogenised in 1% cleaned sodium carboxymethylcellulose (CMC)
3.1.7	Pre-test performed on irritant effects	Yes

Section A6.1.5 **Skin sensitisation**
Annex Point IIA6.1.5 **(Guinea pig maximisation test)**

3.2	**Test animals**	
3.2.1	Species	Guinea pig
3.2.2	Strain	HsdPoc: DH
3.2.3	Source	Harlan Winkelmann, Borchen, Germany
3.2.4	Sex	Female
3.2.5	Age/weight at study initiation	Age: 6–8 weeks Body weight: 415–510 g (upon receipt)
3.2.6	Number of animals per group	10
3.2.7	Control animals	5
3.2.8	Further remarks	For the intradermal pretest animals of the strain/quality "Dunkin Hartley, Crl:HA" of the supplier Charles River Deutschland GmbH were used.
3.3	**Administration/ Exposure**	Adjuvant
3.3.1	Induction schedule	Day 0: intradermal induction Day 7: epicutaneous induction Day 21: challenge
3.3.2	Way of induction	First: intradermal Second: topical
3.3.3	Occlusion	Occlusive (for 48 h)
3.3.4	Concentrations used for induction	Intradermal: 5% test substance in 1% CMC; Epicutaneous: 50% test substance in 1% CMC
3.3.5	Concentration Freund's Complete Adjuvant (FCA)	Freund's Complete Adjuvant (FCA) emulsified with 0.9% aqueous NaCl solution in a ratio of 1:1.
3.3.6	Challenge schedule	Day 21: Three weeks after intradermal induction
3.3.7	Concentrations used for challenge	50% test substance in 1% CMC
3.3.8	Re-challenge	No; since no borderline results were observed, a 2nd challenge was not performed.
3.3.9	Scoring schedule	24h and 48h after challenge
3.3.10	Removal of the test substance	Challenge sites were washed with water after the 24 h exposure period.
3.3.11	Positive control substance	Not tested in this study. However, a separate study with Alpha-Hexylcinnamaldehyde is performed twice a year in the laboratory and is included as an appendix.
3.4	**Examinations**	
3.4.1	Pilot study	Yes
3.5	**Further remarks**	None

Section A6.1.5 **Skin sensitisation**
Annex Point IIA6.1.5 **(Guinea pig maximisation test)**

4 RESULTS

4.1	**Results of pilot studies**	After the intradermal induction intense erythema and swelling were observed at the injection sites at which only Freund's complete adjuvant / 0.9% NaCl solution (1:1) was applied. Intradermal injections of a 5% test substance preparation in 1% CMC-solution in doubly distilled water caused moderate and confluent erythema and swelling. At the injection sites of a 5% test substance preparation in Freund's complete adjuvant / 0.9% aqueous NaCl-solution (1:1) intense erythema and swelling were seen. No skin findings were observed in the animals treated with 50% and 25% test substance preparations 24 and 48 hours after removal of the patch.
4.2	**Results of test**	
4.2.1	24h after challenge	No positive response.
4.2.2	48h after challenge	No positive response.
4.2.3	Other findings	After the intradermal induction intense erythema and swelling were observed at the injection sites at which only Freund's complete adjuvant / 0.9% NaCl solution (1:1) was applied. Intradermal injections of a 5% test substance preparation in 1% CMC-solution in doubly distilled water caused moderate and confluent erythema in addition to swelling. At the injection sites of a 5% test substance preparation in Freund's complete adjuvant / 0.9% aqueous NaCl-solution (1:1) intense erythema and swelling were seen in all test group animals. The control group animals, injected with 1% CMC-solution in doubly distilled water did not show any skin reactions. A 50% formulation of 1% CMC-solution with FCA/NaCl caused intense erythema and swelling in all control group animals. The epicutaneous induction with a 50% test substance preparation in 1% CMC-solution in doubly distilled water led to incrustation, partially open (caused by the intradermal induction) and moderate and confluent erythema in all test group animals.
4.3	**Overall result**	None of the 10 test animals showed positive responses at 24 or 48 hours after removal of the challenge patches. Thus, the test material was considered to be non-sensitising to the skin of Guinea pigs.

Section A6.1.5 **Skin sensitisation**
Annex Point IIA6.1.5 **(Guinea pig maximisation test)**

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	The skin sensitizing potential of Alphacypermethrin was tested using the Guinea pig maximisation test according to OECD 406 (1992), EC method B.6 (1996), OPPTS 870.2600 (2003) and MAFF (Japan, 2000) without any deviation.
5.2	**Results and discussion**	None of the surviving animals showed positive responses at 24 or 48 hours after removal of the challenge patches. Therefore, no classification for Alphacypermethrin is required according to the requirements specified by Directive 67/548/EC and subsequent regulations.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Evaluation by Competent Authorities	
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE (*)
Date	March 2009
Materials and methods	Applicant's version adopted
Results and discussion	Applicant's version adopted
Conclusion	5.3. alpha-cypermethrin does not have a sensitising effect on the skin of the guinea pig in the Maximisation Test under test conditions chosen.
Reliability	1
Acceptability	acceptable
Remarks	none
	COMMENTS FROM APPLICANT
Date	30 April 2009
Materials and methods	
Results and discussion	
Conclusion	5.3.: Thank for this remark, but this is only a repetition of the information provided under 5.2.
Reliability	
Acceptability	
Remarks	
	COMMENTS FROM RAPPORTEUR MEMBER STATE
Date	May 2009
Conclusion	Comments from applicant accepted

Table A6.1.5- 3: Detailed information including induction/challenge/scoring schedule for skin sensitisation test.

	GPMT		Observations/Remarks
	Day	**Application**	
Induction 1	0	Intradermal	Moderate and confluent to intense erythema and swelling at the injection sites of the test substance preparation in all test group animals
Induction 2	7	Topical	Incrustation, partially open (caused by the intradermal induction) could be observed in addition to moderate and confluent erythema and swelling in all test group animals
Challenge	21	Topical	Not stated
Scoring 1	23	–	No positive response
Scoring 2	24	–	No positive response

Table A6.1.5- 4: Result of the skin sensitisation test.

	Number of animals with signs of allergic reactions/ number of animals in group	
	Negative Control	**Test group**
Scored after 24 h	0/5	0/10
Scored after 48 hours	0/5	0/10

Section A6.1.5 **Skin sensitisation**
Annex Point IIA6.1.5 **(Guinea pig maximisation test)**

Official use only

1 REFERENCE

1.1	**Reference**	**Cross-reference to A6.1.1/01:** [redacted] (1993) FASTAC technical: Acute oral and dermal toxicity in rat, skin and eye irritancy in rabbit and skin sensitisation potential in Guinea pig. [redacted], Report no. SBTR.92.033, April 01, 1993, BASF RDI No.: AL-410-003 (unpublished).
1.2	**Data protection**	Yes
1.2.1	Data owner	BASF
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I.

