Competent Authority Report

Programme for Inclusion of Active Substances in Annex I to Council Directive 98/8/EC

Cyphenothrin (PT 18)

CAS-No. 39515-40-7

Sumitomo Chemical (U.K.) PLC

DOCUMENT III-A

Study summaries

Sections A6.1-A6.2

Toxicology section

Rapporteur: Hellas

November 2017

Section A6 – Toxicological and Metabolic Studies

6.1 Acute toxicity

6.1.1 Acute oral

			Official use only
		1. REFERENCE	
1.1	**Reference**	Reference : A6.1.1/01 Author: [redacted] Title: Acute oral toxicity of [redacted] in rats Laboratory : Sumitomo Chemical Company Ltd unpublished Report no : [redacted] Date : February 3, 1983	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Sumitomo	
1.2.2	Companies with letter of access	None	
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 [redacted]	
2.2	**GLP**	Yes	**X**
2.3	**Deviations**	No	**X**
		3. MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	None given	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Stable	**X**
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague Dawley	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male/female	
3.2.5	Age/weight at study initiation	Six-week old weighing 170 - 190 g (male) or 125 - 145 g (female)	
3.2.6	Number of animals per group	20 - 10 animals of each sex	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Oral	

3.3.1	Postexposure period	14 days
3.3.2	Type	Gavage
3.3.3	Concentration	Gavage at 50, 100, 250, 320, 420, 550, 710 and 930 mg/kg bw
3.3.4	Vehicle	Moistened with corn oil
3.3.5	Concentration in vehicle	As necessary to achieve the required dosages
3.3.6	Total volume applied	5ml/kg body weight
3.3.7	Controls	Vehicle
3.3.8	Concentrations	50, 100, 250, 320, 420, 550, 710 and 930 mg/kg body weight for both sexes.
3.4	**Examinations**	The toxic signs and the mortality were observed at 1/6, 1/2, 1, 2 and 4 hours after administration and daily (at 10 a.m.) for 2 weeks thereafter. Body weight of each animal was measured on the 0, 7 and 14 day of the observation period. All animals which succumbed during the course of observation and all animals which were alive at the end of observation period were necropsied for gross pathological examination of main tissues and organs.
3.5	**Method of determination of LD_{50}**	Litchfield and Wilcoxon
3.6	**Further remarks**	-

4. RESULTS AND DISCUSSION

4.1	**Clinical signs**	The mortality data are given in Table A6.1.1-1 The toxic signs observed were as follows. At 0 and 50 mg/kg, no toxic sign was observed. At 100 mg/kg, muscular fibrillation, decrease of spontaneous activity, ataxia (male) were observed. At 250 mg/kg, muscular fibrillation, tremor, decrease of spontaneous activity (female), ataxia, limb paralysis (male), irregular respiration and soft feces and/or diarrhea (male) were observed. At 320 mg/kg and above, hyperexcitability (710 and 930 mg/kg male and 320, 420 and 710 mg/kg female), muscular fibrillation, tremor, decrease of spontaneous activity (except 320 mg/kg female), ataxia, limb paralysis, loss of righting reflex (930 mg/kg), irregular respiration, hyperpnea followed by dyspnea, salivation (except 320, 420, 550 and 710 mg/kg female), urinary incontinence (except 320, 420, 710 and 930 mg/kg male) and soft faeces and/or diarrhea (320, 710 and 930 mg/kg male and 710 and 930 mg/kg female) were observed. Most of these toxic signs developed more than 2 hour after dosing and all the above toxic signs of surviving animals disappeared within 2 to 5 days.

4.2	**Pathology**	Abnormal findings such as attachment of saliva arround the mouth, remnant of-test solution and coloured material, coloured mucus, black point and spot in the stomach, remnant of test solution and coloured material in the small intestine, retention of white substance and urine in the urinary bladder, horn distended with fluid in the uterus, cannibalism and autolysis were found in dead animals. On the other hand, a white substance present in the urinary bladder, horn distended with fluid in the uterus and atrophy of testis were also found in some animals including control which were sacrificed at the end of observation period. From the above, no test compound-related macroscopic changes in main tissues and organs were found in any animals.
4.3	**Other**	The mean body weight gain of 50 and 550 mg/kg (7 day) females was slightly lower than the controls at the 7 and 14 day determinations. However, these changes were not dose-dependent. Therefore, no test compound-related body weight changes were observed in treated groups
4.4	**LD_{50}**	The acute oral LD for male was calculated to be 318 mg/kg body weight with 95% confidence limits. The acute oral LD for female was calculated to be 419 mg/kg body weight with 95% confidence limits

5. APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	An acute oral toxicity study was conducted with cyphenothrin ([redacted] to groups of 10 male and 10 female Sprague Dawley rats. After 7 days acclimatization and quarantine, the animals were fasted for 20 hours prior to dosing. The test material appropriately dissolved in corn oil was orally administered by gavage to sex at a rate of 5 ml per kg body weight. The dose levels used were 0 (Vehicle control), 50, 100, 250, 320, 420, 550, 710 and 930 mg/kg body weight for both sexes. Clinical signs and mortality were observed at 1/6, 1/2, 1, 2 and 4 hours after administration and daily for 2 weeks thereafter. Body weight of each animal was measured at 0, 7 and 14 days post treatment. All animals, which succumbed during the course of observation and all animals, which were alive at the end of observation period were necropsied for gross pathological examination of main tissues and organs.
5.2	**Results and discussion**	Clinical signs were found in both sexes at more than 100 mg/kg. Major toxic signs such as muscular fibrillation, tremor, decrease of spontaneous activity, ataxia, limb paralysis, irregular respiration, hyperpnea followed by dyspnea were observed. These toxic signs developed more than 2 hour after dosing and disappeared within 2 to 5 days. No remarkable test compound—related body weight changes and macroscopic changes in main tissues and organs were found in any group. The following LD_{50} values were obtained. Male : 318 mg/kg Female : 419 mg/kg
5.3	**Conclusion**	

5.3.1	Reliability	2
5.3.2	Deficiencies	The study is not conducted to a recognized OECD Guideline

Table A6.1.1-1 Table for Acute Toxicity

Dose [unit]	Number of dead	Time of death (range)	Observations
Male			
0	0/10	Not applicable	No signs of toxicity
50	0/10	Not applicable	No signs of toxicity
100	0/10	Not applicable	Muscular fibrillation, decrease of spontaneous activity, ataxia
250	4/10	> 24 hours	Muscular fibrillation, ataxia, tremor, limb paralysis, irregular respiration, soft faeces/diarrhoea
320	7/10	> 24 hours	Muscular fibrillation, decrease of spontaneous activity, ataxia, tremor, limb paralysis, irregular respiration, soft faeces/diarrhoea, hyperpnoea & dyspnoea, salivation
420	7/10	> 24 hours	Muscular fibrillation, decrease of spontaneous activity, ataxia, tremor, limb paralysis, irregular respiration, hyperpnoea #& dyspnoea, salivation
550	8/10	> 24 hours	Muscular fibrillation, decrease of spontaneous activity, ataxia, tremor, limb paralysis, irregular respiration, soft faeces/diarrhoea, hyperpnoea & dyspnoea, salivation, hyperexcitability, urinary incontinence
710	10/10	> 24 hours	Muscular fibrillation, decrease of spontaneous activity, ataxia, tremor, limb paralysis, irregular respiration, soft faeces/diarrhoea, hyperpnoea & dyspnoea, salivation, hyperexcitability, urinary incontinence
930	10/10	> 24 hours	Muscular fibrillation, decrease of spontaneous activity, ataxia, tremor, limb paralysis, irregular respiration, soft faeces/diarrhoea, hyperpnoea & dyspnoea, salivation, hyperexcitability, urinary incontinence
LD_{50} value	318 (219 – 463) mg/kg		
Female			
0	0/10	Not applicable	No signs of toxicity
50	0/10	Not applicable	No signs of toxicity
100	0/10	Not applicable	Muscular fibrillation, decrease of spontaneous activity
250	3/10	> 24 hours	Muscular fibrillation, decrease of spontaneous activity, ataxia, tremor, limb paralysis
320	3/10	> 24 hours	Muscular fibrillation,ataxia, tremor, limb paralysis, irregular respiration, hyperpnoea & dyspnoea, hyperexcitability, urinary incontinence
420	5/10	> 24 hours	Muscular fibrillation, decrease of spontaneous activity, ataxia, tremor, limb paralysis, irregular respiration, hyperpnoea & dyspnoea, hyperexcitability, urinary incontinence

550	8/10	> 24 hours	Muscular fibrillation, decrease of spontaneous activity, tremor, limb paralysis, irregular respiration, hyperpnoea & dyspnoea, urinary incontinence
710	8/10	> 24 hours	Muscular fibrillation, decrease of spontaneous activity, ataxia, tremor, limb paralysis, irregular respiration, soft faeces/diarrhoea, hyperpnoea & dyspnoea, hyperexcitability, urinary incontinence
930	8/10	24 – 48 hours	Muscular fibrillation, decrease of spontaneous activity, ataxia, tremor, limb paralysis, irregular respiration, soft faeces/diarrhoea, hyperpnoea & dyspnoea, salivation, urinary incontinence loss of righting reflex
LD_{50} value	419 (281 – 624) mg/kg		

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November 2017
Guidelines and quality assurance	Point 2.2: There is no GLP statement in the study report. Point 2.3: No deviations from the OECD guideline 401 are reported, since the study protocol (which is anyway no longer acceptable) is only broadly followed.
Materials and methods	The applicant's version is acceptable in general. Point 3.1.2.3: There are no stability data in this report. For information on the physicochemical properties of the technical see Section 3.
Conclusion	The applicant's opinion is adopted.
Reliability	Reliability indicator 2: Study conducted in accordance with generally accepted scientific principles with methodological deficiencies, which do not affect the quality of relevant results.
Acceptability	Acceptable.
Remarks	According to the criteria set out in Annex VI to Dir. 67/548/EEC, and taking into consideration that the LD_{50} values after oral administration of the a.i. cyphenothrin to male and female rats are in the range of 200-2000 mg/kg bw, the RMS proposes that cyphenothrin is classified as harmful (Xn) with the risk phrase R22 (harmful if swallowed). According to the new Regulation (EC) 1272/2008 on classification, labelling and packaging of substances (CLP), the a.i. cyphenothrin should be classified as "Category 4" with the hazard statement H302: harmful if swallowed.

