Document IIIA/ Section 6.1.1/01

Acute Toxicity

Acute oral toxicity in the rat

BPD Data set IIA/

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Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1987); FCR 1272 (c.n. cyfluthrin) Study for acute oral toxicity to rats (Formulation acetone and peanut oil), [redacted] Report no. 15847, Study no. T 1020955. BES Ref : M-038006-01-1 Report date 24 June 1987 unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes OECD Guideline for Testing of Chemicals No. 401,"Acute Oral Toxicity", adopted 12.5.1981 and the EPA guideline "Acute oral Toxicity, Office of Pesticides and Toxic Substances, 1983
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	FCR 1272 (cyfluthrin) Cyclopropane carboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl, cyano (4-fluoro-3-phenoxyphenyl) methyl ester
3.1.1	Lot/Batch number	Batch no: 233490583
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Solid yellow-brown mass of oily to pasty consistency
3.1.2.2	Purity	93%
3.1.2.3	Stability	Test compound was kept in a laboratory cupboard at 20° to 27° during the study. Approved for the entire study.

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3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	[redacted]
3.2.3	Source	[redacted]
3.2.4	Sex	Male and female
3.2.5	Age/weight at study initiation	Young adult approximately 160 to 200 gm
3.2.6	Number of animals per group	5 to 10/sex/group
3.2.7	Control animals	No
3.3	**Administration/ Exposure**	Oral
3.3.1	Postexposure period	14 days
		Oral
3.3.2	Type	Gavage
3.3.3	Concentration	Males: 10, 50, 80, 90, 100, 125, 140, 160, 180, 200, 250 mg/kg bw Females: 10, 50, 90, 100, 140, 160, 170, 180, 250 mg/kg bw
3.3.4	Vehicle	Acetone and peanut oil
3.3.5	Concentration in vehicle	Test compound was formulated in acetone (1 ml) with peanut oil (10 ml)
3.3.6	Total volume applied	5 ml/kg body weight
3.3.7	Controls	No controls used
3.4	**Examinations**	Clinical observations, necropsy, body weight
3.5	**Method of determination of LD_{50}**	Bliss, 1938
3.6	**Further remarks**	None

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RESULTS AND DISCUSSION

3.7	**Clinical signs**	Signs of apathy, increased motility, digging and grooming movements, uncoordinated gait, spread gait, rolling, salivation, dyspnoea, temporarily grooming and shaking, bristling coat, in isolated cases convulsed posture and vocalisation, in isolated cases staggering (males only), in isolated cases soft stool. The clinical signs started 15 minutes after application and lasted until the fifth day of observation period. See table 6.1.1/01-1
3.8	**Pathology**	Animals dying during observation had patchy and distended lungs, in isolated cases were dark red, and also in individual females slight fluid in tissues. Liver was patchy, in isolated cases dark (males only), sometimes slight lobulation and pale (females only); spleen was patchy and pale, and in isolated cases dark. Kidneys were mottled and pale, with the glandular stomach sometimes slightly reddened. Stomach and intestinal tract were distended and empty. In one male the intestinal tract was filled with yellow mucus. The animals that were sacrificed at the end of observation period showed no indications of substance-induced grossly apparent organ damage. See table 6.1.1/01-1
3.9	**Body weight**	No effects were noted.
3.10	**LD_{50}**	LD_{50} males: 155 (125-195) mg/kg bw, females: 160 (126-204) mg/kg bw combined: 158 mg/kg bw

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4 APPLICANT'S SUMMARY AND CONCLUSION

4.1 Materials and methods

Groups of 5-10 fasted male and female Wistar rats ([redacted], [redacted]) weighing 160 to 200g received cyfluthrin (Batch no . 233490583, purity: 93%, in acetone/peanut oil) via single oral administration in concentrations of 10, 50, (80)* 90, 100, (125)* 140, 160, (170)+, 180 (200)*, 250 mg/kg bw. Food was provided two hours after dosing. All rats which died during the study were necropsied as soon as possible. Survivors were sacrificed on day 14 after treatment. Recording period: 0-14 days; body weight: days 0, 7, 14. Statistical method: Method after Rosiello, et al., 1977, modified by Pauluhn (1983).

* = Dose only to males; + dose only to females

4.2 Results and discussion

Clinical signs: Apathy, increased motility, digging and grooming movements, uncoordinated gait, spread gait, rolling, salivation, dyspnoea, temporarily grooming and shaking, bristling coat, isolated cases of convulsed p0osture, vocalization, staggering (males only), soft stool. The signs started 15 minutes after application and lasted until the fifth day of observation period.

Gross pathology: Animals dying during observation had patchy and distended lungs, in isolated cases were dark red, and also in individual females slight fluid in tissues. Liver was patchy, in isolated cases dark (males only), sometimes slight lobulation and pale (females only); spleen was patchy and pale, and in isolated cases dark. Kidneys were mottled and pale, with the glandular stomach sometimes slightly reddened. Stomach and intestinal tract were distended and empty. In one male the intestinal tract was filled with yellow mucus.

The animals that were sacrificed at the end of observation period showed no indications of substance-induced grossly apparent organ damage.

4.3 Conclusion

Cyfluthrin has a moderate acute toxicity on oral administration in acetone/peanut oil. X

4.3.1 Reliability 1

4.3.2 Deficiencies None

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Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-24
Materials and Methods	Applicant's version is accepted.
Results and discussion	Applicant's version is adopted.
Conclusion	Other conclusions: Oral LD_{50} (cyfluthrin in peanut oil/acetone): 155 mg/kg bw (M) 160 mg/kg bw (F)
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.1/01-1 Acute Oral Toxicity

Dose mg/kg	Number of dead /number of investigated	Time of death (range)	Observations
Males		14 days	No findings
10	0/5	14 days	No findings
50	0/5	14 days	No findings
80	0/5	14 days	No findings
90	0/5	14 days	No findings
100	3/10	24-48 hours	Lung patchy to dark red, slightly distended; spleen dark; stomach very distended; forestomach completely empty, Lung patchy to dark red, slightly distended; spleen slightly pale; stomach and intestinal tract very distended; empty Lung patchy to dark red, slightly distended; stomach and intestinal tract very distended, empty; abdominal organs autolytic
125	3/5	24 hours	Lung patchy to dark red, slightly distended; spleen sometimes slightly pale; kidneys slightly pale, stomach distended; forestomach completely empty; glandular stomach empty Lungs patchy, slightly distended; spleen slightly patchy, kidneys slightly pale; stomach and intestinal tract very distended, completely empty Lungs patchy, slightly distended; spleen and kidneys slightly pale; stomach and intestinal tract distended, sometimes empty; forestomach reddened
140	2/5	24-48 hours	Lung patchy, distended; stomach and intestinal tract distended, stomach filled with some wood chips, otherwise empty; intestinal tract sometimes empty, sometimes filled with yellow mucus Lung patchy, very distended; spleen patchy; kidneys slightly mottled; stomach and intestinal tract distended; forestomach empty
160	1/5	48 hours	Lung patchy, distended; glandular stomach slightly reddened; intestinal tract distended, empty
180	2/5	24-72 hours	Lung patchy, slightly distended; liver slightly patchy, kidneys slightly mottled; spleen patchy Animal not appraisable since badly gnawed
200	4/5	24-48 hours	Lung patchy, distended; spleen patchy; stomach distended, empty Lung patchy, slightly distended; liver slightly patchy; spleen pale, patchy; kidneys slightly mottled; stomach distended, empty Lung patchy, slightly distended; liver patchy; spleen patchy, pale; stomach distended, empty Lung distended; oesophagus completely filled with wood chips; spleen slightly dark
250	5/5	24-48 hours	Lung patchy, slightly distended; spleen sometimes pale; glandular stomach slightly reddened Lung patchy, distended; spleen very pale,; stomach very distended Lung slightly distended; liver dark; spleen very pale; stomach very distended, completely empty; glandular stomach sometime slightly reddened Lung patchy to dark red; slightly distended; liver slightly dark; spleen very pale; stomach and intestinal tract very distended, empty Lung patchy to dark red, distended; liver slightly patchy; spleen sometimes pale, sometimes very dark; stomach

Dose mg/kg	Number of dead /number of investigated	Time of death (range)	Observations
			distended
LD_{50} value	**155 (125-195) mg/kg bw**		
Females			
10	0/5	14 days	No findings
50	0/5	14 days	No findings
90	0/5	14 days	No findings
100	2/5	24 hours	Lung patchy, slightly distended; liver slightly patchy, other abdominal organs autolytic. Lung patchy, distended; liver slightly patchy, very pale; stomach very distended, empty
140	2/10	24 hours	Lung patchy, distended; liver slightly pale, distinct lobulation; kidneys slightly pale Lung patchy to dark red, slightly distended; kidneys slightly pale, slightly mottled.
160	2/10	24 hours	Lung patchy to dark red, distended; liver patchy, slightly pale; intestinal tract distended, completely empty Lung patchy to dark red, distended; liver slightly patchy, distinct lobulation; intestinal tract distended, completely empty
170	4/5	24 hours	Lung patchy, distended; liver patchy; glandular stomach slightly reddened Lung patchy, distended; liver patchy Lung patchy, distended; liver patchy; glandular stomach slightly reddened Lung patchy, distended; kidneys slightly pale
180	5/5	24-48 hours	Lung patchy, distended; liver patchy Lung patchy, distended, with slight fluid in tissue Lung patchy, distended with slight fluid in tissue; liver slightly pale, slight lobulation; spleen patchy; stomach distended, filled with some wood chips otherwise empty; intestinal tract filled with yellow mucus Lung patchy, distended; abdominal organs autolytic Lung patchy, distended; liver, spleen and kidneys patchy; liver slight lobulation; stomach and intestinal tract distended.
250	5/5	4-24 hours	Lung very distended; liver slight lobulation; kidneys slightly pale Lung slightly distended, liver slight lobulation; kidneys slightly pale Lung patchy to dark red, slightly distended Lung patchy to dark red, slightly distended; liver slightly patchy, pale; spleen dark; stomach distended Lung patchy, slightly distended
LD_{50} value	**160 (126-204) mg/kg bw**		

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Acute Toxicity

Acute oral toxicity in the rat

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			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1982). FCR 1272 – Comparative tests for acute toxicity with various formulation aids. [redacted] Bayer AG Report No.: 10931 BES study No.: M-021687-01-1 Report date: 7 June 1982 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	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. At the time the study was performed, no particular method was compulsory. The method used was largely compliant with contemporaneous EPA Guidelines (Proposed Guidelines for Registering Pesticides in the US, Federal Register, Vol. 43, No. 163, August 22, 1978).	
2.2	**GLP**	No. When the study was performed, GLP was not compulsory (as study started before May 13 2000).	X
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	FCR 1272 (cyfluthrin) Cyclopropane carboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl, cyano (4-fluoro-3-phenoxyphenyl) methyl ester	
3.1.1	Lot/Batch number	Batch no: 816170019	
3.1.2	Specification	As given in section 2	
3.1.2.1	Description	Not stated	
3.1.2.2	Purity	95%	
3.1.2.3	Stability	Not performed	

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Acute Toxicity

Acute oral toxicity in the rat

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3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Wistar [redacted]
3.2.3	Source	[redacted]
3.2.4	Sex	Male
3.2.5	Age/weight at study initiation	Young adult approximately 160 to 200 g
3.2.6	Number of animals per group	5 to 20/group
3.2.7	Control animals	No
3.3	**Administration/ Exposure**	Oral
3.3.1	Postexposure period	14 days
		Oral
3.3.2	Type	Gavage
3.3.3	Concentration	Cremophor EL/distilled water: 13, 15, 17.5 and 20 mg/kg bw
		Acetone and oil : 200, 250, 300, 350 and 500 mg/kg bw
		Dimethyl sulphoxide: 125, 150, 200, 350, 500, 750 and 1000 mg/kg bw
		N-methyl pyrrolidon: 100, 250, 500 and 1000 mg/kg bw
3.3.4	Vehicle	Cremophor EL/distilled water
		Acetone and oil
		Dimethyl sulphoxide
		N-methyl pyrrolidon
3.3.5	Concentration in vehicle	Test compound was formulated in:
		Cremophor EL/distilled water (5 drops to 10 mL)
		Acetone and oil (1:10 ml)
		Dimethyl sulphoxide : not reported
		N-methyl pyrrolidon : not reported
3.3.6	Total volume applied	Cremophor EL/distilled water: volume 10 ml/kg bw
		Acetone and oil: volume 5 mL/kg bw
		Dimethyl sulphoxide: volume 1 ml/kg bw
		N-methyl pyrrolidon: volume 1 ml/kg bw
3.3.7	Controls	None
3.4	**Examinations**	Clinical observations

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Acute oral toxicity in the rat

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3.5	**Method of determination of LD_{50}**	Litchfield and Wilcoxon's method (J. Pharmacol. Exper. Therap. 96, 99, 1949)	
3.6	**Further remarks**	None	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Tremor, rolling movements, disturbed motility and respiration. The symptoms arose within an hour and were apparent for approximately 1 – 5 days.	
		Mortality are given in table A6.1.1/02-1	X
		Test compound formulated in Cremophor EL/distilled water was administered to fasted female mice for comparison. The signs were the same as those seen in rats.	
4.2	**Pathology**	Normal	
4.3	**Body weight**	No effects were noted	
4.4	**LD_{50}**	Cremophor EL/distilled water: 16.2 (13.5 – 19.5) mg/kg bw	
		Acetone and oil: 254 (220 - 294) mg/kg bw	
		Dimethyl sulphoxide: 396 (317 - 494) mg/kg bw	
		N-methyl pyrrolidon: 500 - 1000 mg/kg bw	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The test sample FCR 1272 was tested comparatively for its oral toxicity, using various formulating aids: Cremophor EL/distilled water (5 drops; 10 ml), acetone and oil (1:10 ml), dimethyl sulphoxide and N-methyl pyrrolidon. In order to exclude the possibility of species being sensitive to different degrees to different formulating aids, the test sample formulation with Cremophor EL/distilled water was also administered to fasted female mice.	
		Groups of 5 - 20 fasted male Wistar rats [redacted], [redacted] weight 160 to 200 g) kept unfed for 16 hours, received cyfluthrin (Batch no . 816170019, purity: 95%), in various formulation aids via single oral administration. The post-observation period was 14 days.	
5.2	**Results and discussion**	The signs indicate an effect on the central nervous system (tremor, rolling movements, disturbed motility and respiration). Onset of symptoms arose within an hour and was apparent for 1 to 5 days.	
5.3	**Conclusion**	The results showed that the acute oral toxicity of cyfluthrin varied notably when different formulation aids were used. This was very pronounced with Cremophor EL/distilled water.	X
5.3.1	Reliability	1	
5.3.2	Deficiencies	None	

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Acute Toxicity

Acute oral toxicity in the rat

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Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-24
Materials and Methods	*2.2 GLP:* GLP was not compulsory at the time the study was performed (as study started before June 30 1988).
Results and discussion	*Table A6.1.1/02 -1:* omit last column: "observations" as it suggests that there were no findings at all. In fact, there were symptoms observed but they were summarised in the study report and cannot be allocated different dose groups. Otherwise the applicant's version is adopted.
Conclusion	Other conclusions: LD_{50} of cyfluthrin: in cremophor EL/distilled water: 16.2 (13.5 – 19.5) mg/kg bw in acetone and oil: 254 (220 - 294) mg/kg bw in dimethyl sulphoxide: 396 (317 - 494) mg/kg bw in N-methyl pyrrolidone: 500 - 1000 mg/kg bw
Reliability	2
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.1/02 -1: Acute Oral Toxicity

Dose mg/kg	Number of dead /number of investigated	Time of death (range)	Observations
Cremophor EL/distilled water			
13	1/5	Approx. 3 h	No findings
15	2/5	2 – 3 h	No findings
17.5	3/5	Approx. 2 h	No findings
20	5/5	Approx. 2 h	No findings
LD_{50} 16.2 (13.5 – 19.5) mg/kg bw			

Dose mg/kg	Number of dead /number of investigated	Time of death (range)	Observations
Acetone and oil (1:10 ml)			
200	2/10	2 days	No findings
250	4/10	1 – 2 days	No findings
300	7/10	1 – 2 days	No findings
350	9/10	1 – 2 days	No findings
500	10/10	1 – 2 days	No findings
LD_{50} 254 (220 - 294) mg/kg bw			

Dose mg/kg	Number of dead /number of investigated	Time of death (range)	Observations
Dimethyl sulphoxide			
125	0/10	-	No findings
150	2/10	2 days	No findings
200	6/20	1 – 2 days	No findings
350	4/10	24 h	No findings
500	12/20	1 – 2 days	No findings
750	14/20	1 – 4 days	No findings
1000	9/10	5 h – 5 days	No findings
LD_{50} 396 (317 - 494) mg/kg bw			

Dose mg/kg	Number of dead /number of investigated	Time of death (range)	Observatins
N-methyl pyrrolidon			
100	0/10	-	No findings
250	0/10	-	No findings
500	1/10	5 days	No findings
1000	10/10	Approx. 24 h	
LD_{50} 500 - 1000 mg/kg bw			

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Annex Point VI.6.1.2

Acute Toxicity

Acute dermal toxicity in the rat

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1 REFERENCE

1.1	**Reference**	[redacted] (1980) FCR 1272 Acute toxicity studies. [redacted] Bayer AG Report No.: 8800 BES Ref.: M-0389979-01-1 Report date: 7 January 1980 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2	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, House method according to Noakes and Sanderson's occlusive dressing method. (Brit. J.Ind. Med. 26: 59, 1969).
2.2	**GLP**	No, GLP was not compulsory at the time the study was performed (as study started before June 30 1988).
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	FCR 1272 (cyfluthrin) Cyclopropane carboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl, cyano (4-fluoro-3-phenoxyphenyl) methyl ester
3.1.1	Lot/Batch number	Batch No. 16001/79, Lo-Nr. 2151
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Not given
3.1.2.2	Purity	83.6%
3.1.2.3	Stability	Not specified
3.2	**Test animals**	
3.2.1	Species	Rat
3.2.2	Strain	Wistar rats [redacted]
3.2.3	Source	[redacted]
3.2.4	Sex	Male and female
3.2.5	Age/weight at study initiation	Young adult approximately 160 to 240 g
3.2.6	Number of animals per group	5-10/sex/group
3.2.7	Control animals	No

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Acute dermal toxicity in the rat

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3.3	**Administration/ Exposure**	**Dermal**	
3.3.1	Post-exposure period	14 days	
3.3.2	Area covered	Intact dorsal skin (shaved on the previous day)	
3.3.3	Occlusion	Covered with aluminium foil and wrapped in an adhesive plaster sleeve	
3.3.4	Vehicle	None	
3.3.5	Concentration in vehicle	2500 or 5000 mg/kg bw	
3.3.6	Total volume applied	Test compound was applied in "concentrated" form.	
3.3.7	Duration of exposure	24 hours	
3.3.8	Removal of test substance	Treated skin areas were first removed with acetone and then with soap and water	X
3.3.9	Controls	None	
3.4	**Examinations**	Clinical observations	
3.5	**Method of determination of LD_{50}**	Probit-analysis. (Fink and Hund , Arzneimittelforschung 15, 624, 1965)	
3.6	**Further remarks**		
		RESULTS AND DISCUSSION	
3.7	**Clinical signs**	Symptoms of toxicity included apathy and ataxia that cleared 5-7 days after exposure.	
3.8	**Pathology**	Not described.	
3.9	**Other**		
3.10	**LD_{50}**	Males: > 5000 mg/kg bw	
		Females: > 5000 mg/kg bw	

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Acute Toxicity

Acute dermal toxicity in the rat

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	Groups of 5 male and 5-10 female Wistar rats ([redacted]) weighing 160 to 240 grams received cyfluthrin (batch no: 16001/79, purity: 83.6%, in concentrated form) on the intact dorsal skin (shaved on the previous day) in concentrations of 2500 and 5000 mg/kg bw. After 24 hours the contaminated skin was washed using acetone, soap and water. All rats that died during the study were necropsied as soon as possible. Survivors were sacrificed on day 14 after treatment. Body weight was not determined. Statistical analysis method: Probit-analysis.
4.2	**Results and discussion**	Clinical signs included apathy and atactic movements, disappearing 5-7 days after administration. NOEL (mg/kg bw) 2500, both sexes LD_{50} (mg/kg bw) >5000, both sexes
4.3	**Conclusion**	Cyfluthrin has a low percutaneous acute toxicity in rats.
4.3.1	Reliability	2
4.3.2	Deficiencies	Non-guideline

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-24
Materials and Methods	*3.3.8 Removal of test substance:* Treated skin areas were washed with acetone and then with soap and water. Otherwise applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Reliability	2
Acceptability	Acceptable
Remarks	The results of the gross pathology are not included in the study report. Body weights were not reported.

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Acute Toxicity

Acute dermal toxicity in the rat

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	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document. IIIA/ Section 6.1.3 — Acute Toxicity

Acute inhalation toxicity in the rat

BPD Data set IIA/

Annex Point VI.6.1.3

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1 REFERENCE

1.3	**Reference**	[redacted] (1987) FCR 1272 (Common Name: cyfluthrin) Study of the acute inhalation toxicity to rats using OECD guideline No. 403, [redacted] Bayer AG Report No.: 15612 BES Ref. M-039805-02-1 Report date: 4 March 1987 Unpublished Report addendum : [redacted] (1993) FCR 1272 (Common Name: cyfluthrin) Study of the acute inhalation toxicity to rats according OECD guideline No. 403, [redacted] Bayer AG Report No.: 15612A BES Ref. M-039805-02-1 Report date 22 April 1993 Unpublished
1.4	**Data protection**	Yes
1.4.1	Data owner	Bayer CropScience AG
1.4.2		
1.4.3	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

2.3	**Guideline study**	Yes OECD Guideline for Testing of Chemicals No. 403, EPA Guideline 81-3. The test performed conforms to Directive 92/69 EEC Method B2. The Experimental conditions were modified in such a manner that the appropriate EEC and FIFRA guidelines were also complied with to the extent technically feasible.
2.4	**GLP**	Yes
2.5	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	FCR 1272 (cyfluthrin) Cyclopropane carboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl, cyano (4-fluoro-3-phenoxyphenyl) methyl ester
3.1.1	Lot/Batch number	Batch no: 233 490 583
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Solid yellow-brown mass of oily to pasty consistency
3.1.2.2	Purity	93%
3.1.2.3	Stability	Guaranteed until November 23, 1986 (PF Analytical, May 23, 1986)

Document. IIIA/ Section 6.1.3 — Acute Toxicity

Acute inhalation toxicity in the rat

BPD Data set IIA/

Annex Point VI.6.1.3

3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	[redacted]	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male and female	
3.2.5	Age/weight at study initiation	Young adult 7-11 weeks old, approximately 160 to 200 g	
3.2.6	Number of animals per group	5/sex/group	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	**Inhalation**	
3.3.1	Post-exposure period	14 days	
3.3.2	Concentrations	Nominal concentration: 175, 1500, 2500, 3000, 3500 mg/m³ Analytical concentration: 24.5, 168.3, 368.9, 448.2, 619.3 mg/m³	
3.3.3	Particle size	MMAD (mass median aerodynamic diameter) <5 µm (100% of particles), range 1,48 to 1,78 µm	
3.3.4	Type or preparation of particles	The test material was nebulized into a cylindrical inhalation chamber under dynamic conditions.	
3.3.5	Type of exposure	Whole body or nose/head only	X
3.3.6	Vehicle	Polyethylene glycol E 400 and ethanol (mixing ratio 1:1)	
3.3.7	Concentration in vehicle	Solution of 0,875%, 7,5%, 12,5%, 15% and 17,5% (w/v)	
3.3.8	Duration of exposure	4 hours	
3.3.9	Controls	None	
3.3.10	Total volume applied	200 µl/minute	
3.3.11	Controls	None. Historical data provided in report addendum.	
3.4	**Examinations**	Clinical observations (daily), body weights (0,7, 14 d), gross pathology	
3.5	**Method of determination of LC_{50}**	Rosiello et al., (1977), modified by Pauluhn (1983).	
3.6	**Further remarks**		
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Results are presented in table A6.1.3-1. The observed signs of intoxication were characteristic of cyano-pyrethroids.	