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Magnusson and Kligman (1969) and Magnusson et al. (1979) The conduct of the study was similar to method B.6 (96/54/EC) with the exception that no positive control was reported and that the test site was not treated with 0.5 mL of 10% sodium lauryl sulphate approx. 24 hours before topical induction.
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	As given in Section A2.
3.1.1	Lot/Batch number	02156
3.1.2	Specification	As given in Section A2.
3.1.3	Purity	95.6%
3.1.4	Description	Off-white powder
3.1.5	Stability	Alphacypermethrin technical is thermally and chemically stable, and it is stable to light. It is also stable under acidic or basic conditions, although undergoing hydrolysis in strongly alkaline media. Based on this information it was considered that the test substance was stable for the duration of this study. In addition, the test substance was stable in corn oil for at least four days.
3.1.6	Preparation of test substance for application	For induction: in corn oil For challenge: in corn oil

Section A6.1.5 Skin sensitisation
Annex Point IIA6.1.5 **(Guinea pig maximisation test)**

3.1.7	Pre-test performed on irritant effects	Yes
3.2	**Test animals**	
3.2.1	Species	Guinea pig
3.2.2	Strain	Dunkin-Hartley
3.2.3	Source	Harlan Porcellus
3.2.4	Sex	Male and female
3.2.5	Age/weight at study initiation	Age: 5–9 weeks (upon receipt) Body weight: 268–348 g (upon receipt)
3.2.6	Number of animals per group	10 males and 10 females
3.2.7	Control animals	5 males and 5 females
3.3	**Administration/ Exposure**	Adjuvant
3.3.1	Induction schedule	(i) day 0; (ii) one week after first induction
3.3.2	Way of induction	(i) intra-dermal; (ii) topical
3.3.3	Occlusion	(ii) semi-occlusive (for 48 h)
3.3.4	Concentrations used for induction	(i) 2% m/v test substance in corn oil; (ii) 50% m/v test substance in corn oil
3.3.5	Concentration Freund's Complete Adjuvant (FCA)	50% v/v aqueous emulsion
3.3.6	Challenge schedule	Two weeks after topical induction (for 24 hours)
3.3.7	Concentrations used for challenge	50% m/v test substance in corn oil
3.3.8	Re-challenge	No
3.3.9	Scoring schedule	Shortly after removal of patches, 24h and 48h after challenge
3.3.10	Removal of the test substance	Challenge sites were washed with water after the 24 h exposure period.
3.3.11	Positive control substance	None
3.4	**Examinations**	
3.4.1	Pilot study	Yes
3.5	**Further remarks**	None

Section A6.1.5 **Skin sensitisation**
Annex Point IIA6.1.5 **(Guinea pig maximisation test)**

4 RESULTS

4.1	**Results of pilot studies**	Intra-dermal injection of 0.06–2.0% m/v test substance in corn oil resulted in a score of 1 (slight redness, edges not defined). Topical applications of 10–50% m/v test substance in corn oil caused no difference from the surrounding skin.
4.2	**Results of test**	
4.2.1	24h after challenge	No positive response.
4.2.2	48h after challenge	No positive response.
4.2.3	Other findings	Desquamation was observed in all test and control animals 48 hours after challenge. However, desquamation did not impede assessment of any erythematous reaction.
4.3	**Overall result**	None of the 20 test animals showed positive responses at 24 or 48 hours after removal of the challenge patches. Thus, the test material was considered to be non-sensitising to the skin of Guinea pigs.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	The skin sensitizing potential of Alphacypermethrin was tested using the Guinea pig maximisation test. Although not a guideline study, the method used was similar to method B.6 (96/54/EC) with the exception that no positive control was reported and that the test site was not treated with 0.5 mL of 10% sodium lauryl sulphate approx. 24 hours before topical induction.
5.2	**Results and discussion**	None of the surviving animals showed positive responses at 24 or 48 hours after removal of the challenge patches. Therefore, no classification for Alphacypermethrin is required according to the requirements specified by Directive 67/548/EC and subsequent regulations.
5.3	**Conclusion**	
5.3.1	Reliability	2
5.3.2	Deficiencies	Yes The test site was not treated with 0.5 mL of 10% sodium lauryl sulphate approx. 24 hours before topical induction in order to create local irritation, even though the test substance was not a skin irritant.

Evaluation by Competent Authorities	
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE (*)
Date	March 2009
Materials and methods	Applicant's version adopted
Results and discussion	Applicant's version adopted
Conclusion	5.3. alpha-cypermethrin does not have a sensitising effect on the skin of the guinea pig.
Reliability	2
Acceptability	acceptable
Remarks	none
	COMMENTS FROM APPLICANT
Date	30 April 2009
Materials and methods	
Results and discussion	
Conclusion	5.3.: Thank for this remark, but this is only a repetition of the information provided under 5.2.
	COMMENTS FROM RAPPORTEUR MEMBER STATE
Date	May 2009
Conclusion	Applicant's version adopted
Remarks	Comments from applicant accepted

Table A6.1.5- 5: Detailed information including induction/challenge/scoring schedule for skin sensitisation test.

	GPMT		Observations/Remarks
	Day	**Application**	
Induction 1	0	Intra-dermal	None stated
Induction 2	7	Topical	None stated
Challenge	21	Topical	Desquamation in some test animals at 24 h; desquamation in all test and control animals 48h after challenge
Scoring 1	23	–	No positive response
Scoring 2	24	–	No positive response

Table A6.1.5- 6: Result of the skin sensitisation test.

	Number of animals with signs of allergic reactions/ number of animals in group	
	Negative Control	**Test group**
Scored after 24 h	0/10	0/20
Scored after 48 hours	0/10	0/20

Section A6.2 **Metabolism studies in mammals**
Annex Point IIA6.2 **– Metabolism of a single oral dose in the rat (*in vivo* test) –**

Official use only

1 REFERENCE

1.1	**Reference**	**A6.2/01:** Hutson DH (1982): WL 85871: Metabolism of a single oral dose in the rat. SRC, Sittingbourne, UK, Report no. SBGR.82.205, August 04, 1982 (unpublished), BASF RDI No.: AL-440-007. **A6.2/03:** Hutson DH, Logan CJ (1986) The metabolic fate in rats of the pyrethroid insecticide WL85871, a mixture of two isomers of cypermethrin. Pesticide Science 17: 548-558, BASF RDI No.: AL-905-066.
1.2	**Data protection**	Yes (reference A6.2/01)
1.2.1	Data owner	BASF
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I.

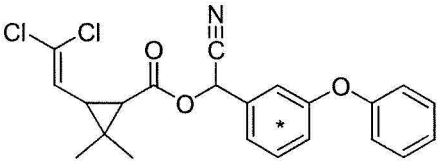
2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Not stated in the report. The conduct of the study was consistent to OECD 417 (1984) in all important aspects, with exception that only one dose level instead of two was used.
2.2	**GLP**	No
2.3	**Deviations**	Not applicable

3 MATERIALS AND METHODS

3.1	**Test material**	Alphacypermethrin (WL 85871) radio-labelled, as given in section 2
3.1.1	Lot/Batch number	Batch 1, OCD 594
3.1.2	Specification	As given in section 2.
3.1.3	Purity	Radiochemical purity: 99.6 %; Chemical purity: 97.9 %
3.1.4	Description	Not stated
3.1.5	Stability	Not stated

Section A6.2 Metabolism studies in mammals
Annex Point IIA6.2 **– Metabolism of a single oral dose in the rat (*in vivo* test) –**