6.1.2 Acute dermal

			Official use only
		1. REFERENCE	
1.1	**Reference**	Reference: A6.1.2/01 Authors : [redacted] Title: Acute dermal toxicity of [redacted] in rats Laboratory : Sumitomo Chemical Company Ltd unpublished Report no : [redacted] Date : February 8, 1983	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Sumitomo	
1.2.2	Companies with letter of access	None	
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 – but broadly follows OECD Guideline 402	
2.2	**GLP**	Yes	**X**
2.3	**Deviations**	No	**X**
		3. MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	None given	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Stable	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague Dawley	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male/female	
3.2.5	Age/weight at study initiation	Six-week old weighing 160-180 g (male) or 140-160 g (female)	
3.2.6	Number of animals per group	20 - 10 male/10 female	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Dermal	
3.3.1	Postexposure period	14 days	
3.3.2	Area covered	ca 30 cm^2	
3.3.3	Occlusion	Semiocclusive	

3.3.4	Vehicle	Corn-oil
3.3.5	Concentration in vehicle	As appropriate to give dosages of 0 (vehicle control), 2,500 and 5,000 mg/kg body weight
3.3.6	Total volume applied	5ml/kg bodyweight
3.3.7	Duration of exposure	24h
3.3.8	Removal of test substance	Solvent-diethyl ether
3.3.9	Controls	vehicle
3.4	**Examinations**	Clinical observations, mortality, bodyweight and gross pathology
3.5	**Method of determination of LD_{50}**	Not applicable as there were no mortalities
3.6	**Further remarks**	
		4. RESULTS AND DISCUSSION
4.1	**Clinical signs**	There were no mortalities or clinical sigs observed during the study
4.2	**Pathology**	Abnormal findings such as vesicle in the kidney, defect of kidney, white substance present and retention of urine in the urinary bladder and horn distended with fluid and atrophy in the uterus were found in some animals including control which were sacrificed at the end of observation period. However, no test compound-related macroscopic changes in main tissues and organs or skin irritation reactions at the application site were found in any animal.
4.3	**Other**	There was no difference in the body weight change between treated and control group.
4.4	**LD_{50}**	>5,000 mg/kg for males and females

5. APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

An acute dermal toxicity study was conducted with cyphenothrin (Technical grade, purity 93.6%) to groups of 10 male and 10 female Sprague Dawley rats.

After 7 days acclimatization and quarantine, the animals were fasted for 20 hours prior to dosing the test material. The dorsal hair of the animals was sheared by using electric clippers. The test material appropriately dissolved in corn oil was spread over the sheared area (ca. 30 cm by using a glass syringe attached gastric probe) to groups of 10 animals of each sex at rate of 5.0 ml/kg body weight.

The dose levels used were 0 (vehicle control), 2,500 and 5,000 mg/kg body weight for both sexes, The treated animals were held on a fixing stand for 4 hours. Then, the treated area was covered with surgical tape to prevent the animals from receiving the substance orally from the treated area. The tape was removed 24 hours after treatment, and the area was cleaned with absorbent cotton dipped in diethyl ether. The control animals were treated in the same way as above except application of the test material.

Clinical signs and mortality were observed at 1/6, 1/2, 1, 2 and 4 hours after administration and daily for 2 weeks thereafter. Body weight of each animal was measured at day 0, 7 and 14 of the observation period. All animals were necropsied for gross pathological examination of main tissues and organs after 14 days observation.

5.2 Results and discussion

No mortality or clinical signs were seen even at the top dose of 5,000 mg/kg.

There was no difference in the body weight change between treated and control group.

Gross pathological findings included vesicle in the kidney, defect of kidney, white substance present and retention of urine in the urinary bladder and horn distended with fluid and atrophy in the uterus in some animals including the controls which were sacrificed at the end of observation period. However, no test compound—related macroscopic changes in main tissues and organs nor skin irritation reactions at the application site were found in any animal.

The LD_{50} was >5,000 mg/kg.

5.3 Conclusion

5.3.1 Reliability: 2

5.3.2 Deficiencies: The study is not conducted to a recognized OECD Guideline

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November 2017
Guidelines and quality assurance	Point 2.2: There is no GLP statement in the study report. Point 2.3: No deviations from the OECD guideline 402 are reported, since the study protocol is only broadly followed.
Materials and methods	The applicant's version is acceptable in general. Point 3.1.2.3: There are no stability data in this report. For information on the physicochemical properties of the technical see Section 3.
Conclusion	The applicant's opinion is adopted.
Reliability	Reliability indicator 2: Study conducted in accordance with generally accepted scientific principles with methodological deficiencies, which do not affect the quality of relevant results.
Acceptability	Acceptable.
Remarks	No further remarks. No classification warranted accoding to either Dir. 67/548/EEC or CLP.

6.1.3 Acute Inhalation

			Official use only
		1. REFERENCE	
1.1	**Reference**	Reference : A6.1.3/01 Authors : [redacted] Title: Acute inhalation toxicity of [redacted] in rats Laboratory : Sumitomo Chemical Co Ltd Unpublished Report no : [redacted] Date : December 29, 1981	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Sumitomo	
1.2.2	Companies with letter of access	None	
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 – but broadly follows OECD Guideline 403	
2.2	**GLP**	Yes	**X**
2.3	**Deviations**	No	**X**
		3. MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2	
3.1.1	Lot/Batch number	[redacted]	**X**
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	brownish and viscous liquid	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Stable	**X**
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague Dawley	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male/female	
3.2.5	Age/weight at study initiation	Five-weeks old weighing 120-140 g (male) or 90-110 g (female),	
3.2.6	Number of animals per group	20 (10 male and 10 female)	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Inhalation	
3.3.1	Postexposure period	14 days	

3.3.2	Concentrations	Analytical concentration 224, 499, 1,090, 1,470 or 1,850 mg/m³	
3.3.9	Particle size	MMAD 0.80 -1.00µm ± GSD 1.41 -1.61 µm	
3.3.10	Type or preparation of particles	Not applicable Not particulate	
3.3.11	Type of exposure	Whole body	
3.3.12	Vehicle	Deodourised kerosene	
3.3.13	Concentration in vehicle	Not given	
3.3.14	Duration of exposure	3 hour	X
3.3.15	Controls	Vehicle and negative control	
3.4	**Examinations**	Mortality, clinical observations, bodyweight and macroscopic histopathology	
3.5	**Method of determination of LD_{50}**	Not applicable; no mortalities in the study	
3.6	**Further remarks**		
		4. RESULTS AND DISCUSSION	
4.1	**Clinical signs**	No mortality was observed at any dose Clinical signs observed were as follows. 224 mg/m³ - no toxic signs seen in any animal. 499 mg/m³ - only hyperpnea and slight salivation were found in both sexes during 2.5 to 3 hr of exposure. 1,090 mg/m³ - hyperpnea followed by deep respiration and slight salivation developed in both sexes 1 hr after initiation of exposure, and disappeared within 30 min post-treatment. 1,470 mg/m³ and above - slight urinary incontinence (only in males) as well as those signs described for lower doses were observed 40 to 60 min after initiation of exposure; muscular fibrillation and tremor were observed in both sexes only at 1,850 mg/m³	
4.2	**Pathology**	Gross pathological examination of tissues and organs of the animals revealed no compound-related change.	
4.3	**Other**	Slightly lower body weight was observed in males at 1,470 mg/m³ and above.	
4.4	**LD_{50}**	>1,850 mg/m³ for both males and females	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	An acute inhlation toxicity study was conducted with cyphenothrin ([redacted]) in Sprague Dawley rats. The animals were kept in an atmosphere of temperature of 23±1 °C with relative humidity of 60±5 % throughout experiment. The animals were exposed (whole body) to concentrations of 224, 499, 1090, 1470 or 1850 mg/m³ and were then observed for 14 days	

5.2	**Results and discussion**	No deaths were observed but signs of toxicity including hyperpnea, hyperpnea followed by deep respiration, salivation and urinary incontinence were observed at 499 mg m^3 and above. The LC_{50} in males and females was > 1850 mg m^3. No remarkable macroscopic changes were observed in treated animals.
5.3	**Conclusion**	
5.3.1	Reliability	2
5.3.2	Deficiencies	The study is not conducted to a recognized OECD Guideline

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November 2017
Guidelines and quality assurance	Point 2.2: There is no GLP statement in the study report. Point 2.3: No deviations from the OECD guideline 403 are reported, since the study protocol is only broadly followed.
Materials and methods	The applicant's version is acceptable in general. Point 3.1.1: The Lot No. as referred to in the study report is [redacted] (this test material is also known as [redacted]) Point 3.1.2.3: There are no stability data in this report. For information on the physicochemical properties of the technical see Section 3. Point 3.3.4: The exposure period was 3 hours rather than the 4-hour exposure duration recommended in the guideline.
Conclusion	For time extrapolation, it is considered valid to apply the modified Haber's law: $C^n \times t = k$, where: - 'C': is the concentration - 'n': is a regression coefficient (default of n=1 for extrapolating from shorter to longer exposure durations), - 't': is the exposure time, and - 'k': is a constant. Based on the study data, the constant k is estimated to be: $k = 1850 \text{ mg/m}^3 \times 3 \text{ hours} = 5550 \text{ mg.hrs/m}^3$. Thus, the concentration C for a 4-hour exposure period is estimated to be: $C = 5550 \text{ mg.hrs/m}^3 / 4 \text{ hours} = 1387.5 \text{ mg/m}^3$ Applying modified Haber's Law, the LC50 is calculated to be > 1387.5 mg/m^3 or > 1.39 mg/L (4-hours exposure). This value lies within the generic concentration limit of 1-5 mg/L for classification of the substance as Acute Tox. 4 with H332 (Harmful if inhaled).
Reliability	Reliability indicator 2: Study conducted in accordance with generally accepted scientific principles with methodological deficiencies, which do not affect the quality of relevant results.
Acceptability	Acceptable.
Remarks	No further remarks.