Document. IIIA/ Section 6.1.3
BPD Data set IIA/
Annex Point VI.6.1.3

Acute Toxicity

Acute inhalation toxicity in the rat

		On the day of exposure, the following signs were observed: choreoathetoid movement sequences with paddle-like movements and rolling, cyanosis, irregular and difficult breathing, vocalization, sternal and lateral recumbency and blepharophimosis. Starting on the first day of observation, the rats were biologically normal except for slightly reduced activity, piloerection, and unpreened hair coat.
4.2	**Pathology**	Rats that died during exposure: Lungs: distended and with hepatoid foci (haemorrhages); nose: bloody; liver and spleen: pale; liver: with lobular pattern; renal pelvis; reddened; glandular stomach and small intestine: reddened, in some cases a yellowish mucus in the intestinal lumen. Rats that were sacrificed at study termination: No dose-related changes in lungs or other damage were noted.
4.3	**Other**	Lung function tests were also performed on female rats, along with the acute inhalation toxicity study. It revealed that during inhalation testing there was a temporary tendency toward impaired ventilation. This was manifested in an increase in the dynamic compliance, reduction in the resistance, and a reduction in the respiratory minute volume. The blood gas analyses showed, however, that these functional lung changes did not coincide with any biologically relevant effect on the blood gases. The NOEL was determined to be 5.2 mg/m^3 air.
4.4	**LD_{50}**	The LC_{50} was determined to be: Males and females: 408 (369-447) mg/m^3 air
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.3	**Materials and methods**	This study conforms to the OECD guideline no. 403, also conforms to the Directive 92/69 EEC method B2, and EPA FIFRA guidelines. Groups of 5 /sex rats [redacted] weighing 160 to 240 grams received cyfluthrin (batch no: 23349-583, purity 93%, in ethanol/polyethylene glycol E 400 (1:1) aerosol) via inhalation (dynamic spraying, head nose only) in analytical concentrations of 24.5, 168.3, 368.9, 448.2, 619.3 mg/m^3 air for 4 hours. All rats that died during the study were necropsied. Survivors were sacrificed on Day 14 post dosing. Clinical signs were recorded daily, body weights were recorded on days 0, 7 and 14. In addition, lung function tests and blood gas analysis were performed on satellite groups.

Document. IIIA/ Section 6.1.3	**Acute Toxicity**
	Acute inhalation toxicity in the rat
BPD Data set IIA/	
Annex Point VI.6.1.3	

5.4	**Results and discussion**	Clinical signs included piloerection, unpreened hair coat, reduced activity, staggering gait, tremor, bloody nose, irregular and difficult breathing, bloody rhinorium, sternal and lateral recumbency, paddle-like movements of the extremities, convulsions, blepharophimosis, non-specific behavioural disturbances, cyanosis, vocalization, rolling. Symptoms started during or shortly after administration and disappeared 2d after. Gross pathology on rats dying on test: lungs distended and pale, liver with lobular pattern, renal pelvis, reddened, glandular stomach and small intestine reddened, in some cases a yellowish mucous in the intestinal lumen. Rats sacrificed at day 14 post-dosing: No treatment-related indications of gross lung or other organ damage. Lung function tests and blood gas analysis: A temporary tendency toward impaired ventilation (manifested in an increase in the dynamic compliance, reduction in the resistance, and a reduction in the respiratory minute volume); at a comparable dose range no coincidence with any biologically relevant effect on the blood gases.	
5.5	**Conclusion**	LC_{50}: in males: approximately 425 mg/m^3 in females: approximately 386 mg/m^3	
5.5.1	Reliability	1	
5.5.2	Deficiencies	No	X

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-25
Materials and Methods	*3.3.5 Type of exposure:* head/nose only
Results and discussion	*5.5.3 Deficiencies* Deviations from OECD 403 guideline (no vehicle control group, historical controls instead, no observation of animals during exposure) are considered not to impair the overall validity of the study. Otherwise the applicant's version is accepted.
Conclusion	Applicant's version is adopted.
Reliability	1
Acceptability	Acceptable
Remarks	-

Document. IIIA/ Section 6.1.3

Acute Toxicity

Acute inhalation toxicity in the rat

BPD Data set IIA/

Annex Point VI.6.1.3

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.3-1. Acute Toxicity

Dose: Nomin. mg/m³ air	**Dose: Analytical mg/m³ air**	**Number of dead / number investigated**	**Duration of Signs (hours)**	**Time of Death**	**Particles ≤ 5µm (%)**
Males					
175	24.5	0/5	4-7 hours	-	100
1500	168.3	0/5	4-5 hours	-	100
2500	368.9	1/5	4hours-2days	4 hours	100
3000	448.2	3/5	2-24 hours	4-5 hours	100
3500	619.3	5/5	2-4 hours	4 hours	100
LC_{50} value	**425 mg/m³ air (approximate)**				
Females					
175	24.5	0/5	4-7 hours	-	100
1500	168.3	0/5	4-5 hours	-	100
2500	368.9	2/5	4-6 hours	4 hours	100
3000	448.2	4/5	2-24 hours	4-5 hours	100
3500	619.3	5/5	4 hours	4 hours	100
LC_{50} value	**386 mg/m³ air (approximate)**				

Time of Death 4 hours: Rats that died during exposure
LC_{50} combined male and female: 405 mg/m3 air
Confidence interval (95%) = 368.5-446.8 mg/m3 air
Slope: 5.95

Document IIIA/ Section 6.1.4/01 Acute Dermal Irritation

BPD Data set IIA/

Annex Point IIA6.1.4

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1982) FCR 1272, Eye and Skin Irritation Study on Rabbits [redacted] Report No.: 233 BES study No.: M-044691-01-1 Report date: 10 June 1982 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	At the time the study was performed, no particular method was compulsory. A specific Japanese test method was used.	
		No guidelines available, but study is acceptable and adheres to protocols developed by OECD and EPA	X
2.2	**GLP**	No, GLP was not compulsory at the time the study was performed (as study started before June 30 1988).	
2.3	**Deviations**	The patches of two animals came off, and the same test was done again using the inside skin of ears of the same animals.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	FCR 1272 (Cyfluthrin)	
		Cyclopropane carboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl, cyano (4-fluoro-3-phenoxyphenyl) methyl ester	
3.1.1	Lot/Batch number	Eg 3/81	
3.1.2	Specification	As given in section 2	
3.1.2.1	Description	Not given	
3.1.2.2	Purity	95%	
3.1.2.3	Stability	Not given	
3.2	**Test Animals**		
3.2.1	Species	Rabbits	
3.2.2	Strain	Albino Japanese	
3.2.3	Source	[redacted]	
3.2.4	Sex	Female	
3.2.5	Age/weight at study	about 2.0 kg	

Document IIIA/ Section 6.1.4/01 Acute Dermal Irritation

BPD Data set IIA/

Annex Point IIA6.1.4

	initiation		
3.2.6	Number of animals per group	6/group	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	**Dermal**	
3.3.1	Application		
3.3.1.1	Preparation of test substance	Test substance was prepared by warming the test substance in a water bath to melt it. 0.1 ml of test substance was dropped into a chamber patch, in which the paper filter was laid and applied to the intact or the abraded skin.	
3.3.1.2	Test site and Preparation of Test Site	On the day before test, hair of dorsal area of the trunk was clipped (10 x 20 cm). The right half of the skin was used as intact skin and the left half was used as abraded skin.	
		Some animals received the substance also on the inside ear skin.	X
3.3.2	Occlusion	The test area on the trunk of animals was girdled with a piece of sponge (width: about 15 cm, length: about 45 cm) and fixed to the test area with surgical tape.	
3.3.3	Vehicle	None	
3.3.4	Concentration in vehicle	Not applicable	
3.3.5	Total volume applied	0.1 ml of cyfluthrin technical	
3.3.6	Removal of test substance	After 4 hours the skin reaction was observed immediately, and at 24 and 72 hours later.	
3.3.7	Duration of exposure	24 hours	
3.3.8	Postexposure period	72 hours	
3.3.9	Controls	None	
3.4	**Examinations**		
3.4.1	Clinical signs	Yes, frequency not stated.	
3.4.2	Dermal examination	Yes, skin reaction was observed immediately at 24 hours and at 72 hours after that.	
3.4.2.1	Scoring system	Draize's evaluation criteria	
3.4.2.2	Examination time points	Immediately after bandage removal, 24 and 72 hours thereafter.	X
Other examinations		None	
3.5	**Further remarks**		

Document IIIA/ Section 6.1.4/01 Acute Dermal Irritation

BPD Data set IIA/

Annex Point IIA6.1.4

4 RESULTS AND DISCUSSION

4.1	**Average score**	
4.1.1	Erythema	Average score for all animals at 24 and 72 hours for intact skin was 0.25 and 0 respectively. Average score for all animals at 24 and 72 hours with abraded skin was 0.5 and 0.25 respectively. See Table A6.1.4/01-1
4.1.2	Edema	The average score for all animals, either intact or abraded at 24 and 72 hours was 0. See Table A6.1.4/01-1
4.2	**Reversibility**	Yes The erythema of intact skin was reversible by 72 hours
4.3	**Other examinations**	In the second trial using the rabbit ear for skin irritation on all 6 animals, all scores for both intact and abraded skin at 24 and 72 hours was 0.
4.4	**Overall result**	In the albino rabbit cyfluthrin showed no skin irritating effects on intact or abraded skin or on the inside of the ear.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Six female rabbits/group (Japanese albino rabbits, [redacted]) received cyfluthrin (batch no: Eg 3/81: purity: 95%) via dermal administration. 0.1 ml of the test compound was dropped on a filter disc, applied to the clipped dorsal area of the trunk (intact and abraded skin) and kept in place by bandage for 24 hours. The animals received the substance also on the inside ear skin. Recording of skin reactions (erythema and edema) 24 and 72 hours post-exposure. Scoring was according to Draize.
5.2	**Results and discussion**	The primary irritation score was 0-0.5 after 24 and 72 hours, whether the skin was intact or abraded and 0 on the ear skin.
5.3	**Conclusion**	Cyfluthrin showed no skin irritating effects on intact or abraded skin or on the inside of the ear.
5.3.1	Reliability	1
5.3.2	Deficiencies	None

Evaluation by Competent Authorities

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

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	2006-08-28
Materials and Methods	*2.1 Guideline study:* Pre-guideline, similar to OECD guideline No. 404 *3.3.1.2 Test site and preparation of test site:* All animals received the substance on the inside of the ear skin. *3.4.2.2 Examination time points:* Immediately after patch removal at 24 h, and at 72 h
Results and discussion	The applicant's version is adopted.

Document IIIA/ Section 6.1.4/01 Acute Dermal Irritation

BPD Data set IIA/

Annex Point IIA6.1.4

Conclusion	The applicant's version is adopted.
Reliability	1
Acceptability	Acceptable
Remarks	Irritation test on dorsal skin was performed in four animals only (two patches came off). The dose was 0.1 ml of cyfluthrin (OECD 404: 0.5 ml) but was applied for 24 h (OECD 404: removing of test substance after 4 h).
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.4/01-1 Skin irritation study

Score (average animals investigated)	Time	Erythema	Edema
Average score	24 h (intact)	0.25	0
Draize scores	72 h (intact)	0	0
(0 to maximum 4)	24 h (abraded)	0.5	0
Other times	72 h (abraded)	0.25	0
Average score (intact and abraded))	24h, 72h	0.25	
Reversibility: *		c	
Average time for reversibility		72h	

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

Document IIIA/ Section 6.1.4/02 Acute Eye Irritation

BPD Data set IIA/

Annex Point IIA6.1.4

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1980) FCR 1272- Acute toxicity studies-[redacted] Bayer AG Report No.: 8800, BES Ref.: M-038979-01-1 Report date: 7 January 1980 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No. At the time the study was performed, no particular method was compulsory. The test was performed by the method recommended by the U.S. Department of Health, Education and Welfare (Fed. Reg. 37 (83), P. 8535, 1972).
2.2	**GLP**	When the study was performed, GLP was not compulsory.
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	FCR 1272 (Cyfluthrin) Cyclopropane carboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl, cyano (4-fluoro-3-phenoxyphenyl) methyl ester
3.1.1	Lot/Batch number	Batch no. 16001/79, Lo-Nr. 2151
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Not given
3.1.2.2	Purity	83.6%
3.1.2.3	Stability	Not given

Document IIIA/ Section 6.1.4/02 Acute Eye Irritation

BPD Data set IIA/

Annex Point IIA6.1.4

3.2	**Test Animals**		
3.2.1	Species	Rabbits	
3.2.2	Strain	New Zealand rabbits	
3.2.3	Source	[redacted]	
3.2.4	Sex	Males and females	
3.2.5	Age/weight at study initiation	3 to 4 kg	
3.2.6	Number of animals per group	5 (5 minute exposure) 3 (24 hour exposure)	
3.2.7	Control animals	No	
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	X
3.3.3	Exposure period	5 min and 24 hours	
3.3.4	Postexposure period	21 days	
3.4	**Examinations**		
3.4.1	Ophthalmoscopic examination	yes	
3.4.1.1	Scoring system	For ocular reaction grades, see Fed. Reg. 37, 83 (1972) p. 8535	
3.4.1.2	Examination time points	60min, 24h, 48h, 72 h and 7, 14 and 21 days	
3.4.2	Other investigations	None	
3.5	**Further remarks**		

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	In both the 5 minute exposure test and the 24-hour exposure test, irritation (moderate to severe redness, mild to moderate chemosis) was seen on the conjunctivae of the treated rabbit eyes.

Document IIIA/ Section 6.1.4/02 Acute Eye Irritation

BPD Data set IIA/

Annex Point IIA6.1.4

4.2	**Average score**	See Table A6.1.4/02-1
4.2.1	Cornea	In the 5-minute and 24-hour exposure the average score for 1, 24, 47 and 72 hours was 0.
4.2.2	Iris	In the 5-minute and 24-hour exposure the average score for 1, 24, 47 and 72 hours was 0.
4.2.3	Conjunctiva	
4.2.3.1	Redness	The average score for all animals in the 5-minute exposure experiment was 3, 2, 1.1, and 0.6 for the 1, 24, 48 and 72 hour times respectively The average score for all animals in the 24-hour exposure experiment was 3, 2, 1, 0.6 for hours 1, 24, 48 and 72 respectively.
4.2.3.2	Chemosis	The average score for all animals in the 5-minute exposure experiment was 0.8, 0.2, 0 and 0 for the 1, 24, 48 and 72 hour times respectively The average score for all animals in the 24-hour exposure experiment was 1.3, 0.6, 0 and 0 for hours 1, 24, 48 and 72 respectively.
4.3	**Reversibility**	Yes
4.4	**Other**	None
4.5	**Overall result**	Cyfluthrin has a primary irritating effect on the mucosa in the eye. But in accordance to the degree of irritation observed the substance is not considered to be classified irritating to eyes.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Cyfluthrin (batch no: 16001/79, purity: 83.6%) was given to rabbits (White New Zealand, [redacted]) via administration into the conjunctival sack of the eye. Five animals were exposed for 5 minutes; three animals were exposed for 24 hours. Recording period: 1 hour to 21 days post-exposure, scoring according to Draize.
5.2	**Results and discussion**	In both the 5-minute and 24-hour exposure test (especially 1 hour after dosing), irritation (moderate to severe redness, mild to moderate chemosis) was seen on the conjunctiva of the treated rabbit eyes.
5.3	**Conclusion**	Cyfluthrin has a primary irritating effect on the mucosae in the eye. But with the degree of irritation observed cyfluthrin is not classifiable as irritating to eyes.
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Document IIIA/ Section 6.1.4/02 Acute Eye Irritation

BPD Data set IIA/

Annex Point IIA6.1.4

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-28
Reference	*1.1 Reference:* [redacted] (1980)
Materials and Methods	*3.3.2 Amount of active substance instilled:* Amount not reported
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Reliability	2
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.1.4/02-1 Results of eye irritation study (eye, contact time: 24 hours)

	Cornea	Iris	Conjunctiva	
			redness	chemosis
Score (average of animals investigated)	**0 to 4**	**0 to 2**	**0 to 3**	**0 to4**
1 h	0	0	3	1.3
24 h	0	0	2	0.6
48 h	0	0	1	0
72 h	0	0	0.6	0
Average 24h, 48h, 72h	0	0	1	0.2
Area effected			conjunctiva	conjunctiva
Maximum average score (including area affected, max 110)	0	0		
Reversibility*	0	0	c	c
average time for reversion	0	0	7 days	48 hours
Give method of calculation maximum average score. * *c : completely reversible* *n c : not completely reversible* *n : not reversible*				

Document IIIA/ Section A6.1.5 — Skin sensitisation

Magnusson-Kligman Maximization Test

BPD Data set IIA/ Annex Point VI.6.1.5

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1994). FCR 1272- Study for skin-sensitizing effects in guinea pigs (Magnusson-Kligman Maximization Test). [redacted]. Report No.: 23060, BES Ref: M-038800-01-1 Report date: 31 May 1994. Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2	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**	OECD 406 (1992) Skin sensitization 84/449/EC (1984) Acute toxicity-Skin sensitization OPPTS § 81-6 (1984)
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	FCR 1272 (Cyfluthrin) Cyclopropane carboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl, cyano (4-fluoro-3-phenoxyphenyl) methyl ester
3.1.1	Lot/Batch number	Batch no: 380368010
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Thick brown oil
3.1.2.2	Purity	96.2 %
3.1.2.3	Stability	Guaranteed stable for the period during which testing occurred
3.1.2.4	Preparation of test substance for application	Immediately prior to treatment, FCR 1272 was dissolved in PEG 400 at 70°C to yield a solution. Stability was analytically verified
3.1.2.5	Pretest performed on irritant effects	No

Document IIIA/ Section A6.1.5 — Skin sensitisation

Magnusson-Kligman Maximization Test

BPD Data set IIA/ Annex Point VI.6.1.5

3.2	**Test Animals**	
3.2.1	Species	Guinea pigs
3.2.2	Strain	[redacted]
3.2.3	Source	[redacted]
3.2.4	Sex	Males
3.2.5	Age/weight at study initiation	Weights 317-411 g, 5-8 weeks
3.2.6	Number of animals per group	20 in main group, 10 each in 2 control groups
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	
3.3.1	Induction schedule	Day 0—intradermal induction Day 7—topical induction
3.3.2	Way of Induction	Intradermal/topical; topical induction was occlusive
3.3.3	Concentrations used for induction	For intradermal induction, backs and flanks of animals were shaved and 3 paired injections made 1) Freund's complete adjuvant: sterile saline (1:1) 2) FCR 1272 5% in PEG 400 3) FCR 1272 5% in PEG 400:Freund's Complete Adjuvant (1:1) Control animals received PEG 400 in place of FCR 1272 For topical induction, treatment area was shaved and treated with 10% formulation of sodium lauryl sulfate in Vaseline one day prior to treatment. Hypoallergenic patches were placed between and on the injection sites, covered with aluminium foil and fixed to the skin with strips of Fermoflex adhesive tape. In the treated group, patches had 0.5 mL 50% FCR 1272. In control group, patches had 0.5 mL PEG 400. Skin was cleaned with sterile saline after 48 hr exposure period.
3.3.4	Concentration Freunds Complete Adjuvant (FCA)	Yes
3.3.5	Challenge schedule	21 days after intradermal induction
3.3.6	Concentrations used for challenge	Hypoallergenic patches moistened with 0.5 mL of 50 % formulation and 0.5 mL 25 % formulation of the test substance were placed on the shaved left flanks of animals in the test and 1st control groups and fixed to the skin for 24 hours with fermoflex adhesive tape. As a control, patches moistened only with PEG 400 were fixed to right flank in same manner. After exposure period, area was washed with sterile saline and 21 hours later, shaved.
3.3.7	Rechallenge	No
3.3.8	Scoring schedule	48 and 72 hours after challenge
3.3.9	Removal of the test substance	Sterile saline

Document IIIA/ Section A6.1.5 — **Skin sensitisation**
Magnusson-Kligman Maximization Test

BPD Data set IIA/ Annex Point VI.6.1.5

3.3.10	Positive control substance	Non-concurrent; 2-mercaptobenzothiazole
3.4	**Examinations**	
3.4.1	Pilot study	Yes
3.5	**Further remarks**	Body weights were recorded
	4 RESULTS AND DISCUSSION	
4.1	**Results of pilot studies**	None
4.2	**Results of test**	
4.2.1	48h after challenge	No animals showed any skin reactions
4.2.2	72h after challenge	One animal in the test group showed slight skin reddening due to 50 % test substance.
4.2.3	Other findings	Body weights were unchanged by treatment.
4.3	**Overall result**	FCR 1272 showed no evidence of sensitizing properties.
	5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	In a guideline Magusson-Kligman Maximization test, 20 male guinea pigs were intradermally induced with 5% FCR 1272, topically induced (1 week later) with 50 % FCR 1272 and 21 days after first induction, challenged with 25 % and 50 % FCR 1272. Negative control animals were induced similarly with PEG 400 substituted for FCR 1272 then challenged with FCR 1272. A control patch with PEG 400 was used to challenge test animals at the same time as challenge with FCR 1272. Skin reactions were graded at 48 and 72 hours post-challenge.
5.2	**Results and discussion**	No skin reaction was seen in any animal in the control group. No skin reaction was seen in any animal in the test group at 48 hrs. At 72 hrs, one animal (out of 20) showed slight skin reddening at the 50% FCR 1272 treatment patch.
5.3	**Conclusion**	FCR 1272 (cyfluthrin) was not a skin sensitiser in an appropriately-conducted Magnusson-Kligman test.
5.3.1	Reliability	1
5.3.2	Deficiencies	None

Document IIIA/ Section A6.1.5 **Skin sensitisation**
Magnusson-Kligman Maximization Test

BPD Data set IIA/ Annex Point VI.6.1.5

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-28
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

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BPD Data set IIA/ Annex Point VI.6.2

Official use only

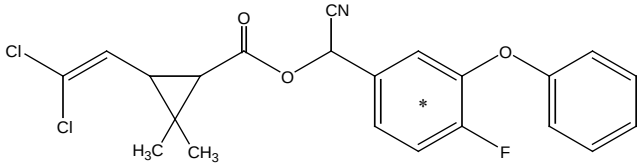
1 REFERENCE

1.1	**Reference**	[redacted] (1983). Biokinetic Part of the General Metabolism Studies in the Rat, [redacted] Report No. PH 11872 (F), BES Ref: M-038565-01-1 June 9, 1983 unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2	Companies with letters of access	
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 EPA Guidelines, comparable to Directive 87/302/EEC, Part B.
2.2	**GLP**	No (not required, as study started before June 30 1988).
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	
3.1.1	Radiolabelled material	[Fluorobenzene-U-^{14}C]cyfluthrin
3.1.2	Lot/Batch number	Not stated
3.1.3	Specification	As described in Section 2
3.1.3.1	Description	Viscous liquid
3.1.3.2	Purity	Radiochemical purity: 98%, 97,5% by gas chromatography Specific activity: 62 µCi/mg
3.1.3.3	Stability	The test compound was stable in the solution in which it was administered (tested for 4 hours and checked by TLC).
3.1.3.4	Radiolabelling	 * indicates label position
3.1.4	3.2 Unlabelled material	Cyfluthrin (Baythroid)