3.1.6	Radiolabelling	Alphacypermethrin [^{14}C-benzyl] WL 85871  * = general radioactivity labelling of the benzene ring to which the benzylic carbon atom is attached.
3.2	**Test animals**	
3.2.1	Species	Rat
3.2.2	Strain	Wistar
3.2.3	Source	Shell Toxicology Laboratory
3.2.4	Sex	Male and female
3.2.5	Age/weight at study initiation	Age: not stated Body weight: 250–288 g (males) 190–205 g (females)
3.2.6	Number of animals per group	5 males and 5 females
3.2.7	Control animals	None
3.3	**Administration/ Exposure**	
3.3.1	Number of applications	Single
3.3.2	Type	Oral by gavage
3.3.3	Dose	1.9 mg/kg
3.3.4	Specific activity of test substance	Specific activity: 29.7 µCi/mg (65934 dpm/µg).
3.3.5	Concentration of radioactivity	1.09 mg/mL (32.4 µC/mL)
3.3.6	Volume applied	Not specified
3.3.7	Vehicle	Corn oil
3.3.8	Post-exposure period	4 days
3.3.9	Samples (sampling time)	Urine and faeces (collection each day for four days); Animals were sacrificed and the following tissues were taken: blood, adrenals, brain, fat, intestine, kidney, liver, lung, muscle, ovaries or testes, skin, spleen and remaining carcass.

Section A6.2 **Metabolism studies in mammals**
Annex Point IIA6.2 **– Metabolism of a single oral dose in the rat (*in vivo* test) –**

3.3.10	Examinations	Total Radioactive Residues (TRR) of daily urine and cage wash was assayed by liquid scintillation counting (LSC) of aliquots. The TRR in faeces, tissues, residual carcass, and blood were determined by combustion of aliquots to C-14 carbon dioxide followed by liquid scintillation counting. Metabolites in urine and faeces were analyzed by thin layer chromatography (TLC).

4 RESULTS

4.1	**Elimination**	The total recovery of eliminated radioactivity was 90-97% (mean 93%), and amount of radiocarbon in cage wash was 1–1.5%. Major parts of radioactivity were excreted via urine (males: 52.7%; females: 50.0%) and faeces (males: 38.2%; females: 42.6%). Elimination was very rapid in both sexes, till 78% being recovered 24 hours after dosing. Results are summarised in Table A6.2- 1.
4.2	**Radioactivity in tissues**	The amount of radiocarbon in the intestines and contents at sacrifice was 0.24-0.34%. Residues were very low in all tissues (<0.06 µg/g of tissue or µg/ml of blood) with the exception of adipose tissue in which 0.42 µg/g in males and 0.22 µg/g in females was retained. Results are presented in Table A6.2- 2.
4.3	**Recovery of labelled compound**	The orally administered [^{14}C]-Alphacypermethrin was recovered nearly quantitatively, i.e. 93.6% for males and 95.4% for females 4 days after dosing.
4.4	**Identification and quantification of metabolites**	The major metabolite in the urine (34–40% of the dose) was: 3-(4-hydroxyphenoxy)benzoic acid-O-sulphate conjugate. Other metabolites identified were: 3-phenoxybenzoic acid (4–5%), 3-(4-hydroxyphenoxy)benzoic acid (2–5%) 3-phenoxybenzoylglycine (1%). Two unknowns accounted for 1–2%. About 75% of radioactivity in faeces (22% of administered dose) was unchanged Alphacypermethrin. There was no evidence for conversion of a cis-isomer into a trans-isomer. Metabolites present at the 1–2% level indicated hydroxylation of the parent molecule at 4'(benzyl) and a trans methyl group (cyclopropane ring). No significant sex-related differences in the metabolite profile were observed.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Five male and female Wistar rats received a single dose of 1.9 mg/kg bw ^{14}C-labelled Alphacypermethrin by gavage. Recovery of radioactivity in elimination and retention was examined in samples of urine, faeces, cage wash, adrenal, blood, brain, carcass, fat, intestine, kidney, liver, lung, muscle ovaries testes, skin and spleen. Although conducted prior to issuing of OECD 417 (1984), the study was consistent to this test guideline in all important aspects, with exception that only one dose level instead of two was used.
5.2	**Results and discussion**	The orally administered [^{14}C]-Alphacypermethrin was rapidly eliminated from the rat. Within 96 hours after dosing, most of the dose was recovered in the faeces and urine (90.9–92.6%). Urinary excretion accounted for 50–52.7%, faeces for 38.2–42.6% and cage wash accounted for 1.1–1.5%. There were minor sex-related differences in elimination of radioactivity. A small proportion of radioactivity was retained in the adipose tissue of the animals. Metabolite identification suggests that most, but not the entire compound, is absorbed from the gut and rapidly metabolized by ester cleavage followed by hydroxylation and sulphate conjugation of the 3-phenoxybenzoic acid portion of the compound. There were no sex-related differences observed in metabolism of Alphacypermethrin.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	No

	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE (*)	
Date	March 2009	
Materials and Methods	Applicant's version adopted	
Results and discussion	Applicant's version adopted	
Conclusion	Applicant's version adopted	
Reliability	1	
Acceptability	acceptable	
Remarks	none	
	COMMENTS FROM ...	
Date		
Materials and Methods		
Results and discussion		
Conclusion		
Reliability		
Acceptability		
Remarks		