6.1.4. Acute skin and eye irritation
6.1.4.1 Acute skin irritation

			Official use only
		1. REFERENCE	
1.1	**Reference**	Reference A6.1.4.1/01 Authors : [redacted] Title: Primary eye and skin irritation tests of [redacted] technical in rabbits Laboratory : Sumitomo Chemical Co Ltd Unpublished Report no : [redacted] Date : August 3, 1981	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Sumitomo	
1.2.2	Companies with letter of access	None	
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 USEPA	
2.2	**GLP**	Yes	**X**
2.3	**Deviations**	No	**X**
		3. MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2	
3.1.1	Lot/Batch number	[redacted]	**X**
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Light-yellow oily liquid	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Stable	**X**
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	New Zealand White	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male	
3.2.5	Age/weight at study initiation	Age not recorded Weight 2.18 - 3.00 kg	
3.2.6	Number of animals per group	6	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	Dermal	

3.3.1	Post exposure period	7 days
3.3.1.1	Preparation of test substance	Test substance was used as delivered
3.3.1.2	Test site and preparation of test site	In all animals, four application sites on the back were clipped free of hair by using electric clippers, and two of them were abraded in "#" shape by using a l8G needle. The scratches were deep enough to disturb the stratum corneum, but not-the dermis
3.3.2	Occlusion	Occlusive
3.3.3	Vehicle	None
3.3.4	Concentration in vehicle	Not applicable
3.3.5	Total volume applied	1 ml
3.3.6	Removal of test substance	Wiped
3.3.7	Duration of exposure	24h
3.4	**Examinations**	Clinical observations, necropsy, histopathology or other
3.4.1	Clinical signs	Yes
3.4.2	Dermal examination	Yes
3.4.2.1	Scoring system	Draize ,
3.4.2.2	Examination time points	24, 48, and 72hours and then at 7 days.
3.4.3	Other examinations	None
3.5	**Further remarks**	

4. RESULTS AND DISCUSSION

4.1	**Average score**	
4.1.1	Erythema	0
4.1.2	Oedema	0
4.2	**Reversibility**	Not applicable
4.3	**Other examinations**	No clinical signs recorded
4.4	**Overall result**	Non irritant

5. APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	A dermal irritation study was run with cyphenothrin ([redacted] in male rabbits according to USEPA protocols and to GLP. Applications were made to both the abraded and unabraded skin of 6 male New Zealand White rabbits. A total of 0.5 ml of test material was applied and then covered with an occlusive bandage. Bandages were held in place for 24 hours. The dressing was removed and the treated area wiped clean. Readings of erythema and edema according to Draize were taken 24, 48 and 72 hours and then 7 dayhs later.
5.2	**Results and discussion**	No signs of irritation were observed in any of the animals with intact or abraded skin up to 7 days after the patch was removed. The test material would be considered as non-irritant.

5.3 Conclusion

5.3.1	Reliability	1
5.3.2	Deficiencies	Yes - the age of the rabbits is not recorded but their weight indicates that they were young adult animals as required by the method

Table A6.1.4.1-1 Table for Skin Irritation Study

Score (average animals investigated)	Time	Erythema	Oedema
Average score Draize scores (0 to maximum 4)	60 min	0	0
	72 h	0	0
Other times	1 week	0	0
Average score	24h, 72h, 1wk	0	0
Reversibility: *		Not applicable	
Average time for reversibility		Not applicable	

* c: completely reversible
nc: not completely reversible
n: not reversible

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November 2017
Guidelines and quality assurance	Point 2.2: There is no GLP statement in the study report. Point 2.3: The study protocol is not in line with the recommended in the Globally Harmonised System (GHS) testing strategy (e.g. no control group, skin abrasion, no description of local and systemic effects apart from the irritation scores). However, since this is a relatively old study, it is not considered essential to extensively report all deviations from currently acceptable protocols.
Materials and methods	The applicant's version is acceptable in general. Point 3.1.2.3: There are no stability data in this report. For information on the physicochemical properties of the technical see Section 3.
Conclusion	The applicant's opinion is adopted.
Reliability	Reliability indicator 3: Study with major methodological and/or reporting deficiencies.
Acceptability	Acceptable.
Remarks	Although major methodological and/or reporting deficiencies were noted in the study, the final conclusion, that the test material is non-irritant to the rabbit skin, is considered to be reliable. Thus, no further testing leading to additional and unnecessary animal suffering is required. No classification is warranted accoding to either Dir. 67/548/EEC or CLP.

6.1.4.2 Acute eye irritation

			Official use only
		1. REFERENCE	
1.1	**Reference**	Reference : A6.1.4.2/01 Authors : [redacted] Title: Primary eye and skin irritation tests of [redacted] technical in rabbits Laboratory : Sumitomo Chemical Co Ltd Unpublished Report no : [redacted] Date : August 3, 1981	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Sumitomo	
1.2.2	Companies with letter of access	None	
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 USEPA	
2.2	**GLP**	Yes	**X**
2.3	**Deviations**	No	**X**
		3. MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2	
3.1.1	Lot/Batch number	[redacted]	**X**
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Light-yellow oily liquid	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Stable	**X**
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	New Zealand White	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male	
3.2.5	Age/weight at study initiation	Age not recorded Weight 2.18 - 3.00 kg	
3.2.6	Number of animals per group	9	
3.2.7	Control animals	No - the untreated eye of the test animals served as controls	
3.3	**Administration/ Exposure**		
3.3.1	Preparation of test substance	Test substance was used as delivered	

3.3.2	Amount of active substance instilled	0.1 ml
3.3.3	Exposure period	The eyes of three test animals were rinsed with water after instillation The eyes of the remaining 6 animals remained unwashed
3.3.4	Postexposure period	7 days
3.4	**Examinations**	
3.4.1	Opthalmoscopic examination	No
3.4.1.1	Scoring system	Draize
3.4.1.2	Examination time points	1, 24, 48, 72 and 96 hours and 1 week
3.4.2	Other investigations	No
3.5	**Further remarks**	No
		4. RESULTS AND DISCUSSION
4.1	**Clinical signs**	None
4.2	**Average score**	None
4.2.1	Cornea	
4.2.2	Iris	0
4.2.3	Conjunctiva	0
4.2.3.1	Redness	(2 out of 6 animals with non rinsed eyes scored 2 for hyperaemia at 24 hours)
4.2.3.2	Chemosis	0
4.3	**Reversibility**	Yes/No
4.4	**Other**	none
4.5	**Overall result**	Non irritant
		5. APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	In an eye irritancy test performed conducted according to USEPA guidelines and to GLP, 0.1 ml of cyphenothrin ([redacted]) was instilled into the conjunctival sac of one eye of each of nine New Zealand White rabbits. The treated eyes of 6 animals remained unwashed and the treated eyes of 3 animals were flushed for 1 minute with approximately 300 ml water, 30 seconds after application. Eye irritation was evaluated according to Draize for 1, 24, 48, 72 and 96 hours and 7 days.
5.2	**Results and discussion**	No lesions occurred in the cornea and iris of any rabbit. However, slight conjunctival hyperaemia occurred in 2/6 animals with unwashed eyes at 1 hour only. Conjunctival effects were not observed in animals with washed eyes.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	The age of the rabbits is not recorded but their weight indicates that they were young adult animals as required by the method

Table A6.1.4.2-1 Results of Eye Irritation Study

	Cornea	**Iris**	**Conjunctiva**	
			Redness	**Chemosis**
Score (average animals investigated)	0 to 4	0 to 2	0 to 3	0 to 4
60 min	0	0	0.7	0
24 h	0	0	0	0
48 h	0	0	0	0
72 h	0	0	0	0
Average 24 h, 48 h, 72 h	0	0	0	0
Maximum average score (including area affected, max 110)	0.1			
Reversibility *	na	na	c	na
Average time for reversion	na	na	<24 hours	na

* c: completely reversible
nc: not completely reversible
n: not reversible
na: not applicable

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November 2017
Guidelines and quality assurance	Point 2.2: There is no GLP statement in the study report. Point 2.3: The study protocol is not in line with the recommended in the Globally Harmonised System (GHS) testing strategy (e.g. no ophthalmoscopic examination, no description of local and systemic effects apart from the irritation scores). However, since this is a relatively old study, it is not considered essential to extensively report all deviations from currently acceptable protocols.
Materials and methods	The applicant's version is acceptable in general. Point 3.1.2.3: There are no stability data in this report. For information on the physicochemical properties of the technical see Section 3.
Conclusion	The applicant's opinion is adopted.
Reliability	Reliability indicator 3: Study with major methodological and/or reporting deficiencies.
Acceptability	Acceptable.
Remarks	Although major methodological and/or reporting deficiencies were noted in the study, the final conclusion, that the test material is non-irritant to the rabbit eye, is considered to be reliable. Thus, no further testing leading to additional and unnecessary animal suffering is required. No classification is warranted accoding to either Dir. 67/548/EEC or CLP.