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3.1.5	Lot/Batch number	Pt-16003/79	
3.1.6	Specification	As described in Section 2	
3.1.6.1	Description	Viscous liquid	
3.1.6.2	Purity	Not stated	
3.1.6.3	Stability	Known to be stable from other studies cited in Section 3 of Doc IIIA	
3.2	**Reference materials**	Cyfluthrin, 97.5% purity with cis/trans ratio of 42/58.	
3.3	**Test Animals**		
3.3.1	Species	Rats	
3.3.2	Strain	Mura: [redacted]	
3.3.3	Source	[redacted]	
3.3.4	Sex	Male and female	
3.3.5	Age/weight at study initiation	average body weight of 200 g at the time of dosing.	X
3.3.6	Number of Animals per Group	Table 6.2/01-1 provides details of the number of animals per group.	
3.3.7	Control animals	No	
3.4	**Administration/ Exposure**	a) single intravenous dose of 0.5 mg/kg body weight (low dose level) b) single oral dose of 0.5 mg/kg bw (low dose level) c) a series of 14 daily oral doses of 0.5 mg/kg bw of non-radioactive substance, followed by a single oral radioactive dose at the same dose level after 24 hours (multiple dose) d) single oral dose of 10 mg/kg bw (high dose level) This dose-scheme was used with either sex	X
3.4.1	Concentration of test substance	The radioactive test substance was dissolved in toluene in a concentration of 8.4 mg/ml. After drying in a vacuum, the test material was diluted with the non-labelled compound and redissolved in NaCl solution containing 5% Cremophor EL. The radioactive concentration of the solution was analysed by liquid scintillation counting.	X
3.4.2	Specific activity of dose material	260 µCi/kg body weight in physiological NaCl solution containing 5% Cremophor EL.	
3.4.3	Volume applied	10 ml/kg body weight except for intraduodenal administration, in which case, 1 ml/kg body weight was administered.	
3.4.4	Exposure period	48 hours	
3.4.5	Sampling time	See Table A6.2 /01-1	
3.5	**Samples**		
3.5.1	Blood level investigation	Blood samples taken at every sampling time were separated into plasma and erythrocytes by centrifugation	X

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BPD Data set IIA/ Annex Point VI.6.2

3.5.2	3.6.2 Tissue Concentrations	Animals were sacrificed at the end of the dosing period using carbon dioxide gas. Tissue and organ samples taken were weighed in the wet state and again after lyopholisation. Finally they were homogenised.	X
3.5.3	Elimination in faeces, urine and air	During these excretion studies, animals were kept in special metabolism cages, which allowed separate and quantitative sampling of the excreta.	
3.5.4	Elimination in Bile	The bile fistulae were fixed one ay prior to administration of the test material.	
3.5.5	Determination of metabolites	This study is the toxicokinetic part of the general metabolism studies of cyfluthrin in rats (refer to Ecker,et al, 1983; Doc IIIA 6.2/02, and metabolites were not determined.	
3.6	**Statistical analysis**	Mean values and standard deviations were calculated for each data set. Plasma-curve analysis including calculation of the biokinetic parameters was carried out with the aid of the programme 'PHANAL' on a DEC_20 computer. The Mann and Whitney 'U-test' was used for tests on significance. Area under the concentration/time curve (AUC), elimination half-life, ($T_{1/2}$), time of peak concentration (T_{max}) and peak concentration were determined.	
		4 RESULTS AND DISCUSSION	
4.1	**Toxic effects, clinical signs**	There was no discussion of effects or clinical signs of the rats. At the top dose used (10 mg/kg) no obviously visible signs would be expected.	
4.2	**Recovery of labelled compound**	Recovery of radioactivity ranged from 91% to 106%.	
4.3	**Pharmacokinetic parameters**	Comparison of blood levels did not show any clear gender-related differences in T_{max}, $T_{1/2}$, and C_{max} at the low dose of 0.5 mg/kg, for single dose administration as well as for the multiple dose administration (series of 14 doses of unlabelled compound followed by 0.5 mg/kg of labelled compound). At the higher single dose, 10 mg/kg, the values were marginally higher in females. AUC was higher in females at both doses (Table A6.2/01-2)	X
4.4	**Tissue Concentrations**	The highest tissue concentrations were found in renal fat (higher in males than in females), while the lowest concentrations were found in the brain. Residual radioactivity in the body and single organs and tissues was higher after intravenous injection than following oral dosing. In females, the tissue concentrations were slightly higher than those for males, with the exception of renal fat. (See Table A6.2/01-5)	X

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4.5 Elimination from intact animals

The radioactivity was rapidly excreted from the body. Two days after oral administration only 1 % and 2 % of the administered radioactivity was still present in the animals. In this period, <0.001 % of the dosed radioactivity was exhaled in the breath, whereas more than 90 to 100 % of the dose was excreted in the urine and faeces. More than half of the radioactivity in the urine was excreted within the first 8 hours after administration

There was no dependence of the excreted amounts on dose level, sex and pre-treatment in orally dosed rats, but there was a marked difference between the sexes with respect to the route of excretion. Male rats excreted about 3 times more of the administered dose via the urine than via the faeces while in females rats this ratio was approximately 1.5. The amount of radioactivity excreted with time was dependent on the route of administration, with intravenous administration showing slightly slower excretion of radioactivity than oral administration (Table A6.2/01-3).

4.6 Biliary Excretion

Biliary elimination was investigated at the low-dose only, with the test material administered via intraduodenal injection. After 48 hours of exposure, recovery of dosed radioactivity was about 103%. Rats with biliary fistulae excreted about one-third of the recovered amount of radioactivity within 2 days, more than 50% of which was excreted within 2 hours and more than 90% within 6 hours of administration. A part of the radioactivity excreted with the bile was subject to enterohepatic circulation (Table A6.2/01-4).

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The toxicokinetic behaviour of cyfluthrin (FCR 1272) was investigated in rats by dosing cyfluthrin which was uniformly labelled with ^{14}C in the fluorobenzene moiety. This substance was administered to male and female rats orally at dose levels of 0.5 and 10 mg/kg body weight (bw), and intravenously at a dose level of 0.5 mg/ kg bw. In an additional test, male and female rats were treated with 14 daily oral doses of 0.5 mg/kg bw of the unlabelled compound followed by a single oral dose of the labelled substance at the same dose level. An additional group of, male rates received a dose of 0.5 mg/kg bw intraduodenally to investigate the biliary excretion of cyfluthrin. Exposure period was up to 48 hours, after which samples taken at various intervals. Radioactivity in the excreta, the body or in the single organs and tissues or bile was determined.

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5.2 Results and discussion

Absorption

Following oral administration the radioactivity was well absorbed by male and female rats. The comparison of the renally excreted radioactivity plus the radioactivity in the body (excluding gastrointestinal tract) at sacrifice (48 h) following intravenous and oral administration showed absorption of nearly 100 % of the administered dose in males and 90 % in females. This was largely confirmed by the results of the study in rats with bile fistulae. Based on the sum of the radioactivity excreted via the bile plus urine the absorption was calculated to be 90 % of the administered dose. Plasma curve analyses revealed that in all cases the absorption started after a lag-phase of about 13 minutes and could be described by a half-life of about 0.5 hours. There was no indication for a dependence on sex, dose level or pre-treatment.

		Distribution The radioactivity of cyfluthrin was slowly distributed from the intravascular space to the tissues. (half-life initially 2.1 h, later 20 h). The concentrations in plasma or tissues were given as relative concentration which was calculated by dividing the radioactivity measured per gram tissue or plasma by the radioactivity administered per gram body weight. This should allow a better comparison of the tissue concentrations between the different dose levels. Maximum relative plasma concentrations of approximately P = 2.3 were reached at both the low dose and the high dose level (uniform distribution = administered dose is uniformly distributed in the body volume: P = 1). The plasma concentrations were around 1.2 times higher in the females than those measured in the males. At the end of the study (48 h after administration) the mean relative body concentration was approximately P = 0.027. At this time the concentration in the fatty tissue was approx. 7 times higher (also higher in males than in females), whilst the lowest levels were to be found in the brain (P = 0.006 - 0.0006). The residual radioactivity in the body and single organs and tissues was higher after intravenous injection than following oral dosing. In females the tissue concentrations were always slightly above those for males with the exception of the renal fat. Excretion The radioactivity was rapidly eliminated from the body. Two days after oral administration only 1 % and 2 % of the dosed radioactivity was still present in the animals excluding the GIT. In this period <0.001 % was exhaled in the breath, whereas more than 90n to 100 % was excreted with the urine and faeces. More than 50 % of the renally excreted radioactivity was excreted within the first 8 hours after administration. In orally dosed groups, there was no dependence of the excreted amounts on dose level, sex and pre-treatment, but there was a marked difference between the sexes with respect to the route of excretion.. The ratio of urinary to faecal excretion was about 3 in the males and about 1.5 in the females. The amount of radioactivity excreted with time was dependent on the route of administration. After intravenous administration only 87 % of the administered dose was excreted within 2 days; approximately 6 % was still present in the carcass (excluding the gastrointestinal tract) at the time of sacrifice. The excretion ratio (urine/faeces) was 2.9 in males and 2.3 in females, respectively. Rats with biliary fistulae excreted about one-third of the recovered amount with the bile within 2 days, more than 50 % of this amount being excreted within 2 hours and more than 90 % within 6 hours following administration.	X
5.3	**Conclusion**	In rats cyfluthrin is completely and rapidly absorbed after oral dosing followed by fast elimination from the body. Thus > 90 % of the orally administered dose had been eliminated after two days. In bile-fistulated rats, one third of the radioactivity was eliminated in the bile within 2 days. A part of the dosed radioactivity was subject to enterohepatic circulation. The distribution of radioactivity from the intravascular space into the tissues was slow and generally low tissue concentrations were reached.. The highest concentration was found in the fat tissue.	X
5.3.1	Reliability	1	

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5.3.2	Deficiencies	The study reports only the toxicokinetic aspects and does not provide information on the metabolic reactions and identity of metabolites. However, these aspects are described in detail in another report ([redacted], 1983) summarised in Doc IIIA 6.2(03). Together, these two studies will fully meet the requirements.

Document. IIIA/ Section 6.2/01 Metabolism Studies in Animals – Basic Toxicokinetics

BPD Data set IIA/ Annex Point VI.6.2

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-25
Materials and Methods	*3.3.5 Age/weight at study initiation:* Apparently the animals have not been weighed as no individual body weights are given in the report. *3.4. Administration/Exposure:* In addition, 5 bile-cannulated males were given a single intraduodenal dose of 0.5 mg/kg bw. *3.4.1 Concentration of test substance:* The results of the concentration analysis are not included in the report. *3.5.1 Blood level investigation:* The sample volume is not reported. No absolute concentration data for plasma, C_{max} and AUC are given in the report. *3.5.2 Tissue Concentrations:* All data are presented as relative concentrations (percentage) only. No absolute tissue concentration data as µg or ng equiv/g are given in the report.
Results and discussion	*4.3 Pharmacokinetic parameters:* Comparison of blood levels did not show any clear gender-related differences in T_{max} and $T_{1/2}$ at the low dose of 0.5 mg/kg, for single dose administration as well as for the multiple dose administration (series of 14 doses of unlabelled compound followed by 0.5 mg/kg of labelled compound). At the single high dose, the values were marginally increased in females. C_{max} in plasma and AUC were consistently higher in females than in males. (Data given for AUC and C_{max} in Table A6.2/01–2 are incorrect; see CA-Table 1). *4.4 Tissue concentrations:* Applicant's version is accepted in general; however, actual tissue concentration data are required. *4.5 –5.1:* Applicant's version is acceptable. *5.2 Distribution:* According to the calculation of the RMS the maximum plasma concentrations were 30 % higher in females compared to males at the single low dose and about 45 % at the single high dose. In the repeat dose experiment they were about 20 % lower than in males. When expressed as area under the concentration time curve (AUC, µg x hr/mL), females in all oral experiments had higher values than males (1.7fold, 1.8fold, and 1.4fold at single low dose, single high dose, and repeated low dose, respectively).
Conclusion	Other conclusions: In rats cyfluthrin is completely and rapidly absorbed after oral dosing followed by fast elimination from the body. Absorption into the circulation was linear in the range of concentrations used. Females experienced 1.4 to 1.8fold higher plasma concentrations than males. More than 90 % of the orally administered dose had been eliminated after two days, about 60-70 % in urine and 25-35 % in faeces. One third of the radioactivity was excreted in the bile with subsequent enterohepatic circulation of about 50 % of the biliary excreted material. Tissue concentrations during the peak of exposure were not measured in this experiment. The highest residual concentration was found in the fat tissue. No other tissues showed any evidence for accumulation of test substance-related material.

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BPD Data set IIA/ Annex Point VI.6.2

Reliability	2
Acceptability	Acceptable
Remarks	-

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.2/01-1: Study Design, Cyfluthrin Toxicokinetics in Rats

Study phase	Dose levels	Number of animals per timepoint	Sampling time
Blood levels	0.5 mg/kg, i.v, p.o.	10 males, 10 females	0.17, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 24, 32, 48 hours after single dose (as well as for multiple dose)
	0.5 mg/kg, p.o. (multi-dosing)	5 males, 5 female	
	10 mg/kg, p.o.	5 males, 5 females	0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 24, 32, 48 hours after single dose
Tissue levels	0.5 mg/kg, i.v., p.o.	10 males, 10 females	48 hours after single dose
	0.5 mg/kg, p.o. (multi-dosing)	5 males, 5 female	48 hours after multiple dose
	10 mg/kg, p.o.	5 males, 5 females	48 hours after single dose
Elimination in urine, faeces	0.5 mg/kg, i.v, p.o.	9 males, 10 females	2, 4, 6, 8, 24, 32, 48 hours
	0.5 mg/kg, p.o (multi-dosing)	5 males, 5 females	
	10 mg/kg, p.o.	9 males, 9 females	2, 4, 6, 8, 24 48 hours after single dose
Elimination in bile	0.5 mg/kg, i.d.	5 males	1, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 42, 48 hours

i.v = intravenous; i.d = intraduodenal; p.o.= oral

RMS: Numbers of animals and sampling times are incorrect. See CA-Table 2

Table A6.2/01 –2: Toxicocokinetic parameters in Rats – Single High and Low Dose ^{14}C-cyflutrhin

Parameter		Low dose (0.5 mg/kg bw)		High dose (10 mg/kg bw)	
		Male	Female	Male	Female
Single dose					
T_{max}	Hours	1.7	1.8	1.9	2.4
C_{max}	ng eq/ml	2.2	2.8	1.8	2.7
$T_{½}$	Hours	0.54	0.5	0.58	0.68
AUC	mg eq. hr/ml	14	26	14	26
Multiple dose (14 daily doses of unlabelled cyfluthrin followed by one single dose of ^{14}C-cyfluthrin					
T_{max}	Hours	1.9	2.0		
C_{max}	ng eq/ml	2.2	1.9		
$T_{½}$	Hours	0.57	0.40		
AUC	mg eq. hr/ml	15	23		

RMS: Values for C_{max} and AUC are incorrect.

Table A6.2/01-3: Elimination of ^{14}C-cyfluthrin from rats after single oral or intravenous low dose, repeated oral low dose and single oral high dose

	Excretion (% administered dose)							
Single oral low dose (0.5 mg/kg bw)								
	Male				**Female**			
Time	**Urine**		**Faeces**		**Urine**		**Faeces**	
(h)	**i.v.**	**oral**	**i.v.**	**oral**	**i.v.**	**oral**	**i.v.**	**oral**
0 – 8	49.61	54.64	4.45	2.5	35.4	37.1	1.1	
0 – 24	61.7	67.5	19.9	21.3	55.9	55.5	20.4	28.6
0 – 48	65.0	69.6	22.5	23.0	60.8	60.7	26.0	36.6
Elimination	87.5	92.6			86.8	97.3		
Carcass	5.3	1.0			6.1	1.6		
Gastrointest.	0.7	0.2			0.7	0.6		
Total Recovery	**93.6**	**93.8**			**93.4**	**99.5**		
Repeated oral low dose (0.5 mg/kg bw)								
Time	**Male**				**Female**			
(h)		**Urine**		**Faeces**		**Urine**		**Faeces**
0-8		50.3		NS		34.5		NS
0-24		64.4		21.8		56.4		2)
0-48		66.4		23.6		60.4		34.6
Elimination		90.0				94.9		
Carcass		1.1				1.1		
Gastrointest.		0.22				0.31		
Total Recovery		**91.4**				**96.3**		
Single oral high dose (10 mg/kg bw)								
Time	**Male**				**Female**			
(h)	**Urine**		**Faeces**		**Urine**		**Faeces**	
0 – 8	42.6	49.1	NS	38.3	24.4	28.17	NS	19.3
0 – 24	69.3	62.9	30.4	31.0	59.5	48.6	23.9	42.3
0 – 48	71.8	65.5	32.7	32.2	65.5	52.9	30.4	45.5
Exhalation (0-48 h)	0.001				0.001			
Elimination	104.5	97.8			95.9	98.4		
Carcass	1.4	1.4			2.1	1.6		
Gastrointest.	0.29	0.23			0.41	0.45		
Total Recovery	**106.2**	**99.3**			**98.4**	**100.5**		

NS: No sample taken at this timepoint

Table A6.2/01 -4: Biliary excretion from Rats (Biliary Fistulae)

	Excretion (% administered dose)			
Time	**Male**			
(h)	Bile	Urine	Faeces	Total
0 – 6	31.9	40.2	NS	72.1
0 – 24	34.1	54.2	11.3	99.6
0 – 48	34.5	55.9	12.0	102.4
Elimination				102.4
Carcass				0.5
Gastrointest.				0.2
Total Recovery				**103.1**

NS: No sample taken at this timepoint

Table A6.2/01 -5 Relative concentration of radioactivity (P) in individual parts of the body of rats after application of [fluorophenyl-UL-14C] cyfluthrin

Admisnis-tration	Intra-venous	Oral	pretreat. Oral	Oral	Intra-venous	Oral	pretreatm. Oral	Oral
Dose (mg/kgbw)	**0.5**	**10**	**0.5**	**10**	**0.5**	**0.5**	**0.5**	**10**
sex	**m**	**m**	**m**	**m**	**f**	**f**	**f**	**f**
Time (h)	**48**	**48**	**48**	**48**	**48**	**48**	**48**	**48**
Body without GIT	0.06	0.011	0.013	0.016	0.066	0.018	0.013	0.018
Plasma	0.017	0.0094	0.011	0.86	0.018	0.032	0.024	0.026
Erythro-cytes	0.045	0.002	0.0031	0.0044	0.047	0.0056	0.0047	0.0052
Testes or ovaries	0.012	0.0016	0.0018	0.0021	0.027	0.032	0.016	0.03
Femur	0.02	0.0038	0.0023	0.0042	0.028	0.0054	0.0039	0.0043
Brain	0.0006	0.00065	0.00057	0.0007	0.0057	0.0013	0.00077	0.0012
Skin	0.062	0.013	0.018	0.018	0.097	0.022	0.018	0.025
Heart	0.034	0.0026	0.0027	0.0029	0.039	0.0067	0.0051	0.008
Spleen	0.013	0.0054	0.0036	0.0027	0.016	0.0048	0.0024	0.0036
Liver	0.014	0.02	0.021	0.025	0.015	0.034	0.023	0.030
Kidney	0.054	0.011	0.013	0.013	0.074	0.032	0.020	0.027
Renal fat	0.053	0.016	0.09	0.018	0.033	0.012	0.053	0.011
Adrenal glands	0.016	0.014	0.023	0.016	0.024	0.039	0.015	0.024

CA: Values are incorrect – see CA-Table 3.