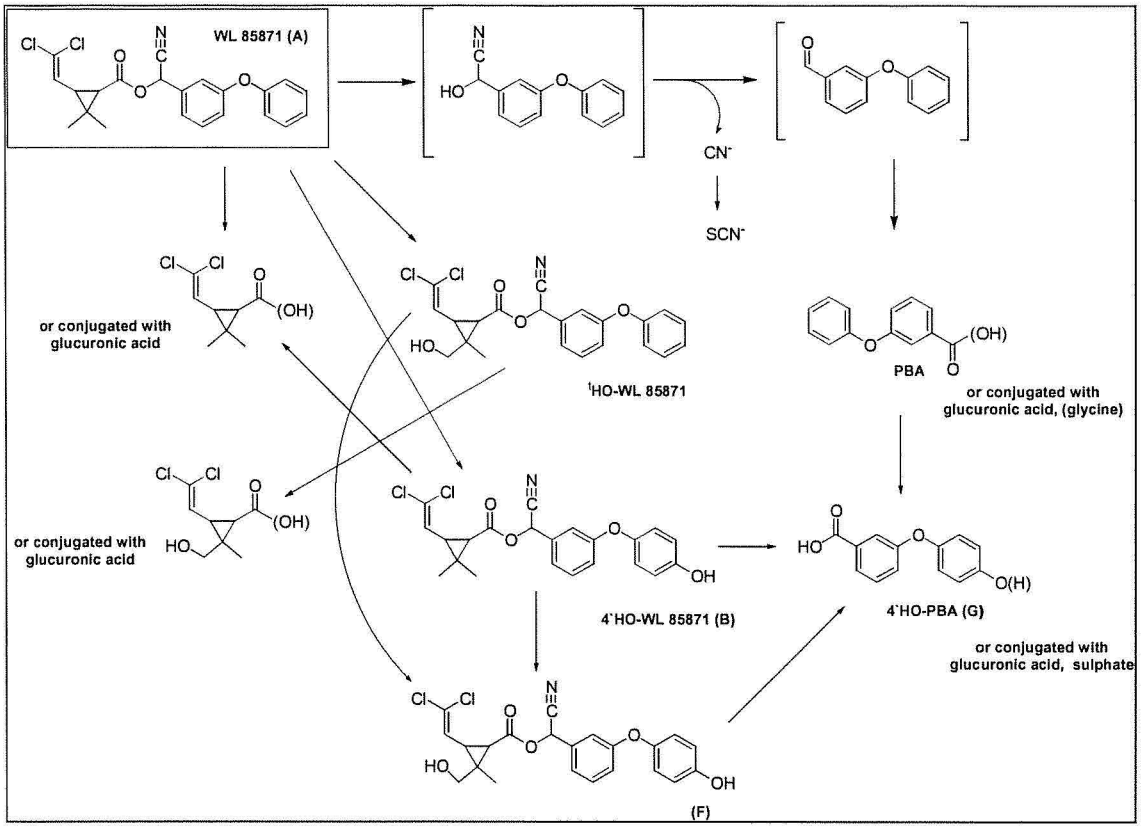


Figure A6.2- 1: Proposed metabolic pathway of Alphacypermethrin in the rat.

Table A6.2- 1: Excretion of radioactivity in % of the administered dose (approx. 1.9 mg/kg bw).

Matrix	**Time interval [h]**	**% of the administered dose**	
		^{14}C-benzyl labelled Alphacypermethrin	
		Males	**Females**
Urine	0–24	46.1	43.3
	24–48	4.7	4.8
	48–72	1.3	1.3
	72–96	0.6	0.6
	0–96	52.7	50.0
Faeces	0–24	30.1	35.0
	24–48	5.6	6.3
	48–72	1.6	1.0
	72–96	0.4	0.3
	0–96	38.2	42.6
Cage wash	After sacrifice	1.1	1.5
Total		**90.9**	**92.6**

Table A6.2- 2: Total recovery of radioactivity of ^{14}C-labelled Alphacypermethrin.

Source of radioactivity	**% of the administered dose (µg/g or mL)**	
	^{14}C-benzyl labelled Alphacypermethrin	
	Males	**Females**
Urine	52.7	50.0
Faeces	38.2	42.6
Cage wash	1.1	1.5
Intestines	0.3	0.2
Carcass	0.9 (0.02)	0.5 (0.01)
Blood	(0.006)	(0.004)
Brain	<0.01 (0.001)	<0.01 (0.001
Testes/Ovaries	<0.01 (0.001)	<0.01 (0.03)
Adrenals	<0.01 (0.05)	<0.01 (0.03)
Spleen	<0.01 (0.005)	<0.01 (0.003)
Lung	<0.01 (0.01)	<0.01 (0.006)
Kidney	<0.01 (0.02)	<0.01 (0.02)
Fat (sample)	<0.01 (0.42)	<0.01 (0.22)
Muscle (sample)	<0.01 (0.005)	<0.01 (0.002)
Liver	0.1 (0.05)	0.1 (0.03)
Skin	0.25 (0.02)	0.5 (0.04)
Totals	**93.6**	**95.4**

Section A6.2 **Metabolism studies in mammals**
Annex Point IIA6.2 **– Depletion of ^{14}C-Alphacypermethrin from tissues of female rats after oral administration of a single dose (*in vivo* test) –**

Official use only

1 REFERENCE

1.1	**Reference**	**A6.2/02:** Logan C (1983) WL85871: Depletion from tissues of female rats after a single oral dose. SRC, Sittingbourne, UK, Report no. SBGR.83.075, March 24, 1983 (unpublished), BASF RDI No.: AL-440-008. **A6.2/03:** Hutson DH, Logan CJ (1986) The metabolic fate in rats of the pyrethroid insecticide WL85871, a mixture of two isomers of cypermethrin. Pesticide Science 17: 548-558, BASF RDI No.: AL-905-066.
1.2	**Data protection**	Yes (reference A6.2/02)
1.2.1	Data owner	BASF
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I.

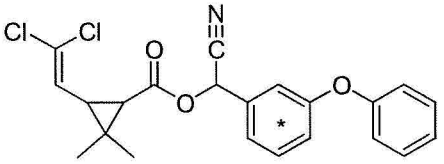
2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Not stated in the report. The conduct of the study was consistent to OECD 417 (1984) in all important aspects, with exception that only one dose level instead of two was used.
2.2	**GLP**	No
2.3	**Deviations**	Not applicable

3 MATERIALS AND METHODS

3.1	**Test material**	Alphacypermethrin (WL 85871), radio-labelled
3.1.1	Lot/Batch number	Batch 1, OCD 594
3.1.2	Specification	As given in section A2.
3.1.3	Purity	Radiochemical purity: 99.6 %; Chemical purity: 97.9 %
3.1.4	Description	Not stated
3.1.5	Stability	Not stated

Section A6.2 **Metabolism studies in mammals**
Annex Point IIA6.2 **– Depletion of ^{14}C-Alphacypermethrin from tissues of female rats after oral administration of a single dose (*in vivo* test) –**

3.1.6	Radiolabelling	Alphacypermethrin [^{14}C-benzyl] WL 85871  * = general radioactivity labelling of the benzene ring to which the benzylic carbon atom is attached.
3.2	**Test animals**	
3.2.1	Species	Rat
3.2.2	Strain	Wistar
3.2.3	Source	Shell Toxicology Laboratory, Tunstall
3.2.4	Sex	Female
3.2.5	Age/weight at study initiation	Age: 9.5–10 weeks Body weight: 183 g (166–199 g)
3.2.6	Number of animals per group	3 (24 animals in total)
3.2.7	Control animals	None
3.3	**Administration/ Exposure**	
3.3.1	Number of applications	Single
3.3.2	Type	Oral by gavage
3.3.3	Dose	2 mg/kg bw
3.3.4	Concentration of test substance	1.02 mg/mL
3.3.5	Specific activity of test substance	29.7 µCi/mg
3.3.6	Total volume applied	2 mL/kg b.w.
3.3.7	Vehicle	Corn oil
3.3.8	Post-exposure period	1–42 days
3.3.9	Samples (sampling time)	Animals were sacrificed in groups of three individuals at 1, 3, 8, 14, 16, 18, 22 and 42 days after dosing and the following tissues were sampled: fat (peri-renal, parovarian, subcutaneous), skin, liver and kidneys.

3.3.10	Examinations	Determination of total radioactive residues (TRR) by liquid scintillation counting (LSC) or by combustion followed by LSC and by TLC. Analysis of the peri-renal and parovarian fat samples after extraction (hexane/acetone) and partitioning between acetonitrile and hexane. Both layers were quantified by LSC and then analysed by chromatographic techniques (GPC/UV, HPLC/UV).