6.1.5 Acute skin sensitisation

			Official use only
		1. REFERENCE	
1.1	**Reference**	Reference : A6.1.5/01 Authors : [redacted] Title: Dermal sensitization test of [redacted] in guinea pigs Laboratory : Sumitomo Chemical Co Ltd Unpublished Report no : [redacted] Date : January 17, 1983	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Sumitomo	
1.2.2	Companies with letter of access	None	
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 – but broadly follows OECD Guideline 406	
2.2	**GLP**	Yes	**X**
2.3	**Deviations**	No	**X**
		3. MATERIALS AND METHODS	
3.1	**Test material**	As given in Section 2	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Not given	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Stable	**X**
3.1.2.4	Preparation of test substance for application	Test substance used as received	
3.1.2.5	Pretest performed on irritant effects	Yes – injection of [redacted] in corn oil caused erythma	
3.2	**Test Animals**		
3.2.1	Species	Guinea pigs	
3.2.2	Strain	Hartley	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male	
3.2.5	Age/weight at study initiation	220 — 260 g	
3.2.6	Number of animals per group	12 - 13	
3.2.7	Control animals	Yes	

3.3	**Administration/ Exposure**	Buehler
3.3.1	Induction schedule	3 times a week with the time intervals of 2 or 3 days – a total 10 times
3.3.2	Way of induction	occlusive
3.3.3	Concentrations used for induction	undiluted
3.3.4	Concentration Freunds Complete Adjuvant (FCA)	Not applicable
3.3.5	Challenge schedule	Two weeks following the 10th induction application
3.3.6	Concentrations used for challenge	Undiluted
3.3.7	Rechallenge	No
3.3.8	Scoring schedule	24 h, 48 h after challenge
3.3.9	Removal of test substance	No
3.3.10	Positive control substance	0.5% 2,4-dinitrochlorobenzene in acetone
3.4	**Examinations**	
3.4.1	Pilot study	No
3.5	**Further remarks**	A Buehler test was chosen as injection of the test substance even at low concentrations ([redacted]) caused erythema

4. RESULTS AND DISCUSSION

4.1	**Results of pilot studies**	Not applicable
4.2	**Results of test**	
4.2.1	24h after challenge	See Table A6.1.5-1
4.2.2	48h after challenge	See Table A6.1.5-1
4.2.3	Other findings	-
4.3	**Overall result**	Not sensitising

5. APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	A sensitisation study was conducted in male Hartley guinea pigs with cyphenothrin [redacted] Cyphenothrin caused erythema in guinea pigs when intradermally injected, even at a concentration of [redacted] (the amount was not stated). Therefore, the skin sensitisation test was performed according to a modified Buehler method. During the induction phase, 0.5 ml of the undiluted test material was applied on a lint patch to the shaved backs of 13 male guinea pigs using occlusive tape for 24 hours. This was performed 3 times a week with time intervals of 2 or 3 d 10 times in total. Two weeks later, each animal was challenged in the same manner as during the induction period. 12 non-induced male control guinea-pigs were also challenged. A positive control (2,4-dinitrochlorobenzene) was also included. Skin reactions were scored 24 and 48 hours after the challenge.

5.2	**Results and discussion**	One test animal died after the third induction treatment, although no abnormal gross findings were observed in this animal. The positive controls treated with DNCB gave the appropriate response. Cyphenothrin was not a skin sensitiser under the conditions of this study.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	The age of the test animals is not given in the report but the recorded weights indicate that they were of a suitable age

Table A6.1.5-1 Detailed information including induction/challenge/scoring schedule for skin sensitisation test

Inductions	**Buehler test**	**Observations/Remarks give information on irritation effects**
	Day of treatment	
Induction 1	day 0	
Pretreatment for non-irritating substances	--	
Induction 2-10	21	Inductions 3 times a week to a total of ten
Challenge	35	
(Rechallenge)		
Scoring 1	36	
Scoring 2	37	

Table A6.1.5-2 Result of skin sensitisation test

	Number of animals with signs of allergic reactions / number of animals in group			
	Test Group Sensitised	**Test Group Un-sensitised**	**Positive control Sensitised**	**Positive control Un-sensitised**
Scored after 24 h	0/12	0/12	13/13[1]	0/12
Scored after 48 h	0/12	0/12	13/13[2]	0/12

[1] 3 animals showing moderate erythema and/or swelling and 10 animals showing severe erythema and/or swelling
[2] 12 animals showing moderate erythema and/or swelling and 1 animal showing severe erythema and/or swelling

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November 2017
Guidelines and quality assurance	Point 2.2: There is no GLP statement in the study report. Point 2.3: No deviations from the OECD guideline 406 are reported, since the study protocol is only broadly followed.

Materials and methods	The applicant's version is acceptable in general. Point 3.1.2.3: There are no stability data in this report. For information on the physicochemical properties of the technical see Section 3.
Conclusion	The applicant's opinion is adopted. It is noted that the available skin sensitization test is a modified 10-induction application test. The study was conducted in accordance with generally accepted scientific principles while any methodological deficiencies are not considered to affect the quality of the relevant results. As in case of the 9-application modified Buehler test, the available study is considered acceptable for C&L purposes.
Reliability	Reliability indicator 2: Study conducted in accordance with generally accepted scientific principles with methodological deficiencies, which do not affect the quality of relevant results.
Acceptability	Acceptable.
Remarks	No further remarks. No classification warranted accoding to either Dir. 67/548/EEC or CLP.

6.2 Metabolism studies in mammals

6.2.1 Metabolism

			Official use only
		1. REFERENCE	
1.1	**Reference**	Reference : A6.2.1/01 Authors : [redacted] Title: Metabolism of (IR)-trans- and (IR)-cis-cyphenothrin in Rats Laboratory : Sumitomo Chemical Co ltd Unpublished Report no : [redacted] Date : May 30, 1988	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Sumitomo	
1.2.2	Companies with letter of access	None	
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 applicable	**X**
2.2	**GLP**	Yes	**X**
2.3	**Deviations**	Not applicable	**X**
		3. MATERIALS AND METHODS	
3.1	**Test material**	Purified technical material	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Not given	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Stable	**X**
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague Dawley	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male and female	
3.2.5	Age/weight at study initiation	4 weeks (for repeat dose study) 6 weeks (for low dose, high dose and tissue level studies)	

4. APPLICANT'S SUMMARY AND CONCLUSION

4.1 Materials and methods

An ADME study was conducted in Sprague-Dawley rats using the 2 cyphenothrin isomers (lR)-trans and (lR)-cis cyphenothrin, both uniformly (^{14}C)-labelled at the phenoxy-phenyl carbons. The radiochemical purities of the isomers were both [redacted] Unlabelled trans cyphenothrin was [redacted] and unlabelled cis cyphenothrin was [redacted]. The vehicle used was corn oil. Levels of 2.5 and 100 mg/kg bw were administered to both male and female rats (5/sex/isomer) as a single oral dose. In addition, rats (5/sex/isomer) were orally dosed with 2.5 mg/kg bw/day unlabelled trans or cis cyphenothrin for 14 consecutive days, followed by dosing on day 15 with 2.5 mg/kg bw of the labelled cyphenothrin. Finally, 5 male rats/isomer/time-point were dosed orally with 2.5 mg/kg bw labelled trans or cis cyphenothrin and tissue levels of (^{14}C) were investigated at 1, 2, 4, 6, 8, 24 hours and 3, 7, 19 and 30 days post-dosing.

4.2 Results and Discussion

In the low dose single administration group, the majority of radiolabel was excreted *via* the urine and faeces in the first 24 hours, with >95% excreted by 7 days (**Table A.6.2.1-1)**. The metabolites in urine and faeces (day 0-2 samples) of these animals were investigated and are reported in **Table A.6.2.1-2**

In the high dose single administration study, the majority of radiolabel was excreted in the first 24 hours, with >96% excreted by 7 days (see **Table A.6.2.1-3**). The 100 mg/kg bw dose level caused overt signs of toxicity including muscular fibrillation, decrease of spontaneous activity and soft faeces and/or diarrhoea, which were seen between 4 and 24 h post-dosing. There were no other signs of severe toxicity or deaths. The metabolites are shown in **Table A.6.2.1-4**.

In the repeat low dose study, the majority of radiolabel was excreted in the first 24 hours, with >97% excreted by 7 days (**Table A.6.2.1-5.**).

Results of the tissues distribution study are shown in **Tables A.6.2.1-6, A.6.2.1-7 and A.6.2.1-8**

Metabolite identification was performed using TLC. The metabolites identified are shown in **Table A.6.2.1-9** which details the full chemical names of these metabolites.

With both cis and trans isomers, the alimentary canal and contents initially showed relatively high radiolabel levels which had declined to insignificant levels by day 7.