Evaluation by Rapporteur Member State, CA-Tables

CA-Table 1 Toxicocokinetic Parameters in Rats – Single High and Low Dose ^{14}C-Cyfluthrin

Parameter		Low dose (0.5 mg/kg bw)		High dose (10 mg/kg bw)	
		Male	Female	Male	Female
Single dose					
T_{max}	Hours	1.7	1.8	1.9	2.4
C_{max}*	µg eq/mL	1.15	1.47	20.3	27.6
$T_{½}$	Hours	0.54	0.5	0.58	0.68
AUC*	mg eq. hr/mL	7.30	12.46	139.64	258.26
Multiple dose (14 daily doses of unlabelled cyfluthrin followed by one single dose of ^{14}C-cyfluthrin					
T_{max}	Hours	1.9	2.0		
C_{max}*	µg eq/mL	1.21	0.965		
$T_{½}$	Hours	0.57	0.40		
AUC*	mg eq. hr/mL	7.85	10.67		

* calculated from relative concentrations (P) given in the report and the dose applied; C_{max} taken from the highest mean value in plasma, AUC calculated by integrating the data for 0-48 hrs with a log trapeziodal function

CA-Table 2: Study Design, Cyfluthrin Toxicokinetics in Rats

Study phase	Dose levels mg/kg bw	Number of animals per time point	Sampling time
Blood levels	0.5, i.v., p.o.	5 M + 5 F	0.17, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 24, 32, 48 hours after single dose (as well as for multiple dose)
	0.5, p.o. (multi-dosing)	5 M + 5 F	
	10, p.o.	5 M + 5 F	0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 24, 32, 48 hours after single dose
Tissue levels	0.5, i.v., p.o.	5 M + 5 F	48 hours
	0.5, p.o. (multi-dosing)	5 M + 5 F	
	10, p.o.	9 M + 9 F	
Elimination in urine, faeces	0.5, i.v, p.o.	5 M + 5 F	urine: 2, 4, 6, 8, 24, 32, 48 hours faeces: 8, 24, 48 hours (10 mg/kg bw 4 animals: urine: 8, 24, 48 hours, faeces: 24, 48 hours)
	0.5, p.o (multi-dosing)	5 M + 5 F	
	10, p.o.	9 M + 9 F	
Elimination in bile	0.5, i.d.	5 M	1, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 42, 48 hours
Elimination in expired air	0.5, p.o.	4 M + 4 F	0 - 48 hours

i.v. = intravenous; i.d. = intraduodenal; p.o.= oral

CA-Table 3: Relative Concentration of Radioactivity (P) in Individual Parts of the Body of Rats after Application of [Fluorophenyl-UL-14C] Cyfluthrin

Admisnis-tration	Intra-venous	Oral	pretreat. Oral	Oral	Intra-venous	Oral	pretreatm. Oral	Oral
Dose (mg/kgbw)	**0.5**	**5**	**0.5**	**10**	**0.5**	**0.5**	**0.5**	**10**
sex	**m**	**m**	**m**	**m**	**f**	**f**	**f**	**f**
Time (h)	**48**	**48**	**48**	**48**	**48**	**48**	**48**	**48**
Body without GIT	0.06	0.011	0.013	0.016	0.066	0.018	0.013	0.018
Plasma	0.17	0.0094	0.011	0.0086	0.18	0.032	0.024	0.026
Erythro-cytes	0.045	0.002	0.0031	0.0044	0.047	0.0056	0.0047	0.0052
Testes or ovaries	0.012	0.0016	0.0018	0.0021	0.027	0.032	0.016	0.03
Femur	0.027	0.0038	0.0042	0.0028	0.027	0.0057	0.0078	0.0064
Brain	0.006	0.00065	0.00057	0.0007	0.0051	0.0013	0.00077	0.0012
Skin	0.062	0.013	0.018	0.018	0.097	0.022	0.018	0.025
Heart	0.034	0.0026	0.0027	0.0029	0.039	0.0067	0.0051	0.008
Spleen	0.13	0.0054	0.0036	0.0027	0.16	0.0048	0.0024	0.0036
Liver	0.14	0.02	0.021	0.025	0.15	0.034	0.023	0.030
Kidney	0.054	0.011	0.013	0.013	0.074	0.032	0.020	0.027
Renal fat	0.53	0.16	0.09	0.18	0.33	0.12	0.053	0.11
Adrenal glands	0.16	0.014	0.023	0.016	0.024	0.039	0.015	0.024

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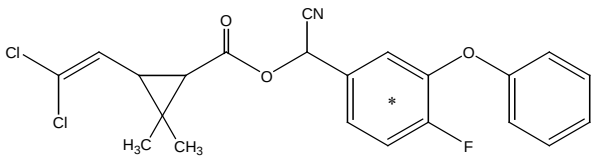
			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1983). [Fluorobenzene-UL-^{14}C]FCR 1272; [Fluorobenzene-UL-^{14}C]cyfluthrin: Metabolism part of the general metabolism studies in the rat, [redacted] Report PF 2059, BES Ref: M-034022-01-1 September 14, 1983 unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes EPA guidelines (NTIS, USD Commerce, Pesticide Assessment Guidelines, Subdivision F, Nov. 1982) The method is compatible to Directive 87/302/EEC, Part B.	
2.2	**GLP**	No (not required, as study started before June 30 1988).	
2.3	**Deviations**	None	
		3 MATERIALS AND METHODS	
3.1	**Test material**		
3.1.1	Radiolabelled material	[Fluorobenzene-UL-^{14}C]cyfluthrin	
3.1.2	Lot/Batch number	Not specified	
3.1.3	Specification	As described in Section 2	
3.1.3.1	Description	Not given	
3.1.3.2	Purity	Radiochemical purity 98%, Specific activity: 26.9 mci/mmole	
3.1.3.3	Stability	The test compound was stable in the solution in which it was administered (tested for 4 hours and checked by TLC).	X
3.1.3.4	Radiolabelling	 *indicates position of radiolabel	
3.2	**Unlabelled material**	Cyfluthrin	

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3.2.1	Lot/Batch number	Not specified	
3.2.2	Specification	As given in Section 2	
3.2.2.1	Description	Not stated	
3.2.2.2	Purity	Not stated	
3.2.2.3	Stability	Known to be stable from other studies cited in Section 3 of Doc IIIA.	
3.3	**Reference materials**	Analytical standards for the following metabolites were provided by the sponsor:FCR 3191 (= COE 5381/78, FPB-acid), FCR 3145 (4'OH-FPB-acid) , FCR 3343 (hippuric acid).	
3.4	**Test Animals**		
3.4.1	Species	Rats	
3.4.2	Strain	Sprague Dawley rats [redacted]	
3.4.3	Source	[redacted]	
3.4.4	Sex	Males and females	
3.4.5	Age/weight at study initiation	Weight ranged from 190-210 g.	X
3.4.6	Number of Animals per Group	4 males and females for each of the following groups: Group A: A single intravenous dose of radiolabelled cyfluthrin at a low dose level (0.5 mg/kg body weight (bw)) Group B: A single dose of radiolabelled cyfluthrin at a low dose level (0.5 mg/kg bw) Group C: 14 daily doses of non-labelled cyfluthrin, followed by a single dose of radiolabelled cyfluthrin, each dose at 0.5 mg/kg bw Group D: A single oral dose of radiolabelled cyfluthrin at a high dose of 10 mg/kg bw	
3.4.7	Control animals	None	
3.5	**Administration/ Exposure**	Oral or intravenous	
3.5.1	Concentration of test substance	The radioactive test substance was dissolved in toluene in a concentration of 8.4 mg/ml. After drying in a vacuum, the test material was diluted with the non-labelled compound and redissolved in NaCl solution containing 5% Cremophor EL. The radioactive concentration of the solution was analysed by liquid scintillation counting. (refer to Klein et. al., 1983, see Doc IIIA 6.2/01)	
3.5.2	Specific activity of dose material	26.9 mCi/mole the same amount of radioactivity (0.031 mCi/kg bw) was dosed to the animals of all groups in physiological NaCl solution containing 5% Cremophor EL.	
3.5.3	Volume applied	10 ml/kg bw	
3.5.4	Exposure period	48 hours	

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3.5.5	Sampling time	See Table 6.2/02-1
3.6	**Samples**	
3.6.1	Elimination in urine, faeces, air	Urine was collected 8, 24, and 48 hours after dosing and faeces were collected 24 and 48 hours after dosing. Faeces were individually lyophilised, homogenised and weighed and aliquots taken for radioassay immediately after freeze drying and homogenisation. The volume of urine samples was measured individually and aliquots were immediately taken for radioassay.
3.6.2	Tissue Concentrations	The animals were sacrificed using carbon dioxide gas 48 hours after administration of the radiolabelled chemical. The animal bodies were divided into skin, body without gastro-intestinal tract (GIT), and GIT, each of these parts being separately homogenized and radioassayed.
3.6.3	Determination of metabolites	Metabolite distribution was determined by TLC analysis of unextracted urine. Lyophilised faeces samples were extracted with trichloromethane (TCM) and the remainder vacuum-dried to remove solvent, weighed, and an aliquot assayed for radioactivity. The solids were re-extracted with methanol and the extracted solids were dried and assayed for radioactivity as were the extracts. Metabolite distribution in the faeces was determined by TLC analysis. TLC analysis TLC analyses were carried out on silica gel F254 (pre-coated, .25 mm thickness on 20x20 glass plates; E. Merck, Darmstadt, Federal Republic of Germany) using the following solvent systems: A: -TCM-methanol-ammonium hydroxide-water (67+28+4+1); B: -TCM-methanol-acetic acid-water (64+29+4+3); C: -toluene- Non-labelled standards were developed with the radioactive samples where appropriate. Standards were located by viewing the plate under UV light, while radioactive zones were located by autoradiography and quantified by use of a radio-chromatogram linear analyzer. Radiometric analysis To determine the ^{14}C radioactivity of wet biological samples like faeces, organs, and tissues, the material was freeze-dried and homogenized in a blender. The resultant pulverized material was compressed into two 2-cm planchets of infinite thickness (required sample amount: approx. 100 mg). The concentration of the radioactivity in the planchets was determined versus plastic standards in automated planchet counters using end-window proportional counting tubes (window thickness: 0.5 mg per square cm). The measurements were evaluated with computer assistance. The radioactivity of liquid samples like urine or faeces extracts was measured using liquid scintillation counters.
3.7	**Statistical analysis**	Mean values and standard deviations were calculated for each data set.
		4 RESULTS AND DISCUSSION
4.1	**Toxic effects, clinical signs**	There was no discussion of effects or clinical signs of the rats. At the high dose used (10 mg/kg bw) no obviously visible signs would be expected.

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4.2	**Recovery of labelled compound**	The recovery of radioactivity ranged from 90 to 97% of administered dose.	X
4.3	**Pharmacokinetic parameters**	This study is a follow-up to a previous study described in Doc IIIA6.2/01, which provided the complete toxicokinetic information. In this study, only the metabolism is reported.	
4.4	**Elimination from intact animals**	The results confirmed the findings in previous studies ([redacted] 1983 and [redacted], 1983) described in Doc IIIA 6.2/01 that excretion was very rapid. The excretion of radioactivity 48 hours after oral or intravenous administration of radiolabelled cyfluthrin was about 90% of the totally administered dose for animals of either sex at low and high dose levels. (Table A6.2/02-2).	
4.5	**Identification of Metabolites (intact rats)**	Table A6.2/02-3 gives the distribution of the metabolites in excreta 48 hours after administration of a single intravenous low dose, a single oral low or high dose and a repeated oral low dose. Data were obtained from pooled samples from each group, combining 50% each of the 0-8, 8-24 and 24-48 hours samples.	
		Metabolite 1 (FCR 3145-conjugate = 4'OH-FPB-acid-conjugate) was the main metabolite appearing almost exclusively in the urine and accounting for 41.1 - 52.0 % of the recovered radioactivity in the low dose groups and for about 36 % in the high dose group. Its free form (4'OH-FPB-acid= FRC 3145) was only measured in levels up to 11.0 % and appeared also in the faeces. The faeces of females contained higher amounts of this metabolite than those of males.	
		Metabolite 2 - presumably a conjugate of hydroxylated FCR 3343 (hippuric acid) - was a minor metabolite representing 3 % or less of the recovered radioactivity.	X
		COE 1938/78 (FCR 3191 = FPB-acid) also appeared mainly in the urine and accounted for up to 12 % of the radioactivity in the low dose groups and for up to 24.1 % in the high dose group, complementing for the relative lack of free and conjugated hydroxylated FCR 3145 (4'OH-FPB-acid) in this group.	
		The amounts of unchanged parent compound (FCR 1272) were relatively low except for the pre-treatment and the high dose group, where they reached levels of 11.6 - 19.0 % of the recovered radioactivity. This fact together with a relatively higher 4'-hydroxylation in the low dose groups indicates a slight dose dependence of metabolism.	X
		A metabolic pathway for cyfluthrin in animals proposed in Fig 6.2/02-1.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The excretion and metabolism of [fluorobenzene-UL-^{14}C] cyfluthrin by rats were studied under four sets of experimental parameters. Four groups of rats, each with 4 males and 4 females, were treated with radiolabelled cyfluthrin, as follows:	
		Group A – a single intravenous dose of the test material at 0.5mg/kg bw	
		Group B – a single oral dose of the test material at 0.5 mg/kg bw	
		Group C – 14 daily oral doses of non-labelled cyfluthrin , followed by a	

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		single oral dose of the radiolabelled test material, each dose at 0.5 mg/kg bw Group D – a single oral dose of radiolabelled test material at 10 mg/kg bw. The total study period was 48 hours. Urine samples were taken at 8, 24, and 48 hours after dosing and faeces samples at 24 and 48 hours after dosing. The animals were sacrificed and samples of skin, body less gastrointestinal tract (GIT), and GIT, each of these parts being homogenized and radioassayed. Urine and faeces samples were assayed for radioactivity using liquid scintillation counting. Metabolites were identified by TLC.	
5.2	**Results and discussion**	The administered radioactivity was rapidly excreted. Within 48 h after oral dosing more than 95 percent of the radioactivity was excreted, and more than 90 percent of the radioactivity was excreted in the same period after intravenous administration. The radioactivity was excreted mainly in urine, the renal to faecal excretion ratio being 2:1 to 3:1 for male animals and approx. 1.7:1 for females. Table A6.2/03-3 gives the distribution of metabolites in excreta, 48 hours after administration of the radiolabelled cyfluthrin. Metabolite 1 (FCR 3145-conjugate = 4'OH-FPB-acid-conjugate) was the main metabolite appearing almost exclusively in the urine and accounting for 41.1 - 52.0 % of the recovered radioactivity in the low dose groups and for about 36 % in the high dose group. Its free form (4'OH-FPB-acid) was only measured in levels up to 11.0 % and appeared also in the faeces. The faeces of females contained higher amounts of this metabolite than those of males. Metabolite 2 - presumably a conjugate of hydroxylated FCR 3343 (hippuric acid) - was a minor metabolite representing 3 % or less of the recovered radioactivity. COE 538/78 (= FCR 3191 = FPB-acid) also appeared mainly in the urine and accounted for up to 12 % of the radioactivity in the low dose groups and for up to 24.1 % in the high dose group, complementing for the relative lack of free and conjugated hydroxylated FCR 3145 (4'OH-FPB-acid) in this group. The amounts of unchanged parent compound (FCR 1272) were relatively low except for the pre-treatment and the high dose group, where they reached levels of 11.6 - 19.0 % of the recovered radioactivity. This fact together with a relatively higher 4'-hydroxylation in the low dose groups indicates a slight dose dependence of metabolism. A proposed metabolic pathway in rats is given in Figure A6.2/03-1. The first step in the process of biotransformation is the cleavage of the ester bond and oxidation to COE 538/78 (FCR 3191 = FPB-acid), which then undergoes further hydroxylation and conjugation or is bound to glycine with formation of the appropriate hippuric acids. After administration of the low dose of 0.5 mg/kg bw these metabolites make up around 65 %-72 % of the radioactivity balance, as compared with around 82 % after repeated administration of the low dose or administration of the higher dose.	X
5.3	**Conclusion**	The administered ^{14}C-labelled cyfluthrin was rapidly excreted, mainly via the urine. Cyfluthrin is metabolised initially by cleavage of the ester bond and oxidation to COE 538/78 (FCR 3191 = FPB-acid), which then undergoes	

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		further hydroxylation and conjugation.
5.3.1	Reliability	1
5.3.2	Deficiencies	Yes. No information was provided on toxicokinetic parameters in this study. However, this is addressed in another study (Klein et al., 1983), which is summarised under Doc IIIA 6.2 (01). These two studies will therefore fully meet the requirements. The studies on the metabolism of cyfluthrin in animals were restricted to [Fluorobenzene-UL-^{14}C]cyfluthrin. Permethric acid (DCVA), which would result from ester cleavage of cyfluthrin, but could not be detected with the radiolabel used, has been extensively investigated in mammals as part of other chemically similar pyrethroids like cypermethrin or permethrin. DCVA has been reported to undergo hydroxylation at the methyl groups followed by oxidation as well as conjugation before or after hydroxylation. DCVA and its metabolites and conjugates were mainly excreted in urine. These results may be also extrapolated to the metabolism of cyfluthrin (see the metabolic pathway given in figure A6.2/03-1).

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-23
Materials and Methods	*3.1.3.3 Stability:* Data from the TLC stability check are not part of the report. *3.1.5 Age/weight at study initiation:* A body weight range is not provided in the report. Body weight is stated to be about 200 g.
Results and discussion	*4.2 Recovery of labelled compound:* The recovery of radioactivity ranged from 87.4 to 97 % of administered dose. *4.5 Identification of Metabolites:* Alternatively to a dose-related change in metabolism, the increased amount of unchanged parent compound in the faeces of the pre-treatment and the high dose group might indicate that absorption from the gastrointestinal tract becomes saturated. The available data do not allow to discriminate between these two possibilities. FCR3343 (hippuric acid) accounted for 6.7 % in the multiple dose group and for <1 % in other groups. *5.2* The administered radioactivity was rapidly excreted. Within 48 h after oral dosing more than 95 percent of the radioactivity was excreted, and about 85 percent of the radioactivity was excreted in the same period after intravenous administration.
Conclusion	Applicant's version is adopted.
Reliability	1
Acceptability	Acceptable

Remarks	Formation and metabolism of the major hypothetical metabolite permetric acid was not investigated.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.2/02 -1: Study Design, Cyfluthrin Toxicokinetics in Rats

Study phase	Dose levels	Number of animals per timepoint	Sampling time
Elimination in urine	Groups A, B, C, D	4 males, 4 females per group	8, 24, 48 hours
Elimination in faeces and air	Groups A, B, C, D	4 males, 4 females per group	2, and 48 hours

Table A6.2/02 -2: Elimination of ^{14}C-cyfluthrin from rats after single intravenous or oral low dose, repeated oral low dose and single oral high dose

Time (hr)	Elimination (% administered dose)*							
	Male				Female			
	Urine	Faeces	Body**	Total	Urine	Faeces	Body**	Total
Group A: Single low dose (0.5 mg/kg bw), intravenous								
0 - 48	60.3	33.9	5.8	90.0	57.1	22.2	8.3	87.6
Group B: Single low dose (0.5 mg/kg bw), oral								
0 - 48	70.8	25.0	1.3	97.1	57.7	34.3	2.0	94.0
Group C: Multiple low dose (0.5 mg/kg bw), oral								
0 - 48	62.8	23.3	1.3	87.4	58.2	33.1	2.2	93.5
Group D: Single high dose (10 mg/kg bw), oral								
0 - 48	61.7	31.7	1.5	94.9	57.8	36.6	2.5	96.6

* Data are averages of values of four animals

** Sum of radioactivity found in skin, body without GIT, and GIT

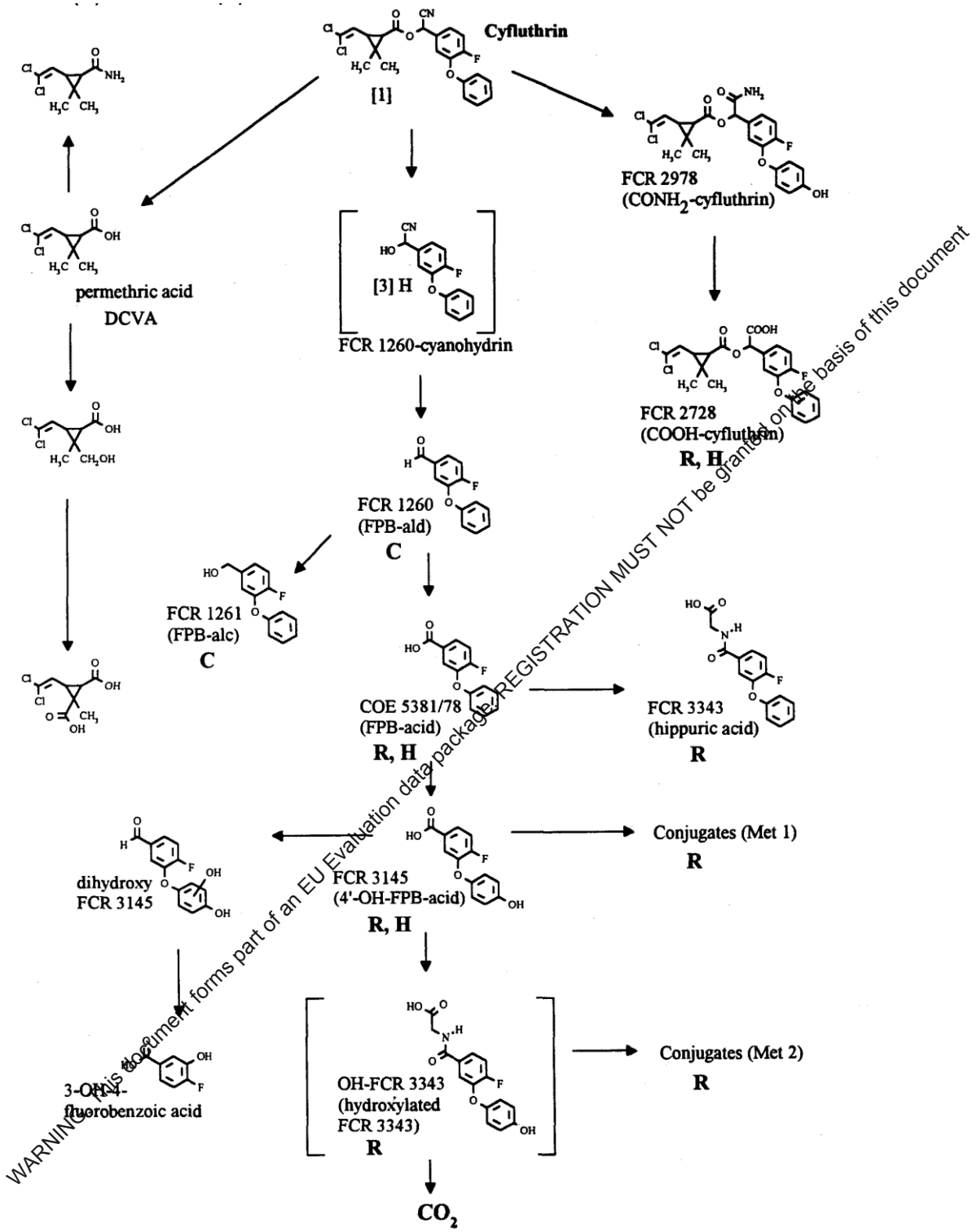
RMS: Mean faecal excretion in males after i.v. dosing was 23.9 % not 33.9 %. Total recovered radioactivity for females after administration of 10 mg/kg bw was 96.9 % not 96.6 %.

Table A6.2/02-3 Distribution of metabolites in the excreta of rats 48 hours after dosing (values given in % of the total recovered radioactivity in urine, faeces and body)

Administration	Dose mg/kg bw	Excretion	Sex	Metabolite 1[a]	4'OH-FPB-acid (FCR 3145)	Metabolite 2[b]	FCR 3343	FPB-acid (COE 538/78 = FCR 3191)	Cyfluthrin (FCR 1272)	Unknown	Un-extractable	Total
Intravenous[1]	0.5	Urine	M	47.0	2.9	1.5	2.4	12.1	-	1.1	-	67.0
Intravenous[1]	0.5	Faeces	M	0.1	1.9	0.1	-		0.4	24.1	8.0	26.6
(GROUP A)		**TOTAL**		**47.1**	**4.8**	**1.6**	**2.4**	**12.1**	**0.4**	**25.2**	**8.0**	**93.6**
Intravenous[1]	0.5	Urine	F	44.4	4.4	1.5	2.3	10.8	-	1.8	-	65.2
Intravenous[1]	0.5	Faeces	F	0.2	4.9	-	-	0.3	0.5	12.1	7.3	25.3
(GROUP A)		**TOTAL**		**44.2**	**9.3**	**1.5**	**2.3**	**11.1**	**0.5**	**13.9**	**7.3**	**90.5**
Oral[1]	0.5	Urine	M	52.0	3.8	2.1	3.6	10.1	-	1.4	-	73.0
Oral[1]	0.5	Faeces	M	-	1.1	0.1	-	-	0.1	19.5	4.9	25.7
(GROUP B)		**TOTAL**		**52.0**	**4.9**	**2.2**	**3.6**	**10.1**	**0.1**	**20.9**	**4.9**	**98.7**
Oral[1]	0.5	Urine	F	41.1	3.9	2.6	2.4	9.9	-	1.5	-	61.4
Oral[1]	0.5	Faeces	F	-	4.6	0.4	0.2	0.3	0.1	23.9	7.0	36.5
(GROUP B)		**TOTAL**		**41.1**	**8.5**	**3.0**	**2.6**	**10.2**	**0.1**	**25.4**	**7.0**	**97.9**
Multi-oral	0.5	Urine	M	47.4	3.2	3.0	6.7	10.5	-	1.0	-	71.8
Multi-oral	0.5	Faeces	M	-	0.8	0.1	-	0.1	11.6	8.9	5.2	26.7
(GROUP C)		**TOTAL**		**47.4**	**4.0**	**3.1**	**6.7**	**10.6**	**11.6**	**9.9**	**5.2**	**98.5**
Multi-oral	0.5	Urine	F	41.8	4.4	2.9	2.7	8.3	-	2.1	-	62.2
Multi-oral	0.5	Faeces	F	-	6.4	-	0.3	-	16.2	8.9	3.6	35.4
(GROUP C)		**TOTAL**		**41.8**	**11.0**	**2.9**	**3.0**	**8.3**	**16.2**	**11.1**	**3.6**	**97.6**
Oral	10	Urine	M	35.9	1.3	0.8	0.5	24.1	-	1.9	-	65.0
Oral	10	Faeces	M	-	1.2	-	0.4	-	16.6	10.2	5.0	33.4
(GROUP D)		**TOTAL**		**35.9**	**3.0**	**0.8**	**0.9**	**24.1**	**16.6**	**12.1**	**5.0**	**98.4**
Oral	**10**	Urine	F	35.2	4.5	2.1	17.3		-	0.5	-	59.6
Oral	**10**	Faeces	F	-	4.3	-	-		19.0	9.5	5.0	37.8
(GROUP D)		**TOTAL**		**35.2**	**8.8**	**2.1**	**17.3**		**19.0**	**10.0**	**5.0**	**97.4**

[a]Metabolite 1 = conjugate of FCR 3145 (4'OH-FPB-acid-conjugate); [b]Metabolite 2 = probably conjugate of hydroxylated FCR 3343 (hippuric acid)
1: in the original report, the header of the tables intravenous was mixed up with oral by mistake

Figure A6.2/02-1 Proposed Metabolic Pathway for Cyfluthrin in Animals



R = Rat; H = Hens; C= cow.