4 RESULTS

4.1	**Half-life periods**	The depletion of total residue from liver and kidney was rapid ($t_{½}$ for both tissues approx. 2 days) and was at or below the limit of detection after two weeks. The depletion from adipose tissue and skin was biphasic with a first $t_{½}$ of 1.6–2.7 days and a second $t_{½}$ of 17–26 days (skin 40 days). Results are summarised in Table A6.2- 3 and Table A6.2- 4.
4.2	**Analysis of residues**	Analysis of the peri-renal and parovarian fat from animals killed 3, 8 and 18 days after dosing was carried out in an attempt to identify the nature of the residues. After extraction the residues were partitioned between hexane and acetonitrile, and Alphacypermethrin partitioned at more than 97% into the acetonitrile fraction. Co-chromatography with Cypermethrin by HPLC showed that more than 98% of the radioactivity chromatographed as Alphacypermethrin, indicating that there was little or no isomeration of the test substance stored in the fat over an extended period. The proportion of radioactivity obtained from fat partitioning into hexane increased with time from 28% in day 3 samples to 48% in day 22 samples, but reached only 0.03 µg/g equivalents.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	24 female Wistar rats received a single oral dose of 2.0 mg/kg bw Alphacypermethrin ^{14}C-labelled by gavage. The rate of depletion was examined in samples of kidney, liver, skin and parovarian, peri-renal and subcutaneous fat tissue. Although conducted prior to issuing of OECD 417 (1984), the study was consistent to this test guideline in all important aspects, with exception that only one dose level instead of two was used.

Section A6.2	**Metabolism studies in mammals**
Annex Point IIA6.2	**– Depletion of ^{14}C-Alphacypermethrin from tissues of female rats after oral administration of a single dose (*in vivo* test) –**

5.2	**Results and discussion**	Alphacypermethrin is rapidly metabolised in female rats via the liver and kidney. The half life period was estimated at 2 days. Residues in tissues fell below the limit of detection within fourteen days. The loss of radioactive residues from the fatty tissues was bi-phasic, with an initial rapid depletion ($t_{½}$ about two days) followed by a slower second phase ($t_{½}$ 17–26 days). Analysis of the fat from animals killed 3, 8 and 18 days after dosing showed that more than 98% of the radioactivity was still attributable to Alphacypermethrin. This indicates that there was little or no isomerisation of Alphacypermethrin in the animal. Further analysis of the fat suggested that an increasing proportion of the residues over time was made up of lipophilic metabolites.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Evaluation by Competent Authorities	
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE (*)
Date	March 2009
Materials and Methods	Applicant's version adopted
Results and discussion	Applicant's version adopted
Conclusion	Applicant's version adopted
Reliability	1
Acceptability	acceptable
Remarks	none
	COMMENTS FROM ...
Date	
Materials and Methods	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Table A6.2- 3: Summary of radioactive residues in tissues of female Wistar rats following a single oral dose of ^{14}C- Alphacypermethrin.

Days after dosing	Mean concentrations expressed as Alphacypermethrin equivalents [µg/g]					
	Fat			Skin	Liver	Kidney
	Peri-renal	Parovarian	Subcutaneous			
1	0.561 (± 0.172)	0.556 (± 0.213)	0.335 (± 0.092)	0.119 (± 0.059)	0.232 (± 0.047)	0.122 (± 0.023)
3	0.428 (± 0.061)	0.453 (± 0.045)	0.269 (± 0.038)	0.044 (± 0.029)	0.031 (± 0.004)	0.031 (± 0.009)
8	0.159 (± 0.069)	0.171 (± 0.085)	0.106 (± 0.049)	0.015 (± 0.007)	0.007 (± 0.003)	0.009 (± 0.004)
14	0.092 (± 0.014)	0.094 (± 0.010)	0.072 (± 0.016)	0.012 (± 0.007)	0.003 (± 0.002)	–
16	0.061 (± 0.027)	0.063 (± 0.026)	0.045 (± 0.020)	0.007 (± 0.003)	–	–
18	0.059 (± 0.017)	0.064 (± 0.022)	0.040 (± 0.009)	0.009 (± 0.008)	–	–
22	0.062 (± 0.019)	0.073 (± 0.023)	0.038 (± 0.018)	0.007 (± 0.004)	–	–
42	0.028 (± 0.003)	0.037 (± 0.008)	0.019 (± 0.003)	0.006 (± 0.003)		

– : Not determined. Limit of detection was 0.003 µg/g.

Values are means of 4 combustions for each animal ± SD

Table A6.2- 4: Half-lives of depletion of radioactivity from tissues after a single oral dose of ^{14}C-Alphacypermethrin to female rats.

	Fat			Skin	Liver	Kidney
	Peri-renal	Parovarian	Subcutaneous			
First half-life period [days]	2.5	2.7	2.5	1.6	2.3	2.0
Second half life period [days]	19.0	26.0	17.3	40.4	–	–

– : Not determined (below the limit of detection)

Section A6.2 **Metabolism studies in mammals**
Annex Point IIA6.2 **– Human oral dose-excretion study –**

Official use only

1 REFERENCE

1.1	**Reference**	**A6.2/04:** [redacted] (1984) Human oral dose-excretion study with Fastac. [redacted], Report no. HSE 85.010, November 1984 (unpublished), BASF RDI No.: AL-445-003.
1.2	**Data protection**	Yes
1.2.1	Data owner	BASF
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I.

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No
2.2	**GLP**	No
2.3	**Deviations**	Not applicable

3 MATERIALS AND METHODS

3.1	**Test material**	As given in Section A2.
3.1.1	Lot/Batch number	Not stated
3.1.2	Specification	As given in Section A2.
3.1.3	Purity	99.8%
3.1.4	Description	Not stated
3.1.5	Stability	Not stated
3.1.6	Radiolabelling	No
3.2	**Test subjects**	
3.2.1	Species	Human
3.2.2	Sex	Male
3.2.3	Age/weight at study initiation	Age: not stated Body weight: not stated
3.2.4	Number of volunteers per group	2 volunteers per dose level (same volunteers for study a and b), i.e. a total of 6 volunteers.
3.2.5	Control subjects	None

3.3	**Administration/ Exposure**	
3.3.1	No of applications	Single and repeated
3.3.2	Type	Oral by capsule
3.3.3	Dose	0.25, 0.50 and 0.75 mg
3.3.4	Concentration of test substance	1.25, 2.50 and 3.75 mg Alphacypermethrin per mL corn oil. One capsule contained 200 µl of the solutions.
3.3.5	Vehicle	Gelatine capsules
3.3.6	Exposure period	(a) Single oral dose (b) Repeated oral dose: 5 successive days
3.3.7	Post-exposure period	(a) Single oral dose: 3 days (b) Repeated oral dose: 5 days
3.3.8	Samples (sampling time)	Urine (collection of a pre-exposure sample and subsequently over 24 hour periods for up to 4 days (a) and up to 10 days (b))
3.3.9	Examinations	Urinary volume, creatinine excretion and excretion of urinary *cis*-cyclopropane carboxylic acid. Pre- and post-exposure urine was analysed for the *cis*-cyclopropane carboxylic acid by sulphuric acid/methanol methylation, extraction, clean-up and gas-liquid chromatography with electron-capture detection. This method detects both the free acid and its glucuronic acid conjugate. Selected samples were confirmed by mass-spectrometric detection.