All tissues, except fat, showed short biological half-lives for the radiolabel. Fat, however, had longer biological half-lives. Over the 1-7 day period, the half-lives for trans and cis cyphenothrin were 3 and 2 days respectively. Over the 7-30 day period, the half-lives for trans and cis cyphenothrin were 6 and 10 days respectively.

Tissue metabolites in liver, kidney, blood and brain were investigated at 1, 2, 4, 6, 8 and 24 hours for both trans and cis isomers. Concentrations of metabolites in each tissue were highest within 4 to 6 hours after dosing with either isomer. In blood, kidney and liver the major metabolites were 3-phenoxybenzoic acid (PB acid) and 3-(4-hydroxyphenoxy) benzoic acid sulfate (OH-PB acid-sul) with either isomer. A variety of minor metabolites which were also detected in urine and faeces were found in kidneys, blood and livers after dosing with trans or cis cyphenothrin. In brain, low concentrations of the parent isomers and 2 metabolites in each case were detected.

In conclusin, to examine the metabolic fate of cyphenothrin [(RS)~-cyano-3-phenoxybenzyl (1R)-~,trans-chrysanthemateJ, (1R)-trans- and (1R)-~-[phenoxyphenYl-^{14}C]cyphenothrin were administered orally to 5 male and 5 female rats at 2.5 mg/kg bw and 100 mg/kg bw as a single dose. In addition, rats (5/sex/isomer) were orally dosed with 2.5 mg/kg/d unlabelled trans- or cis-cyphenothrin for 14 consecutive days, followed by dosing on day 15 with 2.5 mg/kg of the labelled cyphenothrin. Finally, 5 male rats/isomer/time-point were dosed orally with 2.5 mg/kg labelled trans- or cis- cyphenothrin. Tissue levels of (^{14}C) were investigated at 1, 2, 4, 6, 8, 24 hours and 3, 7, 19 and 30 days post-dosing.

The radiocarbon was almost completely eliminated in urine and faeces within 7 days after administration. ^{14}C-Levels in blood reached maximum within 6 hr after administration and thereafter decreased with the half-lives of 5 -12 hr. 14C-Tissue residues were very low and accounted for less than 1 % of the dosed ^{14}C on the 7th day after administration. ^{14}C-Tissue residues in fat were slightly higher as compared with those in other tissues.

The ^{14}C-concentrations in fat were 56 -213 ppb at the low and consecutive doses and 1.20 -5.09 ppm at the high dose on the 7th day after dosing. However, ^{14}C in fat was eliminated with the' half-lives of 6 -10 days from the 7th to 30th day after administration.
The major metabolic reactions for both isomers were oxidation at 4'- and 2'-positions of the alcohol moiety and at methyl groups of the acid moiety, cleavage of the ester linkage, and conjugation of the resultant carboxylic acid and phenols with glucuronic acid, sulfuric acid or glycine. The ester-retained metabolites were found mainly in feces, whereas the ester-cleaved metabolites were found mainly in urine. The sulfate of 3-(4-hydroxyphenoxy)benzoic acid (4'-OH-PBacid) was a major metabolite, whose amounts were 17.6 -50.2 % for (1R)-trans-isomer and 12.3 -40.2 % for (1R)-~-isomer. No marked sex difference in the metabolism of cyphenothrin was observed, and the dosing rates or the consecutive dosing did not effect substantially on the metabolism. A proposed metabolic pathyway is included in **Figure 6.2.1-1**

4.3 Conclusion

4.3.1 Reliability 1

4.3.2 Deficiencies No

Table A.6.2.1-1 Percentage of radiolabel (^{14}C) administered which was excreted by rats dosed once with 2.5 mg/kg

Sex/isomer	Percentage of radiolabel (^{14}C) administered/excreted	
	Day 0-1	Day 0-7
Male/Trans		
Urine	46.6	49.0
Faeces	47.4	49.5
Male/ Cis		
Urine	23.9	26.2
Faeces	60.4	69.4
Female / Trans		
Urine	40.0	43.9
Faeces	48.3	54.5
Female / Cis		
Urine	35.5	38.9
Faeces	51.0	59.5

Table A.6.2.1-2 Amounts of metabolites in urine and faeces within 2 days of single oral administration of (IR)-trans- or (lR)-cis-(phenoxyphenyl-14C)-cyphenothrin to rats at 2.5 mg/ kg (low dose group)

Metabolite	% of the dosed (^{14}C)							
	Trans-				Cis-			
	Male		Female		Male		Female	
	Urine	Faeces	Urine	Faeces	Urine	Faeces	Urine	Faeces
Ester metabolites								
parent compound		39.7 ± 14.65		38.9 ± 15.17		53.3 ± 10.05		29.9 ± 11.52
ωc-acid-c-cyphe						1.5 ± 0.04		0.6 ± 0.09
ωt-acid-t(c)-cyphe		0.2 ± 0.07		0.1 ± 0.03		0.5 ± 0.21		0.3 ± 0.03
ωc-alc-c-cyphe						0.5 ± 0.18		0.3 ± 0.11
ωt-alc-t-(c)-cyphe		0.3 ± 0.09		0.3 ± 0.06		1.5 ± 0.31		1.0 ± 0.47
ωc-acid-4' -OH-c-cyphe						0.4 ± 0.15		0.3 ± 0.04
ωt-acid-4' -OH-c-cyphe						0.1 ± 0.02		0.2 ± 0.06
Alcohol moiety								
PBald	0.01± 0.01	3.8 ± 2.64	0.3 ± 0.16	0.7 ± 0.19		0.1 ± 0.05		0.6 ± 0.28
PBacid free	3.7 ± 1.56	0.4 ± 0.09	1.4 ± 0.81	1.1 ± 0.87	0.9 ± 0.29	0.6 ± 0.19	0.7 ± 0.14	1.0 ± 0.21
glu	0.7 ± 0.30		0.8 ± 0.26		0.9 ± 0.59		0.9 ± 0.63	
giy	1.6 ± 0.73		0.7 ± 0.18		0.5 ± 0.15		0.2 ± 0.07	
2' -OH-PBacid free	0.1 ± 0.05	0.2 ± 0.08	0.1 ± 0.02	0.2 ± 0.10		0.5 ± 0.18		0.97± 0.29
sul	0.3 ± 0.33		0.3 ± 0.06					
4' -OH-PBacid free	0.2 ± 0.07	0.4 ± 0.12	1.7 ± 0.94	2.2 ± 1.76	0.4 ± 0.13	1.4 ± 0.43	1.0 + 0.13	1.7 ± 1.12
sul	34.9 ± 10.84		21.0 ± 7.05		18.7 ± 4.49		20.8 ± 6.30	
glu	0.7 ± 0.15		0.4 ± 0.15					
Others	5.8 ± 1.74	3.2 ± 0.49	15.9 ± 6.87	4.7 ± 2.27	4.1 ± 1.12	5.9 ± 1.56	14.5 ± 3.77	20.0 ± 2.72
Unextractable		1.1 ± 0.27		2.7 ± 1.89		2.6 ± 0.61		2.5 ± 0.72
Total	48.0 ± 14.82	49.3 ± 15.50	42.6 ± 14.03	50.9 ± 13.36	25.5 ± 6.08	68.9 ± 6.65	38.1 ± 9.60	59.2 ± 10.37

Data show the mean values ± S.D. of five rats glu. : glucuronide, gly.: glycine conjugate, sul.: sulfate

Table A.6.2.1-3 Percentage of radiolabel (^{14}C) administered which was excreted by rats dosed once with 100 mg/kg bw

Sex/isomer	Percentage of radiolabel (^{14}C) administered/excreted	
	Day 0-1	Day 0-7
Male/Trans		
Urine	37.4	40.2
Faeces	41.6	59.3
Male/ Cis		
Urine	18.8	21.6
Faeces	67.1	74.4
Female / Trans		
Urine	30.1	32.6
Faeces	48.8	65.7
Female / Cis		
Urine	17.9	21.0
Faeces	70.6	78.2

Table A.6.2,1-4 Amounts of metabolites in urine and faeces within 2 days after single oral administration of (lR)-trans or (lR)-cis(phenoxyphenyl)-^{14}C-cyphenothrin to rats at 100 mg/ kg bw (high dose group)