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Metabolism Studies in Farm Animals (Hen)

A6.2/04

BPD Data set IIA/ Annex Point VI.6.2

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1983). The distribution and metabolism of Baythroid™ in laying hens. [redacted] Bayer AG Report No. MR 86044. BES Ref: M-054113-01-1 Report date: September 20, 1983 Unpublished – (Ref. List location A 6.2./03) [redacted] (1995) Addendum 1: The distribution and metabolism of Baythroid in laying hens. Further characterization of residues in liver, [redacted] Report N°: BR-86044-1 BES Ref : M-053840-01-1 Report date: 23 October 1995 Unpublished – (Ref. List location A 6.2./04)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No. At the time the study was undertaken, no particular method was compulsory.	
2.2	**GLP**	No. When the study was performed, GLP was not compulsory.	X
2.3	**Deviations**	Not relevant.	
		3 MATERIALS AND METHODS	
3.1	**Test material**		
3.1.1	Radiolabelled material	[Phenyl-UL-^{14}C]cyfluthrin	
3.1.2	Lot/Batch number	Synthesised by Bayer AG for the purpose; no batch number provided.	
3.1.3	Specification	As given in Section 2	

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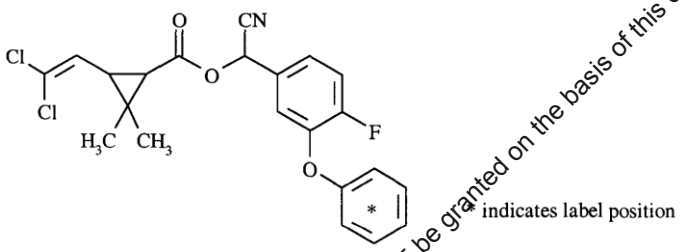
3.1.3.1	Description	Not stated	
3.1.3.2	Purity	Radiochemical purity, >99% (TLC), 21.74 mCi/mmole	X
3.1.3.3	Stability	Not reported	
3.1.3.4	Radiolabelling	 * indicates position of labelling	
3.2	**unlabelled material**	Cyfluthrin (Baythroid)	
3.2.1	Lot/Batch number	Not specified (only used to dilute radiolabelled compound)	
3.2.2	Specification	As given in Section 2	
3.2.2.1	Description	not given	
3.2.2.2	Purity	94.3%	X
3.2.2.3	Stability	Known to be stable from other studies cited in Section 3 of Doc IIIA.	
3.3	**Reference materials**	Cyfluthrin, 94.3% purity and the following reference materials, consisting of possible metabolites were used:	

FCR 2728 (COOH-cyfluthrin)	A-{[(3-2,2-dichloroethenyl)-2,2-dimethylcyclopropyl)carbonyl]oxy}-4-fluoro-3-phenoxybenzeneacetic acid
COE 538/78 (FPB-acid)	4-fluoro-3-phenoxybenzoic acid
FCR 2956 (Me-cyfluthrin)	Methyl α-{[(3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropyl)carbonyl] oxy}-4-fluoro-3-phenoxybenzene acetate
COE 263/78 (Me-FPB-acid)	Methyl-4-fluoro-3-phenoxybenzoate
FCR 2978 (COONH2-cyfluthrin)	2-amino-1-(4-fluoro-3-phenoxy-phenyl) –2 oxoethyl 3-(2,2-dicloro- ethenyl)-2,2-dimethylcyclopropane carboxylate
FCR 2947 (CONH2-FPB-acid)	4-fluoro-3-phenoxybenzamide
FCR 1260 (FPB-ald)	4-fluoro-3-phenoxybenzaldehyde
FCR 1261 (FPB-alc)	4-fluoro-3-phenoxybenzene methanol
FCR 3145 (4'-OH-FPB-acid)	4-fluoro-3-(4-OH-phenoxy) benzoic acid
FCR 3030 (FPB)	1-fluoro-2-phenoxybenzene
FCR 1271 (α-OH-FPB-ACN)	4-fluoro- α-hydroxy-3-phenoxybenzeneacetonitrile

3.4	**Test Animals**	Five laying hens (Gallus gallus, White Leghorn; source [redacted]), with average weight of 1300 g	X

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3.5	**Administration/ Dosing**		
3.5.1	Concentration of test substance	5 mg/kg bw containing [phenyl-UL-^{14}C] cyfluthrin adsorbed into α-lactose and delivered in gelatin capsules	
3.5.2	Specific activity of dose material	Each dose contained 0.11 mCi of ^{14}C.	X
3.5.3	Exposure period	Daily oral treatments with gelatin capsules for 5 successive days given between 9:00-10:00 a.m. at 24-hour intervals.	
3.5.4	Sampling	Eggs were collected at 24 hour intervals and weighed. The hens were sacrificed by asphyxiation with CO_2, 2 hours after the administration of the fifth dose. After sacrifice, the following tissues were taken: liver, heart, kidney, gizzard (minus lining and contents), fat (renal, omental, and subcutaneous), breast muscle, leg and thigh muscle, and skin (minus feathers).	
3.6	**Extraction and preparation of samples**		
3.6.1	Eggs	The eggs were separated from the shells, which were discarded; the egg contents were mixed thoroughly. Egg samples were kept frozen at -10°C until analysis.	
3.6.2	Tissues	The tissues were pulverized with dry ice and stored at *ca* -10°C until analyzed. Each sample was a composite of an equal amount of tissue from each of the five hens. All tissues except fat were homogenized in acetone/chloroform (2:1) and concentrated HC1. The homogenate was vacuum filtered and the filter cake was re-extracted twice with the same solvent mixture. The combined organic filtrate was concentrated to dryness and the oily residue taken up in hexane/acetonitrile (1:1) and partitioned. The acetonitrile was drained off, the process repeated, and the acetonitrile extracts were combined and dried with anhydrous sodium sulfate, radioassayed and subjected to TLC. The fat sample was homogenized in hexane with sodium sulfate, Hyflo Super-Gel, filtered, and the filter cake re-extracted with acetonitrile. The hexane and acetonitrile extracts were partitioned in a separating funnel. The acetonitrile layer was drained off and dried on anhydrous sodium sulfate. The filter cake was re-extracted again with a fresh acetonitrile and partitioned with the first hexane extract. The acetonitrile extracts were combined. The hexane and acetonitrile extracts from each tissue and egg sample were radioassayed. The extracts were concentrated on a rotary evaporator under vacuum at 30 to 40°C to a small volume (1 to 3 ml) for TLC analysis. Solid residues were subjected to acid hydrolysis. The filter cake from each tissue was refluxed with HCL and the hydrolysate extracted 3 times with diethyl ether or chloroform/acetone (2:1, v/v). The organic extract was dried over anhydrous sodium sulfate, radioassayed and concentrated for TLC analysis.	

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Polar residues were subjected to enzyme hydrolysis using β-glucuronidase, arylsufatase and protease. Samples were incubated for 20 hours at 37ºC.

3.7 ^{14}C determination and quantification

For total radioactive residue determinations, triplicate 0.25 g samples of tissues (5-hen composite of each tissue) and eggs were oxidized to $^{14}CO_2$ in a biological sample oxidizer, the $^{14}CO_2$ was trapped in an alkaline solution, scintillation fluid was added, and the samples were radioassayed in a liquid scintillation spectrometer.

3.8 Identification

Metabolites were characterized by TLC and identification was made through co-chromatography of reference materials.

Organosoluble residues were resolved by TLC (normal and reversed phase on silica gel plates). The mobile phase used for the normal phase TLC were hexane/p-dioxane/acetone/acetic acid (80:30:2:1) and toluene/diethyl ether/acetic acid (100:5:1). The mobile phase for the reverse phase TLC was acetonitrile/methanol/0.5 M NaCl (40:40:20). R*f* values for the reference standards are provided in Table 6.2/03-1. Non-radioactive components were detected by fluorescence quenching under UV-light. Radioactive components were detected by autoradiography.

For quantification of cyfluthrin and its metabolites, the silica gel associated with radioactive spots was scraped as bands into scintillation vials containing 10 ml of scintillation fluid. The radioactivity was measured by scintillation counting.

4 RESULTS AND DISCUSSION

4.1 Radioactive residues

Table 6.2/03-2 summarises the results. Total radioactive residues in the excretory organs (liver and kidneys) as well as in the gizzard were the highest and amounted to 4.7, 3.0 and 1.6 mg/kg cyfluthrin equivalents, respectively. All other tissues contained residues in the range of 0.1-0.4 mg/kg. Compared to tissues and organs the residue levels in eggs were much lower. The maximum concentration in eggs was 0.05 mg/kg which occurred 96 hours after the first oral administration.

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4.2	**Metabolites identification**	Between 37% and 83% of the total radioactive residue could be identified in organs, tissues and eggs. Besides the unchanged parent compound which accounted for 9 -75 % of the total radioactive residue depending on the organ or tissue, COE 538/78 (FPB-acid) and FCR 3145 (4'-OH-FPB-acid) were found as main metabolites, the highest levels being found in muscles, gizzard, skin and heart. FCR 2728 (COOH-cyfluthrin) was only found in eggs (6 %) and in liver, kidney and fat (only in traces). Except for kidneys (Ul, 12 %), unidentified metabolites always accounted for < 7 % of the total radioactive residue. Up to 40 % of the total radioactive residue was not extractable. Acid hydrolysis released additional radioactivity, which were mainly attributed to COE 538/78 (FPB-acid) FCR 3145 (4'-OH-FPB-acid). The radioactive residues characterised in various tissues and eggs included unmetabolised cyfluthrin plus FPBacid, 4'-OH-FPBacid and COOH-cyfluthrin. These results were confirmed by investigation conducted in 1995 by Haan, R. A. de. The same liver metabolites were observed, and, a large portion of residue was either very polar in nature or was bound to liver proteins. The polar residues (either extracted or hydrolyzed from proteins) were characterized as multi-functional compounds, but no absolute identifications were made. Quinone-type intermediates may have been formed during the metabolism of cyfluthrin in poultry liver. The reactive nature of these intermediates could lead to multiple sights of conjugation, the resulting metabolites could be easily integrated into the liver protein structure and identification would be extremely difficult.
4.3	**Metabolic pathway**	The proposed metabolic pathway is shown below. The major metabolic reactions involve the cleavage of the ester bond of cyfluthrin leading to FPB-acid which further undergoes hydroxylation at 4'-position to form the 4'-OH-FPBacid. A minor pathway includes the oxidation of cyfluthrin at the nitrile group to yield COOH-cyfluthrin.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Five laying hens were treated orally with gelatin capsules containing phenyl-UL-^{14}C-labelled cyfluthrin in a dose of 5 mg/kg bw per day for 5 successive days. The doses were given in the morning of each day and the hens were sacrificed 2 hours after the final treatment. Samples of tissues, organs and eggs (collected at 24 hour intervals) were analysed for total radioactive residue and for metabolites.

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5.2	**Results and discussion**	The radioactive compound was found to be distributed to all major organs and tissues. . Total radioactive residues in the excretory organs (liver and kidneys) as well as in the gizzard were the highest and amounted to 3.0, 4.7 and 1.6 mg/kg cyfluthrin equivalents, respectively. All other tissues contained residues in the range of 0.1-0.4 mg/kg. Compared to tissues and organs the residue levels in eggs were much lower. The maximum concentration in eggs was 0.05 mg/kg, which occurred 96 hours after the first oral administration. Between 37% and 83% of the total radioactive residue could be identified in organs, tissues and eggs. Besides the unchanged parent compound which accounted for 9 -75 % of the total radioactive residue depending on the organ or tissue, COE 538/78 (FPB-acid) and FCR 3145 (4'-OH-FPB-acid) were found as main metabolites, the highest levels being found in muscles, gizzard, skin and heart. FCR 2728 (COOH-cyfluthrin) was only found in eggs (6 %) and in liver, kidney and fat (only in traces). Except for kidneys (Ul, 12 %), unidentified metabolites always accounted for <7 % of the total radioactive residue. Up to 40 % of the total radioactive residue was not extractable. Acid hydrolysis released additional radioactivity, which were mainly attributed to COE 538/78 (FPB-acid) and FCR 3145 (4'-OH-FPB-acid). The radioactive residues characterised in various tissues and eggs included unmetabolised cyfluthrin plus FPBacid, 4'-OH-FPBacid and COOH-cyfluthrin. The proposed metabolic pathway is shown below in fig 6.2/03-1.
5.3	**Conclusion**	Un-metabolised cyfluthrin was the primary compound found in fat, eggs, gizzard, and breast muscle of hens orally dosed for 5 consecutive days with ^{14}C-cyfluthin. The metabolic pathway involves cleavage of the ester bond of cyfluthrin to yield FBP-acid, which was further hydroxylation 4'-position to form the 4'-OH-FPB-acid. A minor pathway is the oxidation of cyfluthrin at the nitrile group to yield COOH-cyfluthrin.
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	2006-08-29	
Materials and Methods	*1.4 Test animals:* 4 F in the study described in the addendum *1.5.2 Specific activity of dose material:* Each dose contained 0.13 mCi of ^{14}C in the second study. *2.2 GLP:* The study described in the addendum was carried out according to GLP. *3.1.3.2 and 3.2.2.2 Purity:* Radiochemical purity of ^{14}C-labelled test substance used in the second study was 100 %, 56.5 mCi/mmole; unlabelled material was of 98 % purity. *4.1 Test animals:* 4 laying hens (Gallus gallus, White Leghorn; [redacted]) were used in second study.	
Results and discussion	Applicant's version is adopted.	
Conclusion	Applicant's version is adopted.	
Reliability	1	
Acceptability	Acceptable	
Remarks	-	
	COMMENTS FROM ...	
Date	*Give date of comments submitted*	
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*	
Results and discussion	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Reliability	*Discuss if deviating from view of rapporteur member state*	
Acceptability	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Table 6.2/03-1: R*f* values for cyfluthrin and related compounds

Compound[1]	R*f* value/ mobile phase [2]		
	A	B	C
Cyfluthrin (FCR 1272)	0.61	0.86	0.18
FCR 2728 (COOH-cyfluthrin)	0.32	0.08	0.52
FCR 2956	0.69	0.72	0.16
FCR 2978	0.30	0.04	0.35
FCR 1260	0.67	0.62	0.50
FCR 1261	0.47	0.13	0.62
FCR 1271	0.70	0.63	0.51
FCR 2947	0.20	0.03	0.66
FCR 3030	0.87	0.91	0.42
COE 538/78 (FPB-acid)	0.44	0.14	0.74
COE 263/78	0.77	0.69	0.39
FCR 3145 (4'-OH-FPB-acid)	0.17	0.43	0.83

[1] See Point 3.3 (reference materials) for chemical formula of metabolites.

[2] A - hexane/p-dioxane/acetone/acetic acid (8-:30:2:1)
B - toluene/ethyl ether/acetic acid (100:5:1)
C - acetonitrile/metanol/0.5 M NaCl (4;4:2) for reversed phase chromatography.

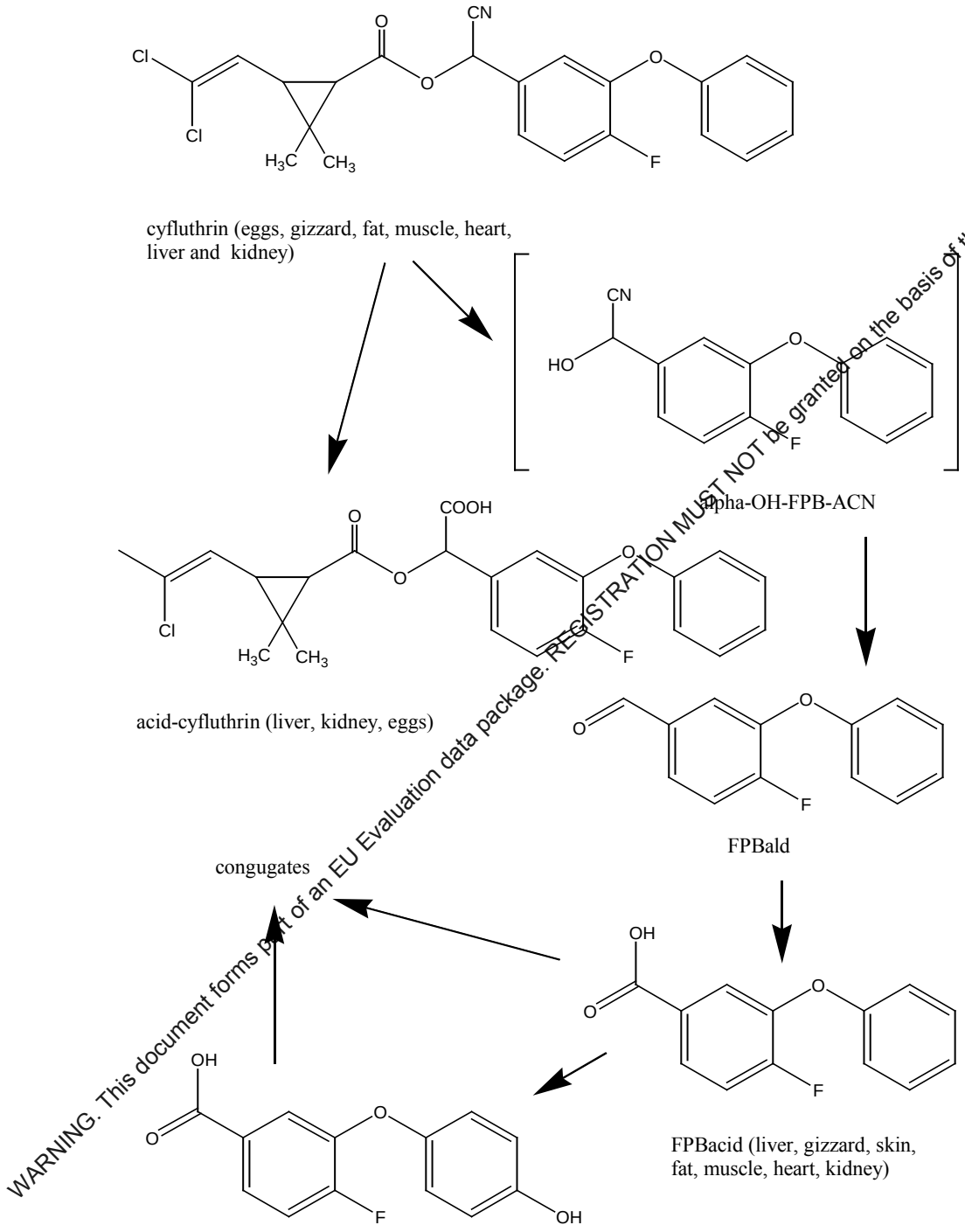
Table 6.2/03-2: Distribution of total radioactive residue (cyfluthrin equivalents) and metabolites in different organs, tissues and eggs after application of [phenyl-UL-^{14}C]cyfluthrin to laying hens (values are given in % of total radioactivity)

Dose mg/kg bw	Time (day)	Organ/ Tissue	FCR 1272 (cyfluthrin)	COE 538/78 (FPB-acid)	FCR 3145 (4'-OH-FPB-acid)	FCR 2728 (COOH-cyfluthrin)	Un-known[1]	Un-extract able[2]	Total residue mg/kg
5 x 5.0	5+ 2h	Liver	12	12	10	1	25	40	3.0
		Kidney	9	11	12	1	28	39	4.7
		Gizzard	40	13	11	0	22	14	1.6
		Breast muscle	39	15	11	0	16	19	0.2
		Skin	28	19	13	0	19	21	0.4
		Leg + thigh muscle	21	21	20	0	20	18	0.3
		Heart	16	26	19	0	20	19	0.4
		Fat	75	3	0	2	3	17	0.1-0.2
	96 h	Egg	56	4	7	6	2	25	0.05

[1] Unknown radioactivity consisted of 2 metabolites (U1 and U2); only one (U1) reached a level of 12% (kidney), usually levels were ≤7% of the total radioactivity. In eggs, U1 and U2 were not detected.

[2] Acid hydrolysis increased the extractability by 5-12%, identification increased by 2-4%, mainly COE538/78 and FCR 3145.

Fig 6.2/03-1: Proposed Metabolic Pathway in a Laying hens



Document IIIA/ Section A6.2/05 BPD Data set IIA/ Annex Point VI.6.2	Dermal absorption assessment	X
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	No data on dermal absorption is available on cyfluthrin active ingredient. **Solfac® EW 050** No data are available on Solfac EW 050. An in vivo dermal penetration study performed on beta-cyfluthrin FS125 and a comparative in vitro dermal penetration study using human and rat skin performed with beta-cyfluthrin are available and are considered as relevant for Solfac EW 050. This approach has been agreed with the Competent Authority (BAuA). These studies are summarised in Document IIIB6_4_01_Solfac and IIIB6_4_02_Solfac. **Raid® Cyfluthrin Foam** No data are available on Raid® Cyfluthrin Foam. EU guidance[i] on the assessment of dermal penetration suggests that, in the absence of data, a 100% dermal penetration factor should be assumed. This assumption may be modified to a lower default value of 10% based on expert judgement if sufficient data is provided to justify a value of only 10%. For cyfluthrin data are as follows: Physico-chemical properties: Chemicals fulfilling both criteria of molecular weight (MW) >500 and log P_{ow} (lipid solubility) –1 < or > 4 are accepted to have a dermal penetration rate of 10% or less. Cyfluthrin has MW 434 and log P_{ow} 5.95; values which (in common with most pyrethroids) are close to the MW criterion and well beyond the P_{ow} criterion. These physico-chemical values strongly suggest dermal penetration substantially less than 10%, as is seen for other pyrethroids (Table A6.2/05-1) which approach but do not exceed the MW criterion. Comparison is particularly valid with cypermethrin (MW 416, log P_{ow} 5.5, dermal penetration in humans 1.8%). Pyrethroids, including cyfluthrin, are derivatives of permithrinic acid; there is a strong read-across in basic chemical characteristics (on which dermal penetration largely depends). Comparison with other Pyrethroids: Publicly available data reporting dermal absorption of pyrethroids show consistently low values. Ray (2001)[ii] states that in humans, the bioavailability of dermal pyrethroids is about 1%. This statement cites Woollen et al (1992)[iii] who determined that urinary excretion of a 31 mg dose of cypermethrin as a soy-oil based formulation to the forearm of each of 6 volunteers, was approximately 1.2% of applied dose (compared to 36% of an oral dose). A review of pyrethroid toxicology by US ATSDR (2001)[iv] estimated dermal penetration at 0.3% - 1.8%, citing (in addition to Woollen et al, 1992) work by Eadsforth et al	

Document IIIA/ Section A6.2/05 BPD Data set IIA/ Annex Point VI.6.2	Dermal absorption assessment	X

(1988) [v] in which approximately 0.1% of a 25 mg cypermethrin dermal dose to each of 2 volunteers was recovered as metabolites in urine. Using permethrin as a dermal cream in scabies patients, van der Rhee et al (1989) estimated from urinary elimination data, absorption of a 1250 mg dose to be approximately 0.5%. Ross et al (2001)[vi] report 2% in vivo dermal absorption of permethrin in humans.