4 RESULTS

4.1	**Elimination**	After single oral administration of Alphacypermethrin, excretion of *cis*-cyclopropane carboxylic acid was rapid. A mean of 43% of the single dose was excreted in urine as *cis*-cyclopropane carboxylic acid (free and conjugated) in the first 24 hour period after dosing, decreasing to 1–5% on the next day. The relationship between the oral dose levels and the excretion of free and conjugated cyclopropane carboxylic acid over the first 24 hours was clearly dose-related. After repeated oral dosing of Alphacypermethrin, urinary excretion of free and conjugated *cis*-cyclopropane carboxylic acid was rapid and consistent over the 5 days period with a mean excretion of 49% of the metabolite each day. Within the following five days values were close to the detection limit. Approximately 1–7% (mean 3%) of the dose were excreted on the day after cessation of dosing. Excretion of free and conjugated cyclopropane carboxylic acid was clearly dose-related. Results are presented in Table A6.2- 5.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Dose-excretion studies were carried out with 6 volunteers who received a single oral dose of Alphacypermethrin at 0.25, 0.50 and 0.75 mg followed later by repeated oral doses of Alphacypermethrin over five consecutive days. The aims of the studies were to establish a quantitative relationship between a well-controlled oral dose of Alphacypermethrin and the excretion of a metabolite in urine and to determine whether there is accumulation of Alphacypermethrin in the body following repeated oral exposure. The study is well documented, meets generally accepted scientific principles and thus is considered to be acceptable for risk assessment.
5.2	**Results and discussion**	Approximately 43% of the dose was excreted in urine as the *cis*-cyclopropane carboxylic acid in the first 24 hour period after single oral dosing. An average of 49% of Alphacypermethrin was excreted in the urine as *cis*-cyclopropane carboxylic acid in each of the subsequent 24 hour periods after repeated oral administration indicating that intake and excretion were in equilibrium after the first dose. On the days following single and the final repeated administration, the excreted amounts of the metabolites fell rapidly to 1–5 or 1–7% of the dose, respectively. Therefore, no evidence of delayed excretion or accumulation following repeated dosing was observed.
5.3	**Conclusion**	There was no evidence of any accumulation after repeated oral administration of Alphacypermethrin to human volunteers. On average, 49% of the dose were excreted in the urine as *cis*-cyclopropane carboxylic acid.
5.3.1	Reliability	2
5.3.2	Deficiencies	No

	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE (*)	
Date	March 2009	
Materials and Methods	Applicant's version adopted	
Results and discussion	Applicant's version adopted	
Conclusion	Applicant's version adopted	
Reliability	2	
Acceptability	acceptable	
Remarks	none	
	COMMENTS FROM ...	
Date		
Materials and Methods		
Results and discussion		
Conclusion		
Reliability		
Acceptability		
Remarks		

Table A6.2- 5: Summary of the urinary excretion of cyclopropane carboxylic acid following administration of Alphacypermethrin, either as a single dose or as a repeated dose over five successive days.

FASTAC dose [mg]	Average excretion [%] of the dose in the subsequent 24 hour period	
	Single dose	Mean repeated dose (range)
0.25	**43**	**65 (60–75)**
0.25	**57**	**55 (44–72)**
0.50	**35**	**41 (37–46)**
0.50	**45**	**48 (37–53)**
0.75	**38**	**32 (30–38)**
0.75	**42**	**51 (46–57)**
Mean	**43**	**49**

Section A6.2 Metabolism studies in mammals
Annex Point IIA6.2 **– Supportive data –**

The following reference is considered to contain additional information concerning metabolism of Alphacypermethrin in mammals and are thus presented in abbreviated format as supportive data:

Reference: **A6.2/05**

[redacted] (1985) WL85871: Percutaneous absorption, metabolism and elimination of WL85871 in the rat. [redacted] Report no. SBGR.85.217, January 17, 1986 (unpublished), BASF RDI no.: AL-440-010.

Guidelines: Non-guideline dermal absorption and metabolism study.

GLP: No

Material and methods:

^{14}C-labelled alphacypermethrin (labelled in the benzyl ring, sample no. 594, radiochemical purity < 99%) dissolved in acetone was applied to the skin of female Fischer 344 rats (single dermal administration) at a dose of 1 mg per individual. Radioactivity was recovered from excreta and various tissues and analysed using standard techniques (radio-HPLC; TLC, LSC).

Findings:

The study is contingently valid since the test substance was dissolved in acetone and applied on the skin, a procedure that damages the stratum corneum. Therefore, penetration was rapid (51, 70 and 98% after 3.5, 30 and 168 h, respectively).

The absorbed radioactivity was mainly eliminated via the faeces (47% of applied dose in 7 days) and the urine (36%).

Tissue residues at 3.5 h and after 30 h were greatest in the intestinal tract, whereas after 168 h, the largest residue was adipose tissue.

Disappearance of radioactivity from all tissues occurred with time, while concentrations in fat were similar at each time point.

The major radioactive product present in the gastro-intestinal tract and eliminated via faeces was unchanged Alphacypermethrin. The major radioactive product in the urine was 3-(4-hydroxyphenoxy)benzoic acid O-sulphate ester.

Conclusions:

In view of the application procedure (administration dissolved in acetone), the study is considered as non-relevant for human exposure assessment and is not taken forward to the risk assessment.

	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE (*)	
Date	March 2009	
Materials and Methods	Applicant's version adopted	
Results and discussion	Applicant's version adopted	
Conclusion	Applicant's version adopted	
Reliability	3 (In view of the application procedure (administration dissolved in acetone), the study is considered as non-relevant for human exposure assessment and is not taken forward to the risk assessment)	
Acceptability	Non acceptable (In view of the application procedure (administration dissolved in acetone), the study is considered as non-relevant for human exposure assessment and is not taken forward to the risk assessment)	
Remarks	none	
	COMMENTS FROM ...	
Date		
Materials and Methods		
Results and discussion		
Conclusion		
Reliability		
Acceptability		
Remarks		

Section A6.2 Metabolism studies in mammals

Annex Point IIA6.2 **– Supportive data –**

The following reference is a metabolism study on Cypermethrin and is considered to contain additional information concerning metabolism of Alphacypermetrin obtained through the analogy with Cypermethrin and is therefore presented in an abbreviated format as supportive data:

Reference: **A6.2/06:**

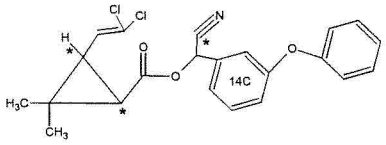
Crawford, M.J.; Hutson, D.H. (1977): The metabolic fate of the cis and trans isomers of WL 43467 (Cypermethrin). Metabolism and elimination of 14C-aryl-labelled cis and trans-isomers in rats, Shell Toxicology Laboratory, Tunstall, UK, unpublished report no.: TLGP.0131.77, December 1977 (unpublished), BASF no: CY-440-004.

Guidelines: Not specified. However, the conduct of the study is similar to method B.36 (88/302/EEC), with the exception that only one dose level was administered.

GLP: No (test was conducted at a time when GLP was not mandatory)

Materials and Methods:

WL 43481 (*cis*-[^{14}C-benzyl]Cypermethrin), radiochemical purity: > 99.5 %; WL 42641 (*trans*-[^{14}C-benzyl]Cypermethrin), radiochemical purity: > 99.5 %; The structural formula of Cypermethrin with the position of the radiolabel (^{14}C) and the chiral carbon atoms (*) is presented below:



α-cyano-3-phenoxy-[^{14}C]-benzyl-cis/trans-2-(2,2-dichlorovinyl)-3,3-dimethylcyclopropanecarboxylate (in this study, both the cis- and the trans-isomer were investigated separately).