Metabolite	% of the dosed (^{14}C)							
	Trans-				Cis-			
	Male		Female		Male		Female	
	Urine	Faeces	Urine	Faeces	Urine	Faeces	Urine	Faeces
Ester metabolites								
parent compound		47.9 ± 12.68		59.7 ± 8.05		57.7 ± 9.85		62.6 ± 11.19
ωc-acid-c-cyphe						0.4 ± 0.11		0.9 ± 0.36
ωt-acid-t(c)-cyphe		0.2±0.08		0.1 ± 0.03		0.4 ± 0.15		0.6 ± 0.05
ωc-alc-c-cyphe						0.6 ± 0.16		0.3 ± 0.14
ωt-alc-t(c)-cyphe		0.4±0.22		0.4 ± 0.07		0.8 ± 0.28		0.8 ± 0.22
ωc-acid-4'-OH-c-cyphe						0.7 ± 0.26		1.0 ± 0.32
ωt-acid-4'-OH-c-cyphe						0.1 ± 0.02		0.1 ± 0.06
Alcohol moiety								
PBald	0.0 ± 0.01	3.5 ± 1.12	0.0 ± 0.03	0.8 ± 0.32		0.1 ± 0.05		2.1 ± 0.75
PBacid free	2.6 ± 0.86	1.0 ± 1.12	1.4 ± 0.81	0.1 ± 0.04	1.3 ± 0.48	1.1 ± 0.18	1.0 ± 0.42	0.5 ± 0.06
glu	0.4 ± 0.12		1.0 ± 0.32		1.0 ± 0.62		1.7 ± 1.42	
giy	1.3 ± 0.44		1.2 ± 0.56		0.5 ± 0.16		0.4 ± 0.18	
2'-OH-PBacid free	0.1 ± 0.06	0.3 ± 0.07	0.0 ± 0.01	0.1 ± 0.00		0.6 ± 0.21		0.9 ± 0.34
sul	0.1 ± 0.06		0.2 ± 0.15					
4'-OH-PBacid free	0.5 ± 0.39	1.3±2.05	1.2 ± 0.66	0.6 ± 0.34	0.3 ± 0.20	1.5 ± 0.52	1.8 ± 1.04	0.7 ± 0.28
sul	28.6 ± 5.34		17.6 ± 4.23		13.8 ± 2.90		12.3 ± 2.34	
glu.	0.6 ± 0.25		0.2 ± 0.09					
Others	5.0 ± 2.09	3.3 ± 3.06	9.4 ± 2.13	2.5 ± 0.54	3.7 ± 1.07	7.2 ± 1.72	3.0 ± 0.92	4.2 ± 1.12
Unextractable		1.2 ± 0.54		0.8 ± 0.18		2.2 ± 1.22		1.5 ± 0.46
Total	39.2 ± 8.14	59.0 ± 8.57	32.1±6.37	65.2 ± 7.71	20.7±4.08	73.6 ± 6.60	20.2 ± 4.26	76.1±7.70

Data show the mean values ± S.D. of five rats glu.: glucuronide, gly.: glycine conjugate, sul.: sulfate

Table A.6.2.1-5 Percentage of the 2.5 mg/kg bw radiolabelled cyphenothrin administered which was excreted by rats pre-treated with 2.5 mg/kg bw of unlabelled cyphenothrin for 14 days

Sex/isomer	Percentage of radiolabel (^{14}C) administered/excreted	
	Day 0-1	Day 0-7
Male/Trans		
Urine	69.3	72.7
Faeces	22.1	24.3
Male/ Cis		
Urine	42.3	46.2
Faeces	46.0	52.6
Female / Trans		
Urine	68.6	73.7
Faeces	19.0	23.9
Female / Cis		
Urine	55.0	59.8
Faeces	31.7	37.3

Table A6.2.1.6 Amounts of metabolites in urine and faeces within 2 days after single oral administration of (lR)-trans- or (lR)-cis-(phenoxyphenyI-14C)-cyphenothrin at 2.5 mg/kg bw to rats pretreated orally with unlabelled each isomer for consecutive 14 days at 2.5 mg/kg (consecutive dose group)

Metabolite	% of the dosed (^{14}C)							
	Trans-				Cis-			
	Male		Female		Male		Female	
	Urine	Faeces	Urine	Faeces	Urine	Faeces	Urine	Faeces
Ester metabolites								
parent compound		16.7 ± 9.12		11.8 ± 10.08		26.8 ± 9.88		8.0 ± 5.28
ωc-acid-c-cyphe						1.4 ± 0.49		2.0 ± 0.31
ωt-acid-t(c)-cyphe		0.1 ± 0.04		0.1 ± 0.02		0.4 ± 0.11		0.9 ± 0.22
ωc-alc-c-cyphe						0.2 ± 0.08		0.2 ± 0.08
ωt-alc-t(c)-cyphe		0.1 ± 0.01		0.2 ± 0.04		1.2 ± 0.27		3.7 ± 0.53
ωc-acid-4' -OH-c-cyphe						0.7 ± 0.15		0.2 ± 0.10
ωt-acid-4' -OH-c-cyphe						0.2 ± 0.04		0.1 ± 0.02
Alcohol moiety								
PBald	0.0 ± 0.01	0.4 ± 0.17	0.0 ± 0.01	5.0 ± 2.19		0.2 ± 0.10		3.8 ± 1.52
PBacid free	4.8 ± 2.44	0.5 ± 0.20	3.1 ± 1.63	0.3 ± 0.09	2.1 ± 0.67	0.3 ± 0.12	1.6 ± 1.15	1.7 ± 0.75
glu.	0.8 ± 0.20		2.5 ± 1.09		0.5 ± 0.05		6.2 ± 2.08	
giy-	2.5 ± 0.58		1.3 ± 0.59		0.8 ± 0.08		0.7 ± 0.21	
2' -OH-PBacid free	0.0 ± 0.01	0.1 ± 0.04	0.1 ± 0.04	0.1 ± 0.02		0.6 ± 0.12		0.7 ± 0.40
sul	0.1 ± 0.03		0.1 ± 0.08					
4' -OH-PBacid free	0.8 ± 0.54	1.4 ± 0.44	1.0 ± 0.62	1.3 ± 0.46	0.7 ± 0.29	1.5 ± 0.65	1.7 ± 1.42	1.3 ± 0.42
sul	50.2 ± 8.46		46.9 ± 6.06		33.6 ± 4.40		40.2 ± 6.47	
glu.	3.6 ± 1.95		0.9 ± 0.31					
Others	8.5 ± 1.95	3.4 ± 0.63	16.3 ± 3.35	3.3 ± 0.87	7.1 ± 1.22	13.0 ± 2.00	7.5± 1.99	9.3 ± 2.21
Unextractable		1.5 ± 0.19		1.5 ± 0.23		5.4 ± 0.66		4.7 ± 0.25
Total	71.1 ± 8.08	24.1 ± 8.72	72.2 ± 9.65	23.5 ± 11.33	44.6 ± 5.30	51.9 ± 6.66	57.8± 7.25	36.7 ± 7.43

Data show the mean values ± S.D. of five rats glu. : glucuronide, gly.: glycine conjugate, sul.: sulfate

Table A.6.2.1-7 Levels of radiolabel found in tissues of rats dosed with trans- cyphenothrin (2.5 mg/kg bw)

Tissue	Highest level found, µg parent compound equivalens/g wet tissue (time in hours)	Lowest level found, µg parent compound equivalens/g wet tissue (time in hours)
Adrenal	0.326 (4)	0.008 (19)
Blood	1.10 (4)	0.003 (19)
Bone	0.200 (4) 0.053 (4)	0.002 (19)
Brain	-	<0.002 (7)
Fat	0.338 (24)	0.008 (30)
Heart	0.322 (4)	0.002 (3)
Kidney	1.23 (4)	0.005 (7)
Liver	0.857 (4)	0.004 (7)
Lung	0.361 (4)	<0.002 (7)
Muscle	0.112 (4)	0.002 (19)
Pancreas	0.200 (4)	<0.002 (19)
Skin	0.343 (4)	0.002 (19)
Spleen	0.235 (2)	<0.002 (19)
Testis	0.129 (6)	<0.002 (7)

Table A.6.2.1-8 Levels of radiolabel found in tissues of rats dosed with cis- cyphenothrin (2.5 mg/kg bw)

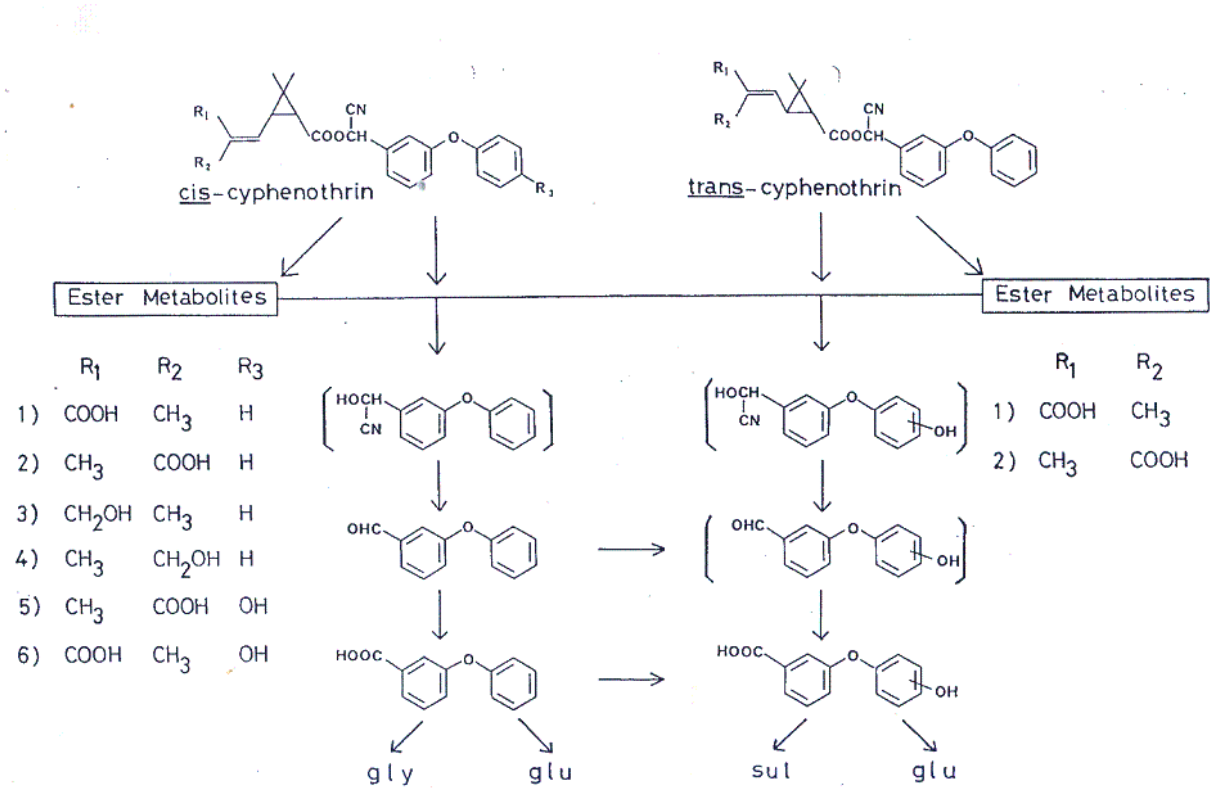
Tissue	Highest level found, (µg parent compound equivalens/g wet tissue (time in hours)	Lowest level found, (µg parent compound equivalens/g wet tissue (time in hours)
Adrenal	0.400 (4)	<0.007 (19)
Blood	0.884 (6)	<0.002 (7)
Bone	0.128 (4)	<0.002 (7)
Brain	0.069 (4)	<0.002 (7)
Fat	0.801 (24)	0.012 (30)
Heart	0.281 (4)	<0.002 (7)
Kidney	0.909 (6)	0.003 (7)
Liver	0.985 (6)	0.003 (7)
Lung	0.354 (6)	0.002 (7)
Muscle	0.140 (4)	<0.002 (7)
Pancreas	0.178 (4)	<0.002 (7)
Skin	0.321 (6)	0.004 (7)
Spleen	0.256 (2)	<0.002 (7)
Testis	0.120 (6)	0.002 (7)