Data publicly available for other pyrethroids listed in Annex 1 to EU Directive 91/414, shows all to have comparable molecular weight and particularly log P_{ow}, to cyfluthrin. Where specific dermal absorption values are given, these are low; in cases where data are absent, the 10% default value has been accepted—including in the case of β-cyfluthrin, a specific sterochemical formulation of cyfluthrin.

Further Considerations:

Human skin is thicker, and for the great majority of chemicals is less permeable, than rat skin. Available data suggests this to be particularly true for the pyrethroids. Scott and Ramsey (1987)[vii] found rat skin to be 20 times more permeable to cypermethrin than was human skin. Ross et al (2001) calculate a rat:human ratio of 14 for dermal absorption of permethrin; the rat:human ratio for this pyrethroid was greater than for any of the other 12 chemicals (all non-pyrethroids) for which data was presented. The 91/414 EFSA Annex 1 critical endpoints for esfenvalerate shows human skin to be very much more protective than rat skin. These data offer further weight of evidence that the dermal penetration of cyfluthrin in humans will be very low, and assumption of a 10% default to be both protective, and consistent with assessment of other pyrethroids.

Dermal penetration is frequently influenced by solvents; the dermal penetration of agrochemicals must be anticipated to be product (formulation) specific. Penetration data of the active material in isolation is therefore not useful or informative, relative to data from a formulation.

Conclusion:

A number of factors are described which, combined, fulfil a requirement for "Expert judgement" and permit selection of a 10% default value for dermal penetration:

- Physico-chemical properties approach values where assumption of a 10% default absorption is suggested in guidance;
- EU evaluation of cyfluthrin under Directive 91/414 has concluded that a default assumption of 10% absorption is appropriate for this compound, in the absence of other data;
- Data from other comparable pyrethroids suggests a dermal penetration value as low as 3% in humans, would remain a protective overestimate.
- Human skin appears particularly refractory to pyrethroid absorption

Document IIIA/ Section A6.2/05 BPD Data set IIA/ Annex Point VI.6.2	Dermal absorption assessment	X
	Current risk assessments for cyfluthrin are satisfied by a dermal penetration factor of 10%. Given current knowledge, a specific dermal penetration study to refine dermal absorption to a value of 10% or less is therefore not an appropriate use of animals.	

Undertaking of intended data submission [ ]	*Give date on which the data will be handed in later (Only acceptable if test or study is already being conducted and the responsible CA has agreed on the delayed data submission.)*	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Heading	Should read "Document IIIA/ Section A6.2/07" (has to be amended following amendments submitted by the applicant).
Date	2013/05/15
Evaluation of applicant's justification	Solfac EW 050: There are two studies submitted on dermal absorption of beta-cyfluthrin (beta-cyfluthrin FS125) in a flowable seed protection formulation summarised in Documents IIIB6.4. Due to the high variability in the in vitro and in vivo data and the overestimated value of in vivo absorption in the rat study (only the amount of radioactivity in tape stripe 1 was reported separately and could be excluded) RMS proposes to use the in vitro data derived with human skin for risk assessment and refrain from a triple test calculation. Based on the result from the in vitro study with human skin and considering uncertainties due to high variations, dermal absorption of the active substance cyfluthrin was estimated to be 1 % for the high (1.25 mg/cm2) and low dose (0.38 mg/cm2) in humans. *Raid Cyfluthrin Foam:* 10 % (based on expert judgement) Physico-chemical properties: The MW of cyfluthrin is 434.3 g/mol. Therefore, the default value of 25%/75% should be applied. Only chemicals fulfilling both criteria of molecular weight (MW) >500 and log Pow (lipid solubility) –1 < or > 4 are accepted to have a dermal penetration rate of 10% or less. Comparison with other Pyrethroids: The comparison is based mostly on the review articles and not on the guideline studies. Therefore this comparison has not any regulatory significance. Additionally, some of the values are extremely underestimated, f. ex. Cypermethrin 0.1-1.8%; while in Annex I submission up to 13 % are assumed.

Document IIIA/ Section A6.2/05 **BPD Data set IIA/ Annex Point VI.6.2**	**Dermal absorption assessment**	X
Conclusion	Acceptable	
Remarks	-	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Table A6.2/05-1: Comparison of dermal penetration characteristics for pyrethroids (particularly where listed in Annex 1 to EC 91/414)

Compound name	Dermal absorption	MW	Log P_{ow}	Product[1]	Reference
Alpha-cypermethrin	10% default assumed	416.3	5.5		http://europa.eu.int/comm/food/plant/protection/evaluation/existactive/list_alpha_cypermethrin.pdf
Deltamethrin	10% default assumed	505.2	4.6	25EC	http://europa.eu.int/comm/food/plant/protection/evaluation/existactive/list1-31_en.pdf
Esfenvalerate	0.6% (human epidermis) 44% (rat skin)	419.9	6.24	EC	http://europa.eu.int/comm/food/plant/protection/evaluation/existactive/list1-15_en.pdf
Lambda-cyhalothrin	<0.3% (human, in-vivo)	449.9	7.0	5EC	http://europa.eu.int/comm/food/plant/protection/evaluation/existactive/list1-24_en.pdf
Permethrin	2% (human, in-vivo)	391.3	6.1		Ross et al (2001)
Cypermethrin	0.1 –1.8% Human in-vivo	416.3	6.6		Handbook of Pesticide Toxicology, Vol 2 p 1268; Eadsforth (1988); Woollen (1992)

1: Product: type is that which appears to be that used for Annex 1 approval, not confirmed.

[i] "Guidance Document on Dermal Absorption" Sanco/222/2000 rev 7,. European Commission, Health and Consumer Protection Directorate-General, Directorate E. 19 March 2004

[ii] Ray DE (2001) "Pyrethroid Insecticides: Mechanisms of Toxicity, Systemic Poisoning Syndromes, Paresthesia, and Therapy" (in) Kreiger R (ed) "Handbook of Pesticide Toxicology", 2nd Edn. p1294. Academic Press: San Diego (2001)

[iii] Woollen BH, Marsh JR, Laird WJ, Lesser JE (1992) "The metabolism of cypermethrin in man: differences in urinary metabolite profiles following oral and dermal administration". Xenobiotica 22(8) 983-991.

[iv] Agency for Toxic Substances and Disease Registry (2003): "Toxicological Profile for Pyrethrins and Pyrethroids" Available at: http://www.atsdr.cdc.gov/toxprofiles/tp155.pdf.

[v] Eadsforth CV, Bragt PC, van Sittert NJ (1988) "Human dose-excretion studies with pyrethroid insecticides cypermethrin and alphacypermethrin: relevance for biological monitoring". Xenobiotica 18(5): 603-14

[vi] Ross, JH, Driver, JH, Cochran, RC, Thongsinthusak, T, Krieger, RI (2001) "Could pesticide toxicology studies be more relevant to occupational risk assessment?". Ann. Occup. Hyg. 45(1001):S5-S17.

[vii] Scott RC, Ramsey JD (1987) "Comparison of the in vivo and in vitro percutaneous absorption of a lipophillic molecule (cypermethrin, a pyrethroid insecticide). J.Invest.Dermatol. 89(2) 142-146.

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A6.2/06

BPD Data set IIA/ Annex Point VI.6.2

Metabolism Studies in Farm Animals (Dairy Cow)

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1983). Metabolism of Baythroid™ in a Dairy Cow, [redacted] Bayer AG Report No. MR86043, BES Ref: M-052654-01-1 Report date: September 27, 1983 Unpublished – (Ref. List location A 6.2./05) Addendum: [redacted] (1985) Baythroid - Identity of major components in cow liver, [redacted] Bayer AG Report No.: MR-8897, BES Ref: M-053779-01-1 Report date: 05.03.1985 Unpublished – (Ref. List location A 6.2./06)
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No. At the time the study was undertaken, no particular method was compulsory.
2.2	**GLP**	No. When the study was performed, GLP was not compulsory.
2.3	**Deviations**	Not relevant.

3 MATERIALS AND METHODS

3.1	**Test material**	
3.1.1	Radiolabelled material	[Phenyl-UL-^{14}C]cyfluthrin
3.1.2	Lot/Batch number	Synthesised by Bayer AG for the purpose; no batch number provided.
3.1.3	Specification	As given in Section 2.

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Metabolism Studies in Farm Animals (Dairy Cow)

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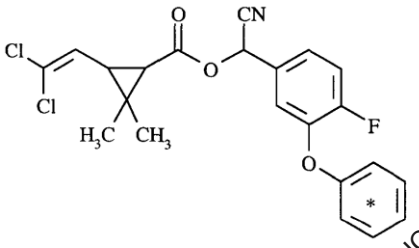
3.1.3.1	Description	
3.1.3.2	Purity	Radiochemical purity, 98.5% (TLC) Specific activity, 21.74 mCi/mmole
3.1.3.3	Stability	Not reported
3.1.3.4	Radiolabelling	 * indicates position of labelling
3.2	**Unlabelled material**	Cyfluthrin (Baythroid)
3.2.1	Lot/Batch number	Not specified (only used to dilute radiolabelled compound)
3.2.2	Specification	As given in Section 2 of Doc IIIA.
3.2.2.1	Description	As given in Sections 2 and 3 of Doc IIIA
3.2.2.2	Purity	98%
3.2.2.3	Stability	Known to be stable from other studies cited in Section 3 of Doc IIIA.
3.3	**Reference substances**	Cyfluthrin, 98% purity . Reference substances, consisting of possible metabolites were used:

FCR 2728 (COOH-cyfluthrin)	A-{[(3-2,2-dichloroethenyl)-2,2-dimethylcyclopropyl)carbonyl]oxy}-4-fluoro-3-phenoxybenzeneacetic acid
COE 538/78 (FPB-acid)	4-fluoro-3-phenoxybenzoic acid
FCR 2956 (Me-cyfluthrin)	Methyl α-{[(3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropyl)carbonyl] oxy}-4-fluoro-3-phenoxybenzene acetate
COE 263/78 (Me-FPBacid)	Methyl-4-fluoro-3-phenoxybenzoate
FCR 2978 (CONH2-cyfluthrin)	2-amino-1-(4-fluoro-3-phenoxy-phenyl) –2 oxoethyl 3-(2,2-dicloro- ethenyl)-2,2-dimethylcyclopropane carboxylate
FCR 2947 (CONH2-FPB-acid)	4-fluoro-3-phenoxybenzamide
FCR 1260 (FPB-ald)	4-fluoro-3-phenoxybenzaldehyde
FCR 1261 (FPB-alc)	4-fluoro-3-phenoxybenzene methanol
FCR 3145 (4'-OH-FPB-acid)	4-fluoro-3-(4-OH-phenoxy) benzoic acid
FCR 3030 (FPB)	1-fluoro-2-phenoxybenzene
FCR 1271 (α-OH-FPB-ACN)	4-fluoro- α-hydroxy-3-phenoxybenzeneacetonitrile

3.4	**Test Animals**	484 kg lactating Holstein cow (Bos taurus, source: [redacted]) X

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Metabolism Studies in Farm Animals (Dairy Cow)

3.5	**Administration/ Dosing**	
3.5.1	Concentration of test substance	0.5 mg/kg bw in gelatin capsules containing [phenyl-UL-^{14}C]cyfluthrin
3.5.2	Specific activity of dose material	Each dose contained 3.25 mCi of ^{14}C.
3.5.3	Exposure period	Daily oral treatments with gelatin capsules for 5 successive days after the evening milking.
3.5.4	Sampling time	Milk was collected each morning and evening during the study. The cow was sacrificed after the morning milking on the sixth day. Samples of brain, heart, liver, kidney, omental fat, subcutaneous fat, renal fat, round muscle, flank muscle and loin muscle were collected.
3.6	**Extraction and preparation of samples**	
3.6.1	Milk	All samples were radioassayed. Aliquots were extracted three times with six volumes of acetone/chloroform (2:1) each time. The combined extracts were concentrated to dryness, the residue was dissolved in hexane, and the hexane was partitioned three times with an equal volume of acetonitrile each time. The hexane and acetonitrile fractions were measured for volume and radioassayed. The acetonitrile fraction was concentrated, radioassayed and subjected to TLC and HPLC.
3.6.2	Tissues	Tissues collected were cut, frozen and pulverised to a fine powder with dry ice pellets, and aliquots radioassayed. Aliquots of all tissues except fat were extracted with five volumes of acetone/chloroform (2:1). HC1 was added to liver and kidney samples. The tissues were homogenized and filtered, combining the filtrates which were evaporated, and the residue partitioned in hexane/acetonitrile. The acetonitrile fractions were concentrated, radioassayed and subjected to TLC and HPLC. Aliquots of fat were homogenized with sodium sulfate, Hyflo Super-Gel and hexane. The homogenate was filtered, and the filter cake was blended with acetonitrile. The homogenate was filtered, and the filtrate was partitioned with the hexane. Blending with acetonitrile and subsequent partitioning with the same hexane was repeated twice more. The hexane and combined acetonitrile fractions were each measured for volume and radioassayed. The acetonitrile fraction was concentrated, radioassayed and subjected to TLC and HPLC.
3.7	**^{14}C determination and quantification**	Liquids samples were analysed by liquid scintillation counting (LSC). Solid samples were analysed for total radioactivity by combusting aliquots to $^{14}CO_2$, trapping the $^{14}CO_2$ in an alkaline solution, and mixing the solution with scintillation fluid for LSC.

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Metabolism Studies in Farm Animals (Dairy Cow)

3.8 Identification

Metabolites were characterized by TLC and HPLC. Identification was made through co-chromatography of reference materials.

TLC was on silica gel plates using solvent system acetic acid/diethyl ether/toluene (1:5:100) and acetone/hexane/p-dioxane/acetic acid (2:80:30:1). R*f* values for the reference standards are provided in Table 6.2/05-1. Detection of reference standards was by fluorescence quenching under UV-light. Radioactive components were detected by autoradiography.

HPLC was conducted on a C_{18} reverse phase column using gradient elution (5% aqueous methanol to 100% methanol at 4%/min). Components were detected using an ultraviolet detector (243 nm) and a flow through radioactivity monitor set in series.

4 RESULTS AND DISCUSSION

4.1 Radioactive residues

Results are summarized in Table 6.2/05-2.

Milk:

Milk production, monitored before and during the study, was virtually unchanged throughout the period. The concentration of radioactivity in the milk reached a maximum of 0.079 mg/kg cyfluthrin equivalents approximately 72 hours after daily dosing began, but declined thereafter, even though another dose was given.

Tissues:

Concentrations of total radioactive residues (cyfluthrin equivalents) in the tissues are given in Table 6.2/05-2. The highest levels were found in liver (0.622 mg/kg), fat (0.195 mg/kg) and kidney (0.188 mg/kg). Brain, skeletal muscle and heart muscle had the lowest radioactive residues ranging from 0.015 to 0.040 mg/kg.

4.2 Metabolites identification

Analysis of the milk showed that 98% of the radioactive residue was organosoluble, and all the extracted radioactivity consisted of unchanged cyfluthrin.

Nearly all of the radioactive residue in each tissue was extractable with organic solvents (>93 %) and in most tissues and organs it consisted only of unchanged parent compound. In heart and kidney 29% and 43% of the residue, respectively, was FCR 1261 (FPB-alc), the remainder being cyfluthrin. The residue in liver was composed of cyfluthrin (86%) and FCR 1260 (FPB-ald, 14%). In total more than 93% of the radioactive residue could be identified.

The proposed metabolic pathway is shown in Fig 6.2/04-1

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Metabolism Studies in Farm Animals (Dairy Cow)

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5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The metabolism of cyfluthrin was studied in a 484 kg lactating Holstein cow (Bos Taurus) that had received daily oral treatments with gelatin capsules containing [phenyl-UL-^{14}C]cyfluthrin in a dose of 0.5 mg/kg bw for 5 successive days after the evening milking. Milk was collected each morning and evening during the study. The cow was sacrificed after the morning milking of the sixth day. Samples of tissues and organs were taken and analysed for total radioactive residues and metabolites.

5.2 Results and discussion

Milk production, monitored before and during the study, was virtually unchanged throughout the period. The concentration of radioactivity in the milk reached a maximum of 0.079 mg/kg cyfluthrin equivalents approximately 72 hours after daily dosing began, but declined thereafter, even though another dose was given. Analysis of the milk showed that 98% of the radioactivity was organosoluble, and all of this extracted radioactivity consisted of unchanged cyfluthrin.

Concentrations of total radioactive residues (cyfluthrin equivalents) in the tissues are given in Table 6.2/05-2. The highest levels were found in liver (0.622 mg/kg), fat (0.195 mg/kg) and kidney (0.188 mg/kg). Brain, skeletal muscle and heart muscle had the lowest radioactive residues ranging from 0.013 to 0.040 mg/kg. Nearly all of the radioactive residue in each tissue was extractable with organic solvents (>93 %) and in most tissues and organs it consisted only of unchanged parent compound. In heart and kidney 29% and 43% of the residue, respectively, was FCR 1261 (FPB-alc), the remainder being cyfluthrin. The residue in liver was composed of cyfluthrin (86 %) and FCR 1260 (FPB-ald , 14 %). In total more than 93 % of the radioactive residue could be identified.

The proposed metabolic pathway is shown below.

5.3 Conclusion

The parent, cyfluthrin is the main residue in milk and tissues after orally dosing a dairy cow for 5 consecutive days with ^{14}C-cyfluthin. In liver, heart and kidney, the metabolism is through cleavage of the ester bond with further hydroxylation and conjugation.

5.3.1 Reliability 1

5.3.2 Deficiencies No

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Metabolism Studies in Farm Animals (Dairy Cow)

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	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/08/28
Materials and Methods	*1.4 Test animals:* 3 F + 1F (control) in the study described in the addendum.
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Tale 6.2/05-1 TLC R*f* values for cyfluthrin and possible metabolites

Compound[1]	R*f* values	
	Acetic acid/ diethyl ether/toluene (1:5:100)	Acetone/hexane/p-dioxane/acetic acid (2:80:30:1)
Cyfluthrin (FCR 1272)	0.83	0.49
FCR 2728(COOH-cyfluthrin)	0.07	0.23
FCR 2956(Me-cyfluthrin)	0.71	0.54
FCR 2978 (CONH2-cyfluthrin)	0.05	0.21
FCR 1260(FPB-ald)	0.61	0.56
FCR 1261 (FPB-alc)	0.18	0.37
FCR 1271(α-OH-FPB-ACN)	0.64	0.64
FCR 2947(CONH2-FPB-acid)	0.04	0.12
FCR 3030 (FPB)	0.91	0.83
FCR 3145(4'-OH-FPB-acid)	0.03	0.07
COE 538/78(FPB-acid)	0.14	0.31
COE 263/78(Me-FPBacid)	0.65	0.74

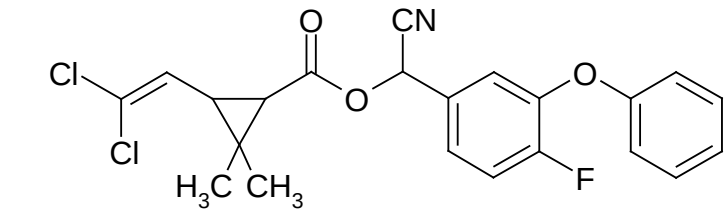
[1] See Point 3.3 (reference materials) for chemical formula of metabolites.

Table 6.2/05-2 Distribution of total radioactive residue (cyfluthrin equivalents) and metabolites in different organs, tissues and milk after application of [phenyl-UL-^{14}C]cyfluthrin to dairy cows (values are given in % of total radioactive residue)

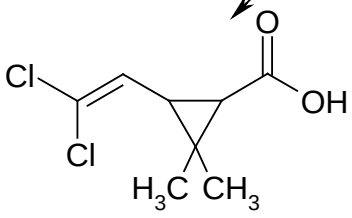
Dose mg/kg bw	Time (day)	Organ/ Tissue	Cyfluthrin (FCR 1272)	FPB-ald (FCR 1260)	FPB-alc (FCR 1261)	% extract-able	Total radioactive residue (mg/kg)
5 x 0.5	6	Muscle, round	99	ND	ND	99	0.022
		Muscle, shoulder	98	ND	ND	98	0.021
		Muscle, loin	100	ND	ND	100	0.028
		Fat, renal	100	ND	ND	100	0.229
		Fat, subcutaneous	93	ND	ND	93	0.122
		Fat, omental	96	ND	ND	96	0.234
		Heart	71	ND	29	100	0.040
		Kidney	56	ND	43	99	0.188
		Liver	86	14	ND	100	0.622
		Brain	-	-	-	-	0.015
	0-6	Milk	98[1]	ND	ND	[1]	0.039-0.079

[1] 98% of the radioactivity was organosoluble and consisted only of unchanged parent compound.