Groups of male and female Wistar rats (12 weeks old, weighing approx. 350 and 250 g, respectively) received single low doses orally as outlined in the table below. Each rat was individually housed in a glass metabolism cage. Radioactivity and the identity of metabolites in urine, faeces, blood and selected organs/tissues were determined by liquid scintillation counting, TLC, GC/MS, radio-GLC and radio-HPLC. Expired $^{14}CO_2$ was collected from one male and one female each dosed with *trans*-[^{14}C]Cypermethrin.

Table A6.2- 6: Dosing scheme.

Group	Animals/sex	Dose	Vehicle	Collection of
1	6 m, 6 f	1.7-2.5 mg/kg *cis*-[^{14}C]Cypermethrin	corn oil	urine and faeces until sacrifice after 24 h, 72 h or 8 days
2	3 m, 3 f	2.4-3.1 mg/kg *trans*-[^{14}C]Cypermethrin	corn oil	urine and faeces until sacrifice after 3 days

Findings:

Elimination: Excretion via urine and faeces was rapid in both sexes dosed with cis-[^{14}C]Cypermethrin, and the subsequent statistical analysis revealed significant sex differences in the quantitative excretion of radioactivity via the two routes. The total recovery of radioactivity was 100.5 % for male rats and 97.3 % for female rats. Excretion via urine and faeces was also rapid in both sexes dosed with trans-[^{14}C]Cypermethrin. However, no sex difference was apparent in the quantitative excretion of radioactivity via the two routes. The total recovery was 103.0 % for male rats and 101.5 % for female rats. The results are summarised in the table below. One animal of each sex dosed with trans-[^{14}C]Cypermethrin afforded only 0.02 % (male) and 0.015 % (female) of the dose in their expired air. This was considered to demonstrate that negligible destruction of the labelled ring occurred.

Table A6.2- 7: Excretion of radioactivity via urine and faeces (%).

Group	Sex	Radioactivity in % of administered dose								
		urine			faeces			Cumulative excretion		
		0-24 h	24-48 h	48-72 h	0-24 h	24-48 h	48-72 h	urine	faeces	total
1	male (SEM)	53.0 (1.56)	6.7 (0.81)	2.4 (0.17)	18.9 (2.44)	7.4 (2.0)	4.5 (0.68)	62.1	30.8	92.9
	female (SEM)	35.4 (4.65)*	7.1 (2.9)	1.4 (0.23)	35.5 (6.6)*	12.1 (3.7)	2.8 (1.4)	43.9	50.4	94.3
2	male	59.2	9.7	2.5	18.9	7.4	1.9	71.4	28.3	99.7
	female	62.0	10.5	1.9	15.8	4.8	2.1	74.4	22.7	97.2

*: significant difference between the sexes (at 0.01 %)

Distribution: The highest residue was found in fat, which was also the most persistent residue. A comparison of the values for the trans-isomer and the cis-isomer revealed a trend to lower values for the former. The results are summarised in the table below.

Table A6.2- 8: Organ distribution of radioactivity.

Tissue	Concentration of radiochemical expressed as Cypermethrin in the tissues [µg/g]							
	Day 1		Day 3				Day 8	
	cis-[^{14}C]Cypermethrin		cis-[^{14}C]Cypermethrin		trans-[^{14}C]Cypermethrin		cis-[^{14}C]Cypermethrin	
	males	females	males	females	males	females	males	females
Liver	0.490	0.695	0.185	0.076	0.052	0.073	0.058	0.041
Kidney	0.165	0.235	0.063	0.032	0.044	0.052	0.018	0.013
Fat	0.995	1.400	0.925	0.935	0.183	0.460	1.148	1.003
Muscle	0.023	0.039	0.007	0.004	0.006	0.004	0.004	0.033
Brain	0.008	0.016	0.002	0.002	0.001	0.001	0.001	0.001
Blood	0.135	0.315	0.028	0.018	0.014	0.019	0.012	0.008

(mean values calculated from the reported raw data by the authors of this summary)

Metabolism: The excreted metabolites of both the cis and the trans-isomer were very similar qualitatively and quantitatively, and indicated that the major metabolic reactions for both esters were arylhydroxylation at the para position of the distal aromatic ring, and ester cleavage. Ester metabolites were detected from the cis-isomer but not from the trans-isomer. The results are presented in the table below.

Table A6.2- 9: Urinary metabolites of cis- and trans-[^{14}C-benzyl]Cypermethrin.

Identity	Percentage of dose			
	cis-isomer		trans-isomer	
	males	females	males	females
in urine				
3-phenoxybenzoic acid	3.2	1.4	5.9	7.1
3-(4-hydroxyphenoxy)benzoic acid	1.5	1.8	1.8	4.1
3-phenoxybenzoylglycine	0.5	0.3	1.8	<0.6
3-(4-hydroxyphenoxy)benzoic acid (sulphate conjugate)	48.2	32.2	49.6	47.8
unknown	0.5	0.3	ND	ND

ND = not detected

Conclusions: The cis and trans isomers were both rapidly metabolised in rats. The absorbed portions of the dose were eliminated predominantly via urine as a mixture of metabolites, whereas faecal metabolites accounted for only 2-4% of the total dose. The cis and trans isomers yielded a similar pattern of metabolites, indicating that the foremost metabolic pathway involves (a) arylhydroxylation in the para position of the distal aromatic ring, and (b) ester cleavage. Whereas ester cleavage of the trans isomer appeared to be essentially complete, the appearance of ester metabolites from the cis-isomer in faeces was interpreted as evidence of a somewhat reduced susceptibility of the cis isomer towards ester hydrolysis. Tissue residues from the cis isomer were low in all cases 24 h p.a., but even lower for the trans isomer.

	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE (*)	
Date	March 2009	
Materials and Methods	Applicant's version adopted	
Results and discussion	Applicant's version adopted	
Conclusion	faecal metabolites accounted for only 1-3% of the total dose	
Reliability	2 because these studies were conducted on cypermethrin or cis-cypermethrin and are therefore supportive data for alpha-cypermethrin	
Acceptability	acceptable	
Remarks	none	
	COMMENTS FROM ...	
Date		
Materials and Methods		
Results and discussion		
Conclusion		
Reliability		
Acceptability		
Remarks		

Section A6.2 Metabolism studies in mammals
Annex Point IIA6.2 **– Supportive data –**

The following reference is a metabolism study on Cypermethrin and is considered to contain additional information concerning metabolism of Alphacypermetrin obtained through the analogy with Cypermethrin and is therefore presented in an abbreviated format as supportive data:

Reference: **A6.2/07**

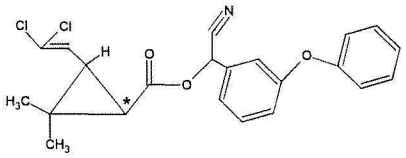
Crawford, M. (1977): The metabolism of WL 43467 in mammals. The fate of a single oral dose of (14C-cyclopropyl) WL 43467 in the rat, Shell Toxicology Laboratory, Tunstall, UK, Report no.: TLGR.0004.77, January 1977 (unpublished), BASF RDI No.: CY-440-003.