Table A.6.2.1-9 Rat Metabolites and their Abbreviations

Compound	Abbreviation
(RS)-a-cyano-3-phenoxybenzyl (IR)- cis-chrysanthemate	c-cyphe
(RS)-a-cyano-3-phenoxybenzyl (1R)- trans-chrysanthemate	t-cyphe
(RS)-a-cyano-3-phenoxybenzyl (1R)- cis-3-[Z)-2-carboxy-1-propenyl]-2,2-dimethylcyclopropanecarboxylate	uc-acid-c-cyphe
(RS)-a-cyano-3-phenoxybenzyl (1R)- trans (cis)-3-[E)-2-carboxy-l-propenyl]-2,2-dimethylcyclopropanecarboxylate	cot-acid-c-cyphe
(RS)-a-cyano-3-phenoxybenzyl (1R)- cis-3-[Z)-2-hydro methyl-1-propenyllcyclopropanecarboxylate	coc-alc-c-cyphe
(RS)-a-cyano-3-phenoxybenzyl (1R)- trans (cis)-3-(E)-2-hydroxymethyl-l-propenyl]cyclopropanecarboxylate	coc-alc-t(c)-cyphe
(RS)-a-cyano-3-(4-hydroxyphenoxy)benzyl (1 R)cis-3-(Z)-2-carboxy-l-propenyl]-2,2-dimethylcyclopropane-carboxylate	cuc-acid-4'-OH-c cyphe
(RS)-a-cyano-3-(4-hydroxyphenoxy)benzyl (1R) - cis-3-(E)-2-carboxy-l-propenyl]-2,2-dimethylcyclopropanecarboxylate	wt-acid-4'-OH c-cyphe
3-phenoxybenzaldehyde	PBald
3-phenoxybenzoic acid	PBacid
3-(2-hydroxyphenoxy) benzoic acid	2'-0H-PBacid
3-(4-hydroxyphenoxy)benzoic acid	4'-OH-PBacid
(RS)-a-cyano-3-phenoxybenzyl cis-3-[(Z)-2-methoxycarbonyl-propenyl]-2,2-dimethylcyclopropanecarboxylate	coc-acid-Me-c cyphe
(RS)-a-cyano-3-phenoxybenzyl cis-3-[(E)-2-methoxycarbonyl-l-propenyl]-2,2-dimethylcyclopropancarboxylate	cut-acid-Me-c cyphe
(RS)-a-cyano-3-phenoxybenzy (1R) -trans-3-[(E)-2-methoxy~ carbonyl-l-propenyl]-2,2-dimethylcyclopropane-carboxylate	cut-acid-Me-t cyphe

(RS)-a-cyano-3-phenoxybenzyl cis-3-[(E)-2-acetoxymethyl 1-propenyl]-2,2-dimethylcyclopropanecarboxylate	wc-alc-Ac-c-cyphe
(RS)-a-cyano-3-phenoxylbenzyl cis-3-[(E)-2-acetoxymethyl l-propenyl]-2,2-dimethylcyclopropanecarboxylate	cot-alc-Ac-c cyphe
(RS)-a-cyano-3-phenoxybenzyl (1R)-trans-3-[(E)-2-acetoxymethyl-1-propenyl]-2,2-dimethylcyclopropane carboxylate	cot-alc-Ac-t cyphe
(RS)-a-cyano-3-(4-methoxyphenoxy)benzyl ds-3-(Z)-2-methoxycarbonyl-l-propenyl]-2,2-dimethylcyclopropane carboxylate	coc-acid-Me-4'OMe-c-cyphe
(RS)-a-cyano-3-(4-methoxyphenoxy)benzyl cis-3-[(E)-2-methoxycarbonyl-l-propenyl]-2,2-dimethylcyclopropane carboxylate	cot-acid-Me-4'OMe-c-cyphe

Figure 6.2.1-1: Proposed metabolic pathway



	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November 2017
Guidelines and quality assurance	Points 2.1 & 2.3: The study is not conducted according to the recommended in the Globally Harmonised System (GHS) testing strategy (EU B.36 testing method) or any other accepted experimental protocol. However, this is an old study and the reviewer has assessed the basic principles of the methodology as well as the quality and adequacy of data generated, without reviewing the potential deviations from currently acceptable protocols. Point 2.2: There is no GLP statement in the study report.
Materials and methods	The applicant's version is acceptable in general. Point 3.1.2.3: There are no stability data in this report. For information on the physicochemical properties of the technical see Section 3.
Results and discussion	The applicant's version is acceptable in general. The high radioactivity levels detected in feaces indicate the presence of an enterohepatic circulation. Since no study with bile-cannulated rats has been conducted, there is no information concerning the amount or the excretion rate of the test compound in the bile. An oral absorption value of 26% (see Table A.6.2.1-1) as a worst case scenario has been considered as the most appropriate.
Conclusion	The applicant's opinion is adopted.
Reliability	Reliability indicator 2: Study conducted in accordance with generally accepted scientific principles with methodological deficiencies, which do not affect the quality of relevant results.
Acceptability	Acceptable.
Remarks	No further remarks.

6.2.2 Percutaneous absorption

			Official use only
		1. REFERENCE	
1.1	**Reference**	Reference: A6.2.2/01 Authors : [redacted] Title: Gokilaht: *in vitro* absorption from a [redacted] Gokilaht formulation through human epidermis. Laboratory : Central Toxicology Laboratory (CTL) Unpublished Report no : [redacted] Date : 13 April 2006	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Sumitomo	
1.2.2	Companies with letter of access	None	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing active substance for the purpose of its entry into Annex IA.	
		2. GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	1) OECD (2004a). Organisation for Economic Co-operation and Development. Test Guideline 428: Skin Absorption: *In Vitro* Method. Organisation for Economic Cooperation and Development, Paris. 2) OECD (2004b). Organisation for Economic Co-operation and Development. Guidance Document No. 28: The Conduct of Skin Absorption Studies. Organisation for Economic Co-operation and Development, Paris. 3) European Commission (2004). Guidance Document on Dermal Absorption.Sanco/222/2000 rev. 7 (19th March 2004).	
2.2	**GLP**	Yes	
2.3	**Deviations**	None	
		3. MATERIALS AND METHODS	
3.1	**Test material**	[redacted]	
3.1.1	Lot/Batch number	050401	
3.1.2	Specification	As given in Section 2.	
3.1.2.1	Description	Yellowish, viscous liquid.	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Stable.	X
3.1.2.4	Radiolabelling	No.	
3.2	**Test system**		
3.2.1	Human epidermis	Extraneous tissue was removed from human whole skin samples, taken *post mortem*. The skin samples were immersed in water at 60°C for 40-45 seconds and the epidermis teased away from the dermis.	

3.2.2	Chamber	The type of glass diffusion cell used in this study has an exposed membrane area of 2.54cm^2. Discs of approximately 3.3cm diameter of prepared skin membrane from three subjects were mounted, dermal side down, in diffusion cells held together with individually numbered clamps and placed in a water bath maintained at 32 ± 1ºC.
3.2.3	Membrane integrity check	Membrane integrity was determined by measurement of their electrical resistance across the skin membrane. Membranes with a measured resistance of <10kΩ (Davies *et al*, 2004) were regarded as having a lower integrity than normal and discarded.
3.2.4	Number of cells per group	5
3.2.5	Reference substances	No
3.2.6	Receptor fluid	50% ethanol in water.
3.2.7	Quantification	HPLC with UV detection. LOQ at 0.025µg/ml.
3.2.8	Endpoints	Absorption, distribution and mass balance.
3.3	**Administration/ Exposure**	
3.3.1	Preparation of test substance	Dissolution in ethanol.
3.3.2	Concentration of test substance	[redacted]
3.3.3	Volume applied	50.8µl
3.3.4	Area of skin	3.3cm diameter. (20µl/cm^2 ≡ 200µg ai/cm^2)
3.3.5	Exposure period	24 hours.
3.3.6	Sampling time	1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours.
	4. RESULTS AND DISCUSSION	
4.1	Absorption data	Table 6.2.2-1 Absorption of cyphenothrin from the [redacted] formulation was relatively linear over the whole of the 24 hour exposure period 90.054µg/cm^2/h). The amounts absorbed during typical working day periods of 6, 8 and 10 hours were 0.205, 0.299 and 0.414µg/cm^2, respectively. The respective amounts expressed as percentages of the applied dose were 0.103, 0.149 and 0.207%. The amount absorbed over the entire 24 hour exposure period was 1.25µg/cm^2 (0.626% of the applied dose).