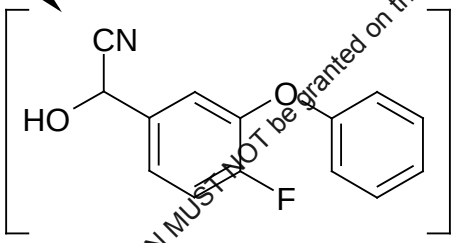
Fig 6.2/05-1: Proposed Metabolic Pathway in a Dairy Cow



cyfluthrin (FCR 1272)
milk, fat, muscle, heart liver and kidney

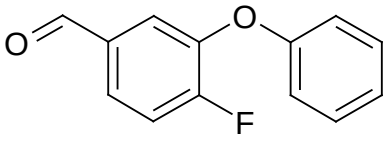


Permethric acid, DCVA

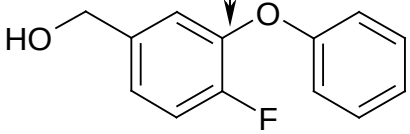


alpha-OH-FPB-ACN (FCR 1271)

conjugates



FPB-ald (FCR1260)
liver



FPB-alc (FCR 1261)
heart, kidney

Document IIIA/ Section A6.3.1 **BPD Data set IIA/ Annex Point VI.6.4**	**Repeated dose toxicity (oral)**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	This test used as a range-finding test is not required as an adequate sub-chronic toxicity study is available in a rodent and summarized in section A6.4.1	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2006-09-06	
Evaluation of applicant's justification	There are two existing 28-d studies in the rat available: [redacted] 1980, [redacted] 1982. These studies were submitted for PPP assessment and were classified "acceptable" ([redacted] B) and „acceptable (supplementary)“ ([redacted] However, submission of these studies would not alter the current risk assessment. Therefore, these studies are regarded dispensable. [redacted] FCR 1272 - Subacute Oral Toxicity Study on Rats - Report no.: 9039 (March 28, 1980); [redacted] (Dates of exp. work: April 1979 - July 1979). [redacted] FCR 1272-Short-term Toxicity Test on Rats (4-week feeding and 4-week recovery tests) - Report no.: 215 (March 15, 1982); [redacted] (Dates of exp. work: October 15 - November 13, 1981).	
Conclusion	Non-submission of the 28 d oral studies is acceptable.	
Remarks	-	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	

Document IIIA/ Section A6.3.1	Repeated dose toxicity (oral)
BPD Data set IIA/ Annex Point VI.6.4	
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section 6.3.2

Short-term repeated dose toxicity

21-day dermal toxicity, rats

BPD Data set IIA/ Annex Point VI.6.4

			Official use only
		1 REFERENCE	
1.1	**Reference**	*From addendum 2 of the monograph p39* [redacted] (1996) 21-day dermal toxicity study with technical grade BAYTHROID in rats. [redacted] Bayer AG Study No.: 107437, BES Ref.: M-041225-01-1 Report date: 6 June 1996 Unpublished	X
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes US-EPA-FIFRA, Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Guideline 82-2, November 1984. Report cites OECD Guidelines for Testing of Chemicals, Section 4, Guideline 411, May 1981, but is actually compliant with Guideline 410 as stated in the addendum on the monograph from PPP dossier. Japan Ministry of Agriculture, Forestry and Fisheries, Guidance on Toxicology Study Data for Application of Agricultural Chemical Registration, 59 NohSan No. 4200, January 1985	
2.2	**GLP**	Yes	
2.3	**Deviations**	None that compromised the validity of the study results	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Test material:	
3.1.1	Lot/Batch number	Technical grade cyfluthrin,	
3.1.2	Specification	Purity: 95.5-95.9 %,	
3.1.2.1	Description	batch no.: 2030025/BF9140-23.	
3.1.2.2	Purity	Chemical stability in dose solution and application pads confirmed by chemical, analysis of replicate samples.	
3.1.2.3	Stability		
3.2	**Test Animals**		
3.2.1	Species	Sprague-Dawley rats [redacted]	

Document IIIA/ Section 6.3.2

BPD Data set IIA/ Annex Point VI.6.4

Short-term repeated dose toxicity

21-day dermal toxicity, rats

3.2.2	Strain	approx. age (Day 0): males 8 wk, females 10 wk	
3.2.3	Source	[redacted]	
3.2.4	Sex		
3.2.5	Age/weight at study initiation		
3.2.6	Number of animals per group		
3.2.7	Control animals		
3.3	**Administration/ Exposure**	Study performed according the OECD Guideline No. 410, as stated in the addendum on the monograph from PPP dossier, no deviations to this guideline were noted.	X
3.3.1	Duration of treatment	Groups of 8 male and 8 female Sprague-Dawley rats were treated dermally for 22 and 23 days, respectively with cyfluthrin at doses of 0, 100, 340 and 1000 mg/kg bw/d.	
3.3.2	Frequency of exposure		
3.3.3	Postexposure period		
3.3.4	Dermal	Study performed according the OECD Guideline No. 410, as stated in the addendum on the monograph from PPP dossier, no deviations to this guideline were noted.	
3.3.4.1	Area covered		
3.3.4.2	Occlusion		
3.3.4.3	Vehicle	Doses were administered with a moistened pad to the shorn backs such that males received 17 and females received 18 occlusive applications within the 22-23-day treatment, each exposure period lasting at least 6 hours. An additional eight rats of each sex were included with the control and high-dose group and were maintained for two weeks beyond treatment.	X
3.3.4.4	Concentration in vehicle		
3.3.4.5	Total volume applied		
3.3.4.6	Duration of exposure		
3.3.4.7	Removal of test substance		
3.3.4.8	Controls		
3.4	**Examinations**	Study performed according the OECD Guideline No. 410, as stated in the addendum on the monograph from PPP dossier, no deviations to this guideline were noted.	
3.4.1	Observations		
3.4.1.1	Clinical signs		
3.4.1.2	Mortality		
3.4.2	Body weight	The following in-life observations and measurements were taken: mortality (daily), body weight (minimum weekly), food consumption (weekly), clinical observations including irritation at the dose site (daily) and ophthalmologic exams (before study start and shortly before sacrifice).	
3.4.3	Food consumption		
3.4.4	Water consumption		
3.4.5	Ophthalmoscopic examination		

Document IIIA/ Section 6.3.2

BPD Data set IIA/ Annex Point VI.6.4

Short-term repeated dose toxicity

21-day dermal toxicity, rats

3.4.6	Haematology	
3.4.7	Clinical Chemistry	
3.4.8	Urinalysis	
3.5	**Sacrifice and pathology**	The following terminal post-mortem observations and measurements were performed: haematology, clinical biochemistry, organ weights (ovaries, liver, kidneys, heart, testicles, thyroid with parathyroid, lungs, spleen, adrenals and brain) and incidence of lesions at gross necropsy. Histopathological examination of the following organs was performed in 0 and 1000 mg/kg bw/d rats of both sexes (from both non-recovery and recovery groups): adrenals, brain, heart, kidneys, liver, lungs, ovaries, parathyroid, pituitary, skin (treated), spleen, testicles and thyroid).
3.5.1	Organ Weights	
3.5.2	Gross and histopathology	
3.5.3	Other examinations	
3.5.4	Statistics	
3.6	**Further remarks**	In addition, "Skin, treated" was examined in 100 and 340 mg/kg bw/d rats of both sexes to establish a no-observed-effect level (NOEL). Gross lesions were processed and examined microscopically in all dose groups.
		4 RESULTS AND DISCUSSION
4.1	**Observations**	No occurrence of moribundity or incidence of mortality was observed. Compound-related clinical signs like red discharge from the nose (1000 mg/kg bw/d males), scabbing at the dose site (1000 mg/kg bw/d males, > 340 mg/kg bw/d females) and urine stains (1000 mg/kg bw/d females) were observed. See Table A 6.3.2-1
4.1.1	Clinical signs	
4.1.2	Mortality	
4.2	**Body weight gain**	No statistically significant decrements in rates of body weight gain were observed.
4.3	**Food consumption and compound intake**	Food consumption in males and females of the 1000 mg/kg bw/d group was significantly reduced on the first week of treatment (approx. by -13 % and -11 % in males and females, respectively).
4.4	**Ophthalmoscopic examination**	No ocular abnormalities were observed.
4.5	**Blood analysis**	No variations in clinical chemistry or haematological parameters were considered as a result of treatment.
4.5.1	Haematology	
4.5.2	Clinical chemistry	
4.5.3	Urinalysis	
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	No variations in organ weights were considered as a result of treatment.

4.6.2	Gross and histopathology	At gross necropsy crusty zones were present on skin from a number of animals at 340, 1000 mg/kg bw/d or 1000 mg/kg bw/d recovery group. Additionally, a discoloured zone was noted on treated skin from one 1000 mg/kg bw/d female and a raised zone in one 340 mg/kg bw/d male was noted. Histopathologically epidermal and dermal alterations were in some males and females at 1000 mg/kg bw/d and in one female at 340 mg/kg bw/day and were considered as treatment related. These microscopic alterations were predominantly characterised by an extensive area of moderate to marked ulceration with bordering epidermis thickened by acanthosis and hyperkeratosis. There was inflammatory cell infiltration in the exposed dermis underlying the ulceration. An accompanying minimal to slight dermal fibrosis in two 1000 mg/kg bw/d females was also noted. Histopathological alterations from the recovery animals were similar to those observed in non-recovery animals. These responses were manifested in one male and two females of the 1000 mg/kg bw/d recovery group. These responses were slightly less severe than from animals sacrificed shortly after treatment indicating some progress towards lesion repair.
4.7	**Other**	

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Technical grade BAYTHROID was applied topically to 6 groups of 8 animals/sex with the following average doses: 0, 100, 340, 1000 mg/kg bw/day (0, 1000 mg/kg bw/day for recovery groups). Doses were administered with a moistened pad to shorn backs. The following in-life observations and measurements were taken: mortality (daily), body weight (minimum weekly), food consumption (weekly), clinical observations including irritation at the dose site (daily), and ophthalmological exams (before study start and shortly before sacrifice). The following terminal post mortem observations and measurements were performed: haematology, clinical biochemistry, organ weights, incidence of lesions at gross necropsy, and histopathologic examination of selected organs.
5.2	**Results and discussion**	No occurrences of moribundity, or incidences of mortality, no ocular abnormalities, and no statistically significant decrements in rates of body weight gain were observed. Food consumption in males and females of 1000 mg/kg/day was significantly reduced on the first week of treatment. Compound-related clinical signs like red discharge from the nose of 1000 mg/kg/day males, scabbing at the dose site from males and females treated with 1000 mg/kg/day as well as 340 mg/kg/day females, and urine stains from 1000 mg/kg/day females were observed. No variations in clinical chemistry or haematological parameters, or in organ weights which were considered as a result of treatment. At gross necropsy crusty zones were present on skin from a number of animals from the 340, 1000 mg/kg/day or 1000 mg/kg/day recovery group. Additionally, at necropsy a discoloured zone was noted on treated skin from one 1000 mg/kg/day female and a raised zone in one 340

Document IIIA/ Section 6.3.2

BPD Data set IIA/ Annex Point VI.6.4

Short-term repeated dose toxicity

21-day dermal toxicity, rats

		mg/kg/day male was noted. Histologically, epidermal and dermal alterations in treated skin were observed from some males and females of the 1000 mg/kg/day group and one female from the 340 mg/kg/day group and were considered as treatment related. These microscopic alterations were predominately characterized by an extensive area of moderate to marked ulceration with bordering epidermis thickened by acanthosis and hyperkeratosis. There was inflammatory cell infiltration in the exposed dermis underlying the ulceration. An accompanying minimal to slight dermal fibrosis in two 1000 mg/kg/day females was also noted. Histopathologic alterations from the recovery animals were similar to those observed in non-recovery animals; these responses were manifested in one male and two females from the 1000 mg/kg/day recovery group. These responses were slightly less severe than from animals sacrificed shortly after treatment thus indicating some progress towards lesion repair.	
5.3	**Conclusion**		
5.3.1	LO(A)EL	The LOAEL/LOEL for systemic toxicity was established at 1000 mg/kg bw/d based on reduced food consumption and red nasal discharge.	
5.3.2	NO(A)EL	The NOAEL/NOEL for systemic toxicity was established at 340 mg/kg bw/d based on reduced food consumption and red nasal discharge at 1000 mg/kg bw/d. Local adverse skin effects were observed at 340 mg/kg bw/d, so that an overall NOEL for systemic and local toxicity of 100 mg/kg bw/d can be derived.	
5.3.3	Other		x
5.3.4	Reliability	1	
5.3.5	Deficiencies	None that compromised the validity of the study.	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2012/12/17
Reference	Study number in report is given as 95-122-ES.
Materials and Methods	Applicants version is acceptable with the following addition: *3.3 Administration/Exposure:* Actual mean doses were 0, 113, 376 and 1077 mg/kg bw/d and 1083 mg/kg bw/d in the high dose recovery group. *3.3.4.5 Total volume applied*:
Results and discussion	Applicant's version is adopted.
Conclusion	5.3.3 Systemic effects

Document IIIA/ Section 6.3.2

Short-term repeated dose toxicity

21-day dermal toxicity, rats

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	NOAEL 376 mg/kg bw/d), LOAEL 1077 mg/kg bw/d Local effects: NOAEC 0.62 - 0.87 mg/cm^2; Median: 0.75 mg/cm^2 and a concentration of 5.7 % (w/w) (corresponding to 113 mg/kg bw/d) LOAEC 2.09 - 2.90 mg/cm^2; Median: 2.50 mg/cm^2 and a concentration of 19.4 % (w/w) (corresponding to 376 mg/kg bw/d) The calculation is made on the assumption that the evaporation of acetone is complete and all pads were rinsed with 0.4 ml H_2O prior to treatment. Cyfluthrin concentration was varying depending on the weight of the animals. The dose range was determined by calculation of cyfluthrin concentration obtained by the study animals of the lowest and the highest weights 200 g and 340 g and application area 36 cm^2 and 44 cm^2 respectively.
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A 6.3.2-1: Summary of Clinical Observations for Rats Treated with Technical Grade BAYTHROID in a Repeated Dose 21-Day Dermal Toxicity Study

Males						
Sign	**Target Dose (mg/kg/day)**					
	0.0	100	340	1000	0.0 (REC)	1000 (REC)
Lesion						
Scab Dose Site						
Incidence (%)	0(0)	0(0)	0(0)	5(62)	0(0)	6(75)
Mean onset (days)	0	0	0	10	0	11
Non-Dose Site						
Incidence (%)	0(0)	3(37)	2(25)	3(37)	4(50)	5(62)
Mean onset (days)	0	5	8	8	5	8
Stains						
Red						
Incidence (%)	0(0)	0(0)	1(12)	1(12)	0(0)	1(12)
Mean onset (days)	0	0	10	10	0	5
Urine						
Incidence (%)	0(0)	0(0)	0(0)	1(12)	0(0)	0(0)
Mean onset (days)	0	0	0	3	0	0
Females						
Sign	**Target Dose (mg/kg/day)**					
	0.0	100	340	1000	0.0 (REC)	1000 (REC)
Lesion						
Scab Dose Site						
Incidence (%)	0(0)	1(12)	6(75)	6(75)	2(25)	6(75)
Mean onset (days)	0	16	11	11	21	17
Non-Dose Site						
Incidence (%)	0(0)	3(37)	5(62)	8(100)	2(25)	6(75)
Mean onset (days)	0	2	2	8	2	6
Stains						
Red						
Incidence (%)	0(0)	0(0)	1(12)	0(0)	0(0)	0(0)
Mean onset (days)	0	0	22	0	0	0
Urine						
Incidence (%)	0(0)	0(0)	0(0)	2(25)	0(0)	2(25)
Mean onset (days)	0	0	0	2	0	1

Document IIIA/ Section A6.3.3 **BPD Data set IIA/ Annex Point VI.6.4**	**Repeated dose toxicity (Inhalation)**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	This test used as a range-finding test is not required as an adequate sub-chronic toxicity study is available in a rodent and summarized in section A6.4.3	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2006-09-06	
Evaluation of applicant's justification	There are two existing 28-d inhalation studies in the rat available: [redacted], 1989 [redacted] 1980. These studies were submitted for PPP assessment and were classified "acceptable". However, submission of these studies would not alter the current risk assessment. Therefore, these studies are regarded dispensable. [redacted] 4-Week Inhalation Toxicity Study - Report no.: 18565 (November 28, 1989); [redacted] (Dates of exp. work: February - March 1989) [redacted] FCR 1272, Subacute Inhalational Toxicity Study on Rats - Report no.: 9373 (August 20, 1980); [redacted] y (Dates of exp. work: experiment 1: June 07 - 29, 1979, experiment 2: November 1 - 23, 1979)	
Conclusion	Non-submission of the 28 d inhalation studies is acceptable.	
Remarks	-	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	

Document IIIA/ Section A6.3.3	Repeated dose toxicity (Inhalation)
BPD Data set IIA/ Annex Point VI.6.4	
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section 6.4.1.1

Subchronic oral toxicity test

3 Month Oral Toxicity, Rats

BPD Data set IIA/ Annex Point VI.6.4

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1983) Three-month subacute toxicity study of FCR 1272 in rats. [redacted] File No.: 264 BES Ref.: M-044018-01-1 Report date: 31 Jul 1983 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes Testing guideline of MAFF, Japan (47 Nosei, No. 2538, June 14, 1972) and EPA Guideline (Proposed Guidelines for registering Pesticides in the U.S., Federal Register. Vol. 43. No. 163, August 22, 1978)	
2.2	**GLP**	No. When the study was performed, GLP was not compulsory (as study started before June 30 1988).	
2.3	**Deviations**	Main deviations from Directive 87/302/EEC, Part B, (OECD guideline 408) are: electrolytes, total bilirubin, γ-glutamyl transpeptidase and albumin were not determined on blood. Ophthalmologic examinations were not performed. These deviations do not affect the scientific integrity of the study.	X
		3 MATERIALS AND METHODS	
3.1	**Test material**	FCR 1272 (cyfluthrin)	
3.1.1	Lot/Batch number	Batch No. 816170019	
3.1.2	Specification	As given in sections 2	
3.1.2.1	Description	Not given	
3.1.2.2	Purity	95%	
3.1.2.3	Stability	Confirmed by concentration check	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague-Dawley	
3.2.3	Source	[redacted]	
3.2.4	Sex	Males & females	

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3.2.5	Age/weight at study initiation	Approximately 4 weeks of age at test initiation, weight range 117-141 g for males and 94-115 g for females.
3.2.6	Number of animals per group	112 male, 112 female (28 per dosage group including satellite groups of 8 animals each for testing reversibility of effects after a 4-week recovery period)
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	Oral by dietary administration
3.3.1	Duration of treatment	3-month feeding plus 4-week recovery
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	4 week
3.3.4	Oral	
3.3.4.1	Type	Dietary
3.3.4.2	Concentration	0-100-300-1000 ppm corresponding to: 6.21, 18.98 or 60.90 mg/kg bw/day in males, 7.29, 21.22 or 68.47 mg/kg bw/day in females
3.3.4.3	Vehicle	Incorporated into the powdered basal diet [redacted] at the respective concentrations
3.3.4.4	Concentration in vehicle	See 3.3.4.2
3.3.4.5	Total volume applied	Not applicable, diet given *ad-libitum*
3.3.4.6	Controls	Plain diet only
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Daily for any adverse changes in appearance or behaviour.
3.4.1.2	Mortality	Checks for mortality and moribundity on days 1, 3, 7, 14, thereafter bi-weekly and at the end of the recovery period.
3.4.2	Body weight	Weekly.
3.4.3	Food consumption	Yes, 3 times weekly.
3.4.4	Water consumption	No
3.4.5	Ophthalmoscopic examination	No
3.4.6	Haematology	Erythrocyte count, leukocyte count, haemoglobin, MCV, MCH, MCHC, thrombocyte count, haematocrit, differential blood count (after 3 months and at the end of the recovery period).

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3 Month Oral Toxicity, Rats

3.4.7	Clinical Chemistry	Alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, creatinine, urea, glucose, cholesterol, total protein (after 3 months and at the end of the recovery period)
3.4.8	Urinalysis	Glucose, blood, protein, pH, ketone bodies, bilirubin, urine sediment (leukocytes, erythrocytes, small round epithelial cells, phosphates, urates, bacteria, sperm, magnesium ammonium phosphates, squamous epithelia, erythrocyte casts) (after 3 months and at the end of the recovery period).
3.5	**Sacrifice and pathology**	All descendants and surviving animals were sacrificed and subjected to histopathological examination.
3.5.1	Organ Weights	Brain, submaxillary glands, heart, lungs, liver, spleen, kidneys, adrenals, testes, ovaries, pituitary (after 3 months and at the end of the recovery period).
3.5.2	Gross and histopathology	Bone marrow, brain, cecum, colon, duodenum, heart, ileum, jejunum, kidneys, liver, lungs, mesenteric lymph nodes, oesophagus, ovaries, pancreas, peripheral nerves (femoral, sciatic), pituitary, prostate, rectum, skeletal muscle (femur, gastrocnemius), spinal cord cervical, thoracic, lumbar), spleen, stomach, submaxillary glands, testes, thyroid, thymus, trachea, urinary bladder, uterus (after 3 months and at the end of the recovery period).
3.5.3	Other examinations	
3.5.4	Statistics	The significance of intergroup differences were checked using Student's t-test. Data on differential leukocyte counts were analysed after reverse sinusoidal transformation. Data on blood biochemical tests and organ weights were analysed after using Smirnoff's rejection test.
3.6	**Further remarks**	
		4 RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical signs	The animals on 1000 ppm exhibited a slightly straddle-legged gait and salivation in the first half of the treatment period. No signs were recorded towards the end of the treatment or during the recovery period. See Table A 6.4.1.1-1
4.1.2	Mortality	No treatment-related mortality was observed.
4.2	**Body weight gain**	At 1000 ppm both sexes showed reduced food consumption and a depressed body weight gain. See Table A 6.4.1.1-2 to A 6.4.1.1-4
4.3	**Food consumption and compound intake**	
4.4	**Ophthalmoscopic examination**	Not conducted
4.5	**Blood analysis**	
4.5.1	Haematology	No abnormalities detected
4.5.2	Clinical chemistry	Of the clinicochemical parameters studied the blood sugar was reduced (in male rats on 300 and 1000 ppm and in females on 1000 ppm). The

		effect was reversible. BUN was significantly elevated in males receiving 300 ppm and above and in females receiving 1000 ppm. Males in the 1000 ppm group displayed a significant elevation of serum ASAT. See Table A 6.4.1.1-5
4.5.3	Urinalysis	No abnormalities detected
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	The organ weight determinations were not suggestive of any effects attributable to the treatment. The significant changes in absolute and relative organ weights were related to the bodyweight decrease at termination. See Table A 6.4.1.1-6
4.6.2	Gross and histopathology	1000 ppm: slight axonal degeneration of single nerve fibres in the sciatic nerve of 5/20 males and 3/20 females at termination of treatment and of 1/8 males at the end of the recovery period.
4.7	**Other**	

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Groups of 28 male and 28 female specific pathogen free rats of the Sprague-Dawley strain were given FCR 1272 in diet containing at four graded concentrations of 0 (control) 100, 300, or 1000 ppm, daily for a period of three months. Twenty rats were subjected to various laboratory tests and pathologic examinations at the termination of the 3-month feeding (main groups). The remaining 8 rats in each group were further maintained for an ensuing one month on a basal commercial diet, followed by the laboratory tests and pathologic examinations (recovery groups).
5.2	**Results and discussion**	The animals on 1000 ppm exhibited a slightly straddle-legged gait and salivation in the first half of the treatment period. No signs were recorded towards the end of the treatment or during the recovery period. At 1000 ppm both sexes showed reduced food consumption and a depressed body weight gain. No influence on the hematological or urinanalytical parameters was detectable. Of the clinicochemical parameters studied the blood sugar was reduced (in male rats on 300 and 1000 ppm and in females on 1000 ppm). The effect was reversible. The results of the necropsies and the organ weight determinations were not suggestive of any effects attributable to the treatment. The significant changes in absolute and relative organ weights were related to the bodyweight decrease at termination. Histopathological analysis revealed slight axonal degeneration of individual sciatic nerve fibres in 5 out of 20 males and 3 out of 20 females on 1000 ppm. Examination at the end of the follow-up period revealed similar alterations in 1 out of 8 males in the 1000 ppm group. These results suggested that morphologic change of sciatic nerve seen in animals receiving cyfluthrin was not progressive, and found gradually repairable following withdrawal of the compound. A NOAEL at 300 ppm should be set in male rats.