Guidelines: Not specified. However, the conduct of the study is similar to method B.36 (88/302/EEC), with the exception that only one dose level was administered, and that the excreta were only measured for 3 days, yielding only 85 % in males (the excreta should be measured several times after exposure, either until about 95 % of the administered dose has been excreted or for seven days, whichever comes first).

GLP: No (test was conducted at a time when GLP was not mandatory)

Materials and Methods:

[^{14}C-cyclopropyl]WL 43467 [^{14}C-cyclopropyl-Cypermethrin], radiochemical purity: > 99 %. The structural formula of [^{14}C-cyclopropyl]-Cypermethrin with the position of the radiolabel (*) is presented below:



α-cyano(3-phenoxyphenyl)-methyl-cis,trans-2-(2,2-dichloroethenyl)-3,3-dimethyl-[^{14}C]-cyclopropanecarboxylate (cis/trans mixture)

A single low dose of 0.5 mg of [^{14}C-cyclopropyl]-Cypermethrin (1:1 *cis/trans* mixture) in corn oil was administered orally to groups of three male and female Wistar rats (approx. 430 and 240 g, respectively). Each rat was individually housed in a glass metabolism cage. Urine and faeces were collected daily. The animals were sacrificed three days after administration. Radioactivity in urine, faeces, blood and selected organs/tissues was determined by liquid scintillation counting. Additionally, one male rat and one female rat were dosed as described above for determination of expired $^{14}CO_2$ and were sacrificed after 15 days.

Findings:

Elimination: The urinary excretion of the compound was rapid in both sexes, male rats excreting 53 % of the dose in 48 hours, and female rats 66 %. Excretion via faeces was slower in some animals, male rats excreting 29 % of the dose in 72 hours and females 27 %. The amount of radioactivity excreted via expired air accounted for only 0.09 % of the dose. The excretion of radioactivity via urine and faeces in % of administered dose are presented in the following table.

Table A6.2- 10: Excretion of radioactivity via urine and faeces (%).

Group	Excretion via urine [%]			Excretion via faeces [%]			Cumulative excretion [%]		
	0-24 h	24-48 h	48-72 h	0-24 h	24-48 h	48-72 h	urine	faeces	total
male	32.3	20.7	2.8	–	–	–	55.8	28.7	84.5
female	54.7	12.6	2.1	–	–	–	69.4	27.0	96.4

– due to a very low yield of faeces in the period 0-24 hours some samples were combined and no mean values were calculated

Distribution: Total recoveries, including cage washings were 104 % for male rats and 107 % for the female animals. Female rats showed 2-3 fold higher Cypermethrin residues in fat than males. The results are summarised in the following table.

Table A6.2- 11: Organ distribution of radioactivity (mean values of 3 animals per sex).

Sex	Concentration of radiochemical expressed as Cypermethrin in the tissues [µg/g]					
	Liver	Kidney	Fat	Muscle	Brain	Blood
male	0.37	0.1	0.31	0.01	0.009	0.05
female	0.12	0.06	0.72	0.009	0.008	0.04

Conclusions: The rate and route of elimination of Cypermethrin radiolabelled in the cyclopropyl moiety does not differ significantly form the results obtained with the separate cis- and trans-isomers (see above) labelled either in the distal phenyl or the benzyl moiety. Excretion was rapid and almost quantitative within 72 hours, without any clear sex difference. The ratio of urinary to faecal excretion was approximately 2:1, and elimination via expired air was negligible.

	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE (*)	
Date	March 2009	
Materials and Methods	Applicant's version adopted	
Results and discussion	Applicant's version adopted	
Conclusion	Applicant's version adopted	
Reliability	2 because these studies were conducted on cypermethrin or cis-cypermethrin and are therefore supportive data for alpha-cypermethrin	
Acceptability	acceptable	
Remarks	none	
	COMMENTS FROM ...	
Date		
Materials and Methods		
Results and discussion		
Conclusion		
Reliability		
Acceptability		
Remarks		

Section A6.2 Metabolism studies in mammals

Annex Point IIA6.2 **– Supportive data –**

The following reference is a metabolism study on Cypermethrin and is considered to contain additional information concerning metabolism of Alphacypermetrin obtained through the analogy with Cypermethrin and is therefore presented in an abbreviated format as supportive data:

Reference: **A6.2/08**

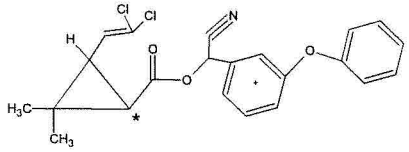
Logan, C.J. (1980): Cypermethrin – excretion and retention of Cypermethrin and its metabolites in rats following a single oral dose (ca. 200 mg/kg). Shell Toxicology Laboratory, Tunstall, UK, Report no.: TLER.80.083, October 1980 (unpublished), BASF RDI No.:CY-440-033.

Guidelines: Not specified. However, the conduct of the study is similar to method B.36 (88/302/EEC), with the exception that only one dose level was administered.

GLP: No (test was conducted at a time when GLP was not mandatory)

Materials and methods:

Cypermethrin (unlabelled), batch no.: 30, purity: 96.4 %; *cis* and *trans* isomers (48.5%:51.5%) of [^{14}C-benzyl]-Cypermethrin, radiochemical purity: > 99.5 %; *cis* and *trans* isomers (48.8%:51.2%) of [^{14}C-cyclopropyl]-Cypermethrin, radiochemical purity: > 99.6 %; The structural formula of Cypermethrin with the position of the [^{14}C-benzyl]- and the [^{14}C-cyclopropyl]- radiolabel (*) is presented below:



α-cyano-3-phenoxy-[14C]-benzyl-cis/trans-2-(2,2-dichlorovinyl)-3,3-dimethyl-[14C]-cyclopropanecarboxylate (in this study, both the cis- and the trans-isomer were investigated in combination at a ratio of 1:1).

A single high dose of approx. 200 mg/kg bw of [^{14}C-benzyl]-Cypermethrin or [^{14}C-cyclopropyl]-Cypermethrin in corn oil was administered orally to groups of five female and five male Wistar rats (200-250 g; 275-295 g, respectively). The animals were housed individually in all-glass metabolism cages. The excreta were collected over seven days at which time the animals were sacrificed and samples of selected tissues taken for analysis. Additionally one animal of each sex was dosed with [^{14}C-benzyl]-Cypermethrin or [^{14}C-cyclopropyl]-Cypermethrin for CO_2 collection. Radioactivity was determined by liquid scintillation counting.

Findings:

Signs of toxicity: Two of the males dosed with [^{14}C-cyclopropyl]-Cypermethrin were killed 7 h and 9 h after dosing, respectively, in order to relieve them from excessive suffering.

Elimination: Neither the male nor the female dosed with [^{14}C-benzyl]-Cypermethrin expired a detectable amount of $^{14}CO_2$ (limit of detection 0.005 % of dose). The male dosed with [^{14}C-cyclopropyl]-Cypermethrin expired 0.06 % of the administered dose as $^{14}CO_2$, whilst the similarly dosed female expired 0.03 % of the administered dose as $^{14}CO_2$, indicating only a minor breakdown of the cyclopropyl ring during the metabolism of Cypermethrin. The excretion of radioactivity via urine and faeces in percentage of the administered dose is presented in the tables below.