4.2	Mass balance and distribution	Table 6.2.2-1 Analysis of cyphenothrin and similar test materials in a mass balance procedures using non radio-labelled material can be very difficult, particularly from the complex matrices of skin, swabs and tape strips. Recovery of the applied dose in these experiments (80.2%) was considered to be acceptable for a study using non radio-labelled techniques, as swab/skin interaction during cell decontamination was shown to occur in a preliminary study using pig epidermis. Here the material was thought to be binding to the skin and/or swab, and subsequently yielded a low recovery (approximately 67.4%). However it is more than likely that the receptor fluid concentrations were accurate. Mild skin washing at 24 hours removed the vast majority (mean of 68.8%) of the applied dose from the surface of the skin. The mean total proportion of cyphenothrin found in the *stratum corneum* was 4.08% (8.17µg/cm^2) of the applied dose. A further 1.75% (3.51µg/cm^2) was recovered from the remaining epidermis. The amount (1.25µg/cm^2) recovered from the receptor fluid accounted for 0.626% of the applied dose.	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The absorption of cyphenothrin from a nominal [redacted] cyphenothrin formulation, (actual content [redacted]) was measured *in vitro* through human epidermis. The formulation was applied to the epidermal membranes at a rate of 20µl/cm^2. All applications were left unoccluded for an exposure period of 24h. This application was designed to simulate potential human dermal exposure to the formulation during normal use. At the end of the exposure period, the distribution of cyphenothrin within the test system (skin wash, donor chamber, s*tratum corneum* and remaining epidermis) and a 24 hour absorption profile (µg/cm^2/h) were determined.	X

5.2 Results

Absorption data

Absorption of cyphenothrin from the [redacted] formulation was relatively linear over the whole of the 24 hour exposure period (0.054µg/cm^2/h). The amounts absorbed during typical working day periods of 6, 8 and 10 hours were 0.205, 0.299 and 0.414µg/cm^2, respectively. The respective amounts expressed as percentages of the applied dose were 0.103, 0.149 and 0.207%. The amount absorbed over the entire 24 hour exposure period was 1.25µg/cm^2 (0.626% of the applied dose).

Mass balance and distribution

Analysis of cyphenothrin or similar test materials in a mass balance procedure using non-radiolabelled material can be very difficult, particularly from the complex matrices of skin, swabs and tape strips. Recovery of the applied dose in these experiments (80.2%) was considered to be acceptable for a study using non radio-labelled techniques, as swab/skin interaction during cell decontamination was shown to occur in a preliminary study using pig epidermis. Here the material was thought to be binding to the skin and/or swab, and subsequently yielded a low recovery (approximately 67.4%). However it is more than likely that the receptor fluid concentrations were accurate. Mild skin washing at 24 hours removed the vast majority (mean of 68.8%) of the applied dose from the surface of the skin. The mean total proportion of cyphenothrin found in the *stratum corneum* was 4.08% (8.17µg/cm^2) of the applied dose. A further 1.75% (3.51µg/cm^2) was recovered from the remaining epidermis. The amount (1.25µg/cm^2) recovered from the receptor fluid accounted for 0.626% of the applied dose.

Conclusion

The results obtained in this study indicate that:

1. The absorption of cyphenothrin from the [redacted] formulation through human epidermis was very slow.

2. The vast majority of the cyphenothrin applied as formulation can be removed by normal washing procedures at 24 hours.

3. The recovery values obtained in this study were considered to be acceptable (mean of 80.2%). Investigations showed that this low recovery was likely to be as a result of poor extraction from the swabs and/or skin following swab/skin interaction during the skin wash procedure.

4. The proportions of cyphenothrin recovered from the *stratum corneum* reduced with increasing depth into the membrane.

5. These data predict that the dermal absorption of cyphenothrin from potential exposure to this cyphenothrin [redacted] formulation would be minimal.

5.3 Conclusion

5.3.1 Reliability 1

5.3.2 Deficiencies No

Table 6.2.2-1 Summary of cyphenothrin absorption through human epidermis

Details of test material application	Mean absorption rates		Mean amount and percentage of dose absorbed		
	Time period (h)	Absorption rate (µg/cm2/h ± SEM)	Time (h)	Amount (µg/cm²)	Percentage absorbed
Cyphenothrin formulation [redacted] 20µl/cm² (200µg a i/cm²) Unoccluded Exposure period 24h n = 5	0 - 24	0.054± 0.007	6	0.205	0.103
			8	0.299	0.149
			10	0.414	0.207
			24	1.25	0.626
			LOQ	0.044	0.022

SEM - standard error of the mean

Table 6.2.2-2 Summary of cyphenothrin distribution in the test system from the 1% formulation

Test compartment	µg Gokilaht per cm²		% of applied dose	
n = 5	**Mean**	**SEM**	**Mean**	**SEM**
Donor chamber	9.89	2.82	4.94	~~4.94~~1.41
Skin wash	138	9.68	68.8	~~68.8~~4.84
Stratum corneum	8.17	1.66	4.08	~~4.08~~0.829
Remaining epidermis	3.51	0.502	1.75	~~1.75~~0.251
Absorbed	1.25	0.181	0.626	~~0.626~~0.091
Total recovered	160	8.42	80.2	~~80.2~~4.21

SEM - standard error of the mean
Stratum corneum – amount in tape strips
Remaining epidermis – epidermal tissue remaining after tape stripping
Absorbed – amount in receptor fluid

EVALUATION BY COMPETENT AUTHORITIES

EVALUATION BY RAPPORTEUR MEMBER STATE

Date November 2017

Materials and methods Point 3.1.2.3: The stability of the dose preparation solution was not analyzed for stability.
Point 5.1: The applied volume is twice the recommended in the guideline i.e. 20µl/cm^2.
It is noted that the number of donors is 3.

Results and discussion Point 4.2: Five (5) tape strips were used. No information concerning the amount of the test article detected in the individual tape strips was presented, neither in the study summary nor in the study report.

The statistical analysis of the results, i.e. SEM instead of SD -Table 6.2.2-2, is not the most appropriate one in order to assess dermal absorption. For this reason, the eCA has calculated the SD based on the individual results for each cell.

Results have been amended as follows:

Summary of cyphenothrin distribution in the test system from the 1% formulation

Test compartment	µg Gokilaht per cm^2		% of applied dose	
n = 5	Mean	SEM	Mean	SD
Donor chamber	9.89	2.82	4.94	3.15
Skin wash	138	9.68	68.8	10.8
Stratum corneum	8.17	1.66	4.08	1.85
Remaining epidermis	3.51	0.502	1.75	0.56
Absorbed	1.25	0.181	0.626	0.20
Total recovered	160	8.42	80.2	9.4

SEM - standard error of the mean
Stratum corneum – amount in tape strips
Remaining epidermis – epidermal tissue remaining after tape stripping
Absorbed – amount in receptor fluid

According to the EFSA Guidance on Dermal Absorption (2012) when, less than 75% of total absorption occurs within half of the study duration, then the tape-stripped material cannot be excluded and the amount recovered from *stratum corneum* should be considered as potentially absorbed.

Based on the above, for the derivation of the dermal absorption value, the amount directly absorbed and the one remaining in epidermis and in *stratum corneum* (all 5 tape-strips since results for each tape-strip are not available) should be considered.

The individual results for each cell are presented below:

Potentially absorbed amount	Cell No						
	1	2	3	4	5	Mean	SD

Absorbed + Remaining epidermis + *Stratum corneum*	7.985	7.845	8.026	c	3.702	6.4622	2.074644

Based on the above, and taking also into account that the SD is higher that 25% of the mean, a dermal absorption value of 8.5% is derived.

This value should be further corrected for low recovery (80.2%) according to the EFSA Guidance, resulting in a value of 10.6%, rounded to 11%.

Conclusively, based on the available data, a value of 11% is concluded for a [redacted].

Conclusion The dermal absorption value for an [redacted] solution in ethanol was estimated to be 11% [See Results and discussion].

Reliability 1

Acceptability Acceptable.

Remarks It is acknowledged that the applied volume is higher than the one recommended in the OECD protocol (20 µl/cm^2 instead of 10 µl/cm^2). However, this deviation is not considered to alter significantly the results by giving an underestimation of the dermal absorption. It is also noted that for the calculated value the amount detected in all tape-strips is considered and correction has been performed twice for the SD and the low recovery. Therefore, overall any deviation that could change the absorption has been covered.
The "normalisation" approach rather than the addition of the missing material to absorption has been followed, in order to correct for low recovery.
Normalization is one of two options the EFSA Guidance proposes for low recovery correction. However, critical evaluation of the available data should be performed to determine if significant amounts of the missing material could have been absorbed. According to the study author the observed low recoveries were most likely to be as a result of poor extraction from the swabs.
Please note that these losses are considered to be from non-absorbed material and therefore, according to the EFSA Guidance have no impact on the results.