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Subchronic oral toxicity test

3 Month Oral Toxicity, Rats

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5.3	**Conclusion**	
5.3.1	LO(A)EL	Based upon effects such as abnormality in the gait and degeneration in the sciatic nerves etc, the LOAEL was 1000 ppm in females and 300 ppm in males..
5.3.2	NO(A)EL	The NOEL of 100 ppm, corresponding to 6.21 mg/kg bw/d in male rats and of 300 ppm, corresponding to 21.22 mg/kg bw/d in female rats was based on transitory reductions in blood glucose levels of male rats on 300 ppm and of female rats on 1000 ppm. Furthermore, abnormal gait, salivation and morphological changes in nerve fibres were observed at the highest dose level. All changes were repairable following withdrawal of the compound. NOEL: 100 ppm (6.21 mg/kg bw/day in males) and 300 ppm (21.22 mg/kg bw/day in females) Overall NOAEL: 300 ppm (18.98 mg/kg/day in males)
5.3.3	Other	
5.3.4	Reliability	2
5.3.5	Deficiencies	Main deviations from Directive 87/302/EEC, Part B, sub-chronic oral toxicity test (OECD guideline 408) are: blood clotting, electrolytes, total bilirubin γ-glutamyl transpeptidase, ornithine decarboxylase and albumin were not determined on blood. Ophthalmologic examinations were not performed.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-29
Materials and Methods	*2.3 Deviations*: Regarding OECD guideline No. 408 this study is considered pre-guideline. *(*Also, functional observations were not performed. Blood clotting time/potential has not been determined. Epididymides, uteri and thymi were not weighed.) *3.5 Sacrifice and pathology:* Deceased and surviving animals after sacrifice were subjected to histopathological examination. Since the animals were not mated in this study, descendants have not been examined.
Results and discussion	Applicant's version is adopted.
Conclusion	LO(A)EL: 1000 ppm (60.9 mg/kg bw/ in males, 68.5 mg/kg bw/d in females) based on reduced food consumption and body weight gain, gait anomalies and sciatic nerve degeneration NO(A)EL: 300 ppm (19.0 mg/kg bw/ in males, 21.2 mg/kg bw/d in females)
Reliability	2
Acceptability	Acceptable

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Subchronic oral toxicity test

3 Month Oral Toxicity, Rats

BPD Data set IIA/ Annex Point VI.6.4

Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A 6.4.1.1-1: General Observations Main Group and Recovery Subgroup

Dose (ppm)	No. of Animals	Poisoning Symptoms	Total *	Day			Week					
				1	3	7	2	4	6	8	10	12
Male Main Group												
0	20	Not Found										
1000	20	Straddle Gait	16	9	15	16	16	12	7	4	3	1
		Salivation	5	5	5	2						
		Lacrimation	1							1	1	
300	20	Not Found										
100	20	Not Found										
Female Main Group												
0	20	Not Found										
1000	20	Straddle Gait	15	4	10	10	12	7	1			
		Salivation	5	1	3	2						
300	20	Not Found										
100	20	Not Found										
Male Revcovery Subgroup												
0	8	Not Found										
1000	8	Straddle Gait	5	1	3	4	5	2				
		Salivation	2		2	1						
300	8	Not Found										
100	8	Not Found										
Female Recovery Subgroup												
0	8	Not Found										
1000	8	Straddle Gait	6	2	5	6	6	4	1			
		Salivation	1	1	1							
300	8	Not Found										
100	8	Not Found										

* Total number of animals displaying symptom during test period,

Table A 6.4.1.1-2: Body Weight Gain (g) Main Group

Dose ppm	# of Animals		Week													
			0	1	2	3	4	5	6	7	8	9	10	11	12	13
Male																
0	20	Weight	127	183	232	271	300	330	348	366	383	398	412	424	435	447
		S.D.	6	9	12	14	14	18	20	21	25	27	29	29	31	34
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
1000	20	Weight	126	160**	201**	233**	260**	285**	308**	326**	337**	350**	363**	376**	388**	394**
		S.D.	6	10	17	20	24	30	31	37	40	39	40	37	38	40
		%	99.5	87.6	86.6	86.0	86.8	86.4	88.6	89.1	87.8	87.9	88.0	88.7	89.1	88.3
300	20	Weight	128	181	229	267	297	321	343	363	378	393	405	416	427	436
		S.D.	6	9	10	14	16	19	20	23	25	29†	32†	36†	37†	38†
		%	100.3	98.6	99.0	98.7	99.0	97.4	98.6	99.2	98.6	98.6	98.2	98.1	98.0	97.6
100	20	Weight	126	178	227	266	295	324	346	365	381	393	408	421	434	442
		S.D.	4	6	11	18	21	26	30	32	35	35	38	40	42	44
		%	99.0	97.3	97.9	98.1	98.5	98.3	99.3	99.6	99.5	98.7	98.9	99.4	99.8	98.9
Female																
0	20	Weight	105	136	156	172	188	202	212	222	225	234	237	242	246	251
		S.D.	5	7	9	12	13	14	15	15	16	19	18	19	20	22
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
1000	20	Weight	105	126**	149*	160**	174**	185**	194**	201**	289**	213**	216**	223**	224**	227**
		S.D.	5	9	11	13	15	16	17	18	18	20	22	21	23	24
		%	100.2	93.1	95.4	92.7	92.5	91.6	91.3	90.8	92.8	91.0	91.0	92.2	91.2	90.5

300	20	Weight	104	136	158	173	190	205	214	223	229	234	237	241	246	247
		S.D.	7	11	12	13	14	16	19	19	17	18	19	18	19	18
		%	99.3	99.7	110.5	100.6	100.6	101.3	100.8	100.5	102.0	99.8	100.0	99.9	99.9	98.4
100	20	Weight	104	133	154	171	187	202	212	221	227	236	238	246	251	254
		S.D.	6	7	9	13	17	17	16	18	19	22	21	21	21	21
		%	98.5	97.7	98.6	99.5	99.2	100.1	99.9	99.8	100.8	100.8	100.3	101.8	102.2	101.0

S.D. = Standard deviation

% = Percent of control group

* P<0.05

** P<0.01

† 19 Male rats

Table A 6.4.1.1-3: Body Weight Gain (g) Recovery Subgroup

Dose ppm	# of Animals		Week										Recovery Week			
			0	1	2	3	4	5	7	9	11	13	1	2	3	4
Male																
0	20	Weight	130	180	229	271	305	332	374	409	437	463	471	479	492	503
		S.D.	7	15	17	23	26	27	33	36	39	43	46	48	50	50
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
1000	20	Weight	128	158**	202**	236**	266**	290**	330**	355**	377**	396**	409**	418**	436*	435**
		S.D.	4	11	11	10	10	9	14	17	20	24	28	27	29	29
		%	98.4	87.7	88.4	86.9	87.3	87.2	88.3	86.9	86.3	85.4	86.8	87.2	88.7	86.5
300	20	Weight	126	177	221	261	293	317	358	385	411	429	439	446	456	466
		S.D.	6	9	13	10	12	12	17	22	26	32	30	32	35	35

		%	97.2	98.0	96.4	96.1	96.1	95.5	95.6	94.2	94.1	92.3	93.2	93.1	92.7	92.6
100	20	Weight	124	182	228	265	296	326	371	402	427	456	457	468	481	190
		S.D.	6	13	16	20	29	33	43	54	63	71	71	73	71	75
		%	95.8	100.6	99.7	97.6	96.9	98.1	99.2	98.2	97.7	97.2	97.0	97.7	97.9	97.4
Female																
0	20	Weight	103	131	153	170	185	198	220	230	241	248	258	255	261	268
		S.D.	7	12	14	14	15	18	16	15	17	18	20	16	22	23
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
1000	20	Weight	105	127	146	162	174	184*	205*	215*	224*	230*	241	242	249	252
		S.D.	7	10	9	6	5	6	10	8	6	9	11	10	14	18
		%	101.3	96.9	95.7	95.2	94.1	92.9	93.5	93.4	92.8	92.8	93.2	95.0	95.3	94.2
300	20	Weight	103	132	151	170	184	198	216	229	237	245	250	251	252	259
		S.D.	5	10	10	15	12	13	14	15	18	15	18	16	12	17
		%	99.8	100.6	98.8	99.7	99.5	100.0	98.1	99.6	98.4	98.8	96.9	98.6	96.4	96.6
100	20	Weight	102	131	151	168	181	196	217	228	238	247	253	253	261	251
		S.D.	3	5	10	11	11	14	15	17	18	21	18	21	20	27
		%	99.2	99.8	98.9	98.3	97.7	99.1	98.9	99.0	98.6	99.4	98.1	99.2	100.0	93.9

S.D. = Standard deviation

% = Percent of control group

* P<0.05

** P<0.01 Significant

Table A 6.4.1.1-4: Mean Food Consumption (g), Main Group

Dose ppm	No. of Cages		Week												
			1	2	3	4	5	6	7	8	9	10	11	12	13
Male															
0	5	Mean	17.9	20.1	20.3	21.4	22.2	21.8	22.1	21.6	20.4	20.2	20.7	20.5	20.4
		S.D..	0.5	1.4	0.6	0.7	0.6	1.1	1.0	0.9	0.8	1.2	1.0	0.8	0.7
1000	5	Mean	12.1**	16.3**	15.8**	17.4**	19.2**	19.8	18.8**	18.6**	18.3**	19.6	18.8*	19.0*	18.5**
		S.D.	1.1	1.0	1.0	1.4	0.7	1.6	0.8	1.3	0.6	0.7	0.8	1.0	0.5
300	5	Mean	16.5**	19.6	19.4	20.2	20.5**	21.6	21.3	21.3	20.7	20.9	20.0	20.0	20.1
		S.D.	0.4	0.6	1.1	1.0	0.7	1.1	1.2	0.8	1.4	1.1	0.8	1.0	0.8
100	5	Mean	17.4	19.9	20.2	22.0	21.6	21.5	21.6	20.9	19.8	19.5	20.5	20.5	20.3
		S.D.	0.5	0.9	0.4	0.8	0.7	0.6	0.7	0.8	0.7	0.6	0.6	0.6	1.0
Female															
0	5	Mean	13.9	13.9	14.5	16.0	15.6	16.4	16.7	16.4	14.9	13.9	14.7	14.8	14.5
		S.D.	0.4	0.7	0.5	1.2	0.8	1.4	1.0	1.3	1.4	0.9	0.3	1.0	1.0
1000	5	Mean	10.3**	12.9*	11.5**	12.9**	13.4**	13.5**	13.5**	13.8**	12.6**	12.5*	12.8**	13.0*	13.0*
		S.D.	0.4	0.4	0.4	0.9	0.7	0.7	0.5	0.2	0.3	0.6	0.6	0.7	0.6
300	5	Mean	13.1	14.0	13.7	13.9	15.3	15.6	15.4*	16.3	14.0	13.5	13.9	14.0	13.5
		S.D.	0.7	0.7	0.6	0.4	1.2	1.7	1.0	0.9	0.7	0.7	1.0	0.5	1.0
100	5	Mean	12.7**	13.7	14.0	15.0	16.1	17.2	15.6	15.6	14.4	14.2	14.5	14.6	14.1
		S.D.	0.6	0.4	0.9	1.6	1.2	0.6	1.7	1.1	0.9	0.9	0.9	0.8	0.8

S.D. = Standard deviation

* P<0.05

** P<0.01 Significant by t-test

Table A 6.4.1.1-5: Blood Chemistry Examinations: Glucose

Dose ppm	Number of Animals	Glucose mg/dL	Standard Deviation
Male Main Group			
0	20	112	18
1000	20	79**	8†
300	19	95**	18
100	20	106	17
Female Main Group			
0	20	101	12†
1000	20	84**	10†
300	19	97	13
100	20	99	15†
Male Recovery Subgroup			
0	8	138	20
1000	8	127	28
300	8	138	13
100	8	143	16
Female Recovery Subgroup			
0	8	109	21
1000	8	112	21
300	8	106	23
100	8	90*	12

* P<0.05

** P<0.01 Significant by t-test

† One datum was rejected by Smirnoff Test

Table A 6.4.1.1-6: Relative Organ Weights (mg), Main Group:

Dose ppm	No. of Animals	Submax.		Heart		Kidneys		Gonads	
		Weight	St. Dev.	Weight	St. Dev.	Weight	St. Dev.	Weight	St. Dev.
Male									
0	20	161	15	297	26	564	43	703	64
1000	20	188*	55	287	30	608*	73	776**	63†
300	20	157	21	314*	27	606*	65	754**	46
100	20	147*	25	301	46	615*	82	709	50†
Female									
0	20	152	32	308	31	601	70	41.5	6.6
1000	20	177*	42	341**	43	624	45†	40.4‡	7.4‡

300	20	182*	47	360**	47	649	87	40.9	6.6†
100	20	174	56	350**	51	635	44†	37.4*	6.1†

* P<0.05

* P<0.01 Significant

† One datum was rejected by Smirnoff Test

‡ 19 animals inspected for this parameter

CA: ** P<0.01 Significant

Document IIIA/ Section 6.4.1.2

BPD Data set IIA/ Annex Point VI.6.4

Subchronic oral toxicity test

6 Month Oral Toxicity, Dogs

X

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1981) FCR 1272 - Chronic study on dogs (six-month feeding experiment). [redacted] Bayer AG Report No.: 9991, BES Ref.: M-074935-01-1 Report date: 2 June 1981 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes The study was performed and complied with to a great extent to then in force EPA Guidelines current at the time (Proposed Guidelines for Registering Pesticides in the US, Federal Register, Vol. 43, No. 163, August 22, 1978).
2.2	**GLP**	No. When the study was performed, GLP was not compulsory (as study started before June 30 1988).
2.3	**Deviations**	Deviations from the OECD Guideline for Testing Chemicals no. 452 which complies to Directive 87/302/EEC part B: Ornithine decarboxylase and gamma glutamyl transpeptidase were not determined. Histopathology: Brain and intestine were studied as one organ each and not in 3 and 6 different parts, respectively. In addition were determined: Body temperature, pulse rate, cytochrome P 450 and N- demethylase. No deviations are considered significant enough to affect the scientific integrity of the study.

X

3 MATERIALS AND METHODS

3.1	**Test material**	FCR 1272 (cyfluthrin)
3.1.1	Lot/Batch number	Batch no. 16003/79
3.1.2	Specification	50% premix (FCR 1272 + colloidal silicic acid (Wessalon)); The test compound is a mixture of four isomers, viz. I, II, III and IV. Chemical analysis showed that the premix had a 47.1 % content of this isomeric mixture.

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3.1.2.1	Description	
3.1.2.2	Purity	84.8%
3.1.2.3	Stability	Ensured for the study period. Tested at the beginning of the study, concentration in the diet was check prior to treatment, in week 7 and at the end of the treatment period.
3.2	**Test Animals**	
3.2.1	Species	Dog
3.2.2	Strain	Beagle
3.2.3	Source	[redacted]
3.2.4	Sex	Male and female
3.2.5	Age/weight at study initiation	At the start of the study, the dogs weighed between 6.6 and 10.0 kg and were between 24 and 31 weeks old.
3.2.6	Number of animals per group	Each of the test groups consisted of 6 male dogs and 6 female dogs.
3.2.7	Control animals	Yes, plain diet
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	6 months
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	The interval between the final feeding, and hence the final application of FCR 1272, and necropsy did not exceed 24 hours.
3.3.4	**Oral**	
3.3.4.1	Type	Diet
3.3.4.2	Concentration	Food consumption per day: up to 300 grams per day (weeks 1-19), up to 330 grams per day (weeks 20-26)
3.3.4.3	Vehicle	The dogs of each group were fed ssniff HH Dog Breeding Diet (ground twice) with lukewarm tap water added to it in a ratio of 1:1.
3.3.4.4	Concentration in vehicle	0, 65 ppm, 200 ppm, and 600 ppm (concentration of FCR 1272) equivalent to 1.6, 5 and 15 mg/kg bw/d. X
3.3.4.5	Total volume applied	Not applicable, diet given *ad-libitum*
3.3.4.6	Controls	Plain diet only, without test material
3.4	**Examinations**	
3.4.1	Observations	

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x

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3.4.1.1	Clinical signs	Daily check toxic signs (all animals). Prior to the commencement of treatment, and at weeks 4, 7, 13 and 26 reflexes, body temperature, pulse rate were monitored in all animals.
3.4.1.2	Mortality	Daily
3.4.2	Body weight	Weekly
3.4.3	Food consumption	Daily
3.4.4	Water consumption	Number of occasions dogs took water from the automated dispenser was recorded, though actual consumption was not calculated.
3.4.5	Ophthalmoscopic examination	Yes, (all animals; before treatment, 4, 7, 13, 26 weeks after start of treatment).
3.4.6	Haematology	The following parameters were measured: haematocrit, haemoglobin, erythrocyte count, leucocyte count, MCV, MCH, MCHC, thrombocyte count, reticulocyte count, thromboplastin time, blood sedimentation time, differential blood count (all animals; before treatment and at 4, 7, 13 and 26 weeks after start of treatment).
3.4.7	Clinical Chemistry	The following parameters were measured: glucose, plasma urea, creatinine, bilirubin, cholesterol, alkaline phosphatase, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, glutamate dehydrogenase, total protein, serum protein, sodium, potassium, calcium, chloride (all animals; before treatment and at 4, 7, 13 and 26 weeks after start of treatment). In addition, cytochrome P450 and N-demethylase were determined from liver tissue.
3.4.8	Urinalysis	The following parameters were measured: protein, glucose, blood, pH-value, bilirubin, ketone bodies, volume, deposits and specific gravity (all animals; before treatment and at 4, 7, 13 and 26 weeks after start of treatment).
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	The following tissues were taken: heart, lungs, liver, kidneys, spleen, thyroid, adrenals, thymus, prostate, brain, pancreas, testes and ovaries.
3.5.2	Gross and histopathology	The following tissues were examined microscopically: heart, aorta, lungs, liver, gall bladder, stomach, oesophagus, intestines, pancreas, parotic gland, spleen, lymph nodes, thymus, kidneys, urinary bladder, testes, epididymides, prostate, mammary gland, adrenals, pituitary gland, thyroid, brain, spinal cord, peripheral nerve, optic nerve, eyes, skeletal muscle and bone marrow. Tissues were fixed in Bouin's solution, embedded in Paraplast, sectioned and stained with haemalum and eosin (HE). Kidney sections were additionally stained with PAS reagent. Liver sections were stained with ORO.
3.5.3	Other examinations	
3.5.4	Statistics	Calculation of arithmetic means and standard deviation.
3.6	**Further remarks**	

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Subchronic oral toxicity test

6 Month Oral Toxicity, Dogs

X

		4 RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	The animals on the highest dose exhibited a higher incidence of diarrhea and vomiting throughout the entire study. From around the 21st week of treatment disturbances of movement, chiefly of the hind legs, were observed in several animals in the highest dose group. A hunched posture and co-ordination disturbances were also recorded.	
4.1.2	Mortality	No mortalities at any dose	X
4.2	**Body weight gain**	The growth rate in the 200 ppm and 600 ppm groups was slightly lower than in the other groups. See table 6.4.1.2-1	X
4.3	**Food consumption and compound intake**	Group I 65 ppm FCR 1272, 19.6 mg/dog/day (= 1.6 mg/kg bw/day) Group II: 200 ppm FCR 1272, 60.3 mg/dog/day (= 5 mg/kg bw/day) Group III: 600 ppm FCR 1272, 178.4 mg/dog/day (= 15 mg/kg bw/day) At the start of treatment, animals in the 600ppm group ate slightly less food.	X
4.4	**Ophtalmoscopic examination**	No abnormalities detected	
4.5	**Blood analysis**		
4.5.1	Haematology	No abnormalities detected	
4.5.2	Clinical chemistry	No abnormalities detected	
4.5.3	Urinalysis	No abnormalities detected	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	600 ppm: reduction of thymus size See table 6.4.1.2-2	X
4.6.2	Gross and histopathology	No abnormalities detected	
4.7	**Other**	Reflex tests did not show any deviations from the control group.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	In a chronic toxicity study, groups of 6 male and 6 female Beagle dogs were maintained for 26 weeks on a diet containing the test compound FCR 1272 at the following concentrations: Control group: 0 ppm Group I 65 ppm FCR 1272, 19.6 mg/dog/day (= 1.6 mg/kg bw/day) Group II: 200 ppm FCR 1272, 60.3 mg/dog/day (= 5 mg/kg bw/day) Group III: 600 ppm FCR 1272, 178.4 mg/dog/day (= 15 mg/kg bw/day)	X
5.2	**Results and discussion**	All the animals survived the treatment, which had no effect on their appearance. At the start of the treatment the animals on 600 ppm ate slightly less food. The average growth rate after 200 and 600 ppm was slightly lower than in the other groups. The animals on the highest dose exhibited a higher incidence of diarrhea and vomiting throughout the	

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X

		entire study. From around the 21st week of treatment disturbances of movement, chiefly of the hind legs, were observed in several animals in the highest dose group. A hunched posture and co-ordination disturbances were also recorded. However, the reflex tests and the gross pathological and histopathological examinations of nerve tissue (thoracic and lumbar cord, sciatic nerve) did not reveal any deviations from the physiological norm. The ophthalmic examinations did not reveal any evidence of alterations to the eye that could be attributed to the treatment. Likewise no evidence of damage to the blood or of an impairment of blood coagulation was discernible at cyfluthrin concentrations of up to and including 600 ppm. Neither the laboratory parameters nor the gross pathological and histopathological investigations revealed any signs of damage to the liver or kidneys. The gross pathological examinations and the comparison of organ weights revealed increased thymus involution - possibly attributable to the treatment - in the animals on 600 ppm.	
5.3	**Conclusion**		
5.3.1	LO(A)EL	600 ppm (15 mg/kg bw/day) based on a reduced growth rate and thymus effects	X
5.3.2	NO(A)EL	It is concluded from the results of the clinical tests, laboratory tests, macroscopic examinations and histopathological examinations that six-month dietary administration of FCR 1272 at 65 ppm (equivalent to 1.6 mg/kg bw/day) was tolerated by dogs without having any untoward effects (NOEL). An additional NOAEL at 200 ppm (5 mg/kg/d) could be established (based on reduction in weight gain).	X
5.3.3	Other		
5.3.4	Reliability	2	
5.3.5	Deficiencies	Yes, minor deviations from the OECD Guideline for Testing Chemicals No. 452 concern only histopathology: brain and intestine were studied as one organ and not in 3 and 6 different parts, respectively.	X

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	/2014/04/08
Materials and Methods	2.3 Regarding OECD 452 this study is considered as pre-guideline. 3.3.4.4 0, 65 ppm, 200 ppm, and 600 ppm (concentration of FCR 1272) equivalent to 2, 6.5 and 20 mg/kg bw/d.
Results and discussion	4.1.2 No cyfluthrin-related mortalities at any dose (1 ♂ died after being attacked by another ♂)

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Subchronic oral toxicity test

6 Month Oral Toxicity, Dogs

x

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	4.2 See CA-Table 1. However, there was no dose-dependent decrease in body weight gain of males and no statistically significant decrease at 15 mg/kg bw/d. 4.3 Group I 65 ppm FCR 1272, 19.6 mg/dog/day (= 2 mg/kg bw/day) Group II: 200 ppm FCR 1272, 60.3 mg/dog/day (= 6.5 mg/kg bw/day) Group III: 600 ppm FCR 1272, 178.4 mg/dog/day (= 20 mg/kg bw/day) 4.6.1 Reduction in thymus weight was observed at 6.5 and 20 mg/kg bw/d. See CA-Table 2.
Conclusion	5.1 Group I 65 ppm FCR 1272, 19.6 mg/dog/day (= 2 mg/kg bw/day) Group II: 200 ppm FCR 1272, 60.3 mg/dog/day (= 6.5 mg/kg bw/day) Group III: 600 ppm FCR 1272, 178.4 mg/dog/day (= 20 mg/kg bw/day) LO(A)EL: 20 mg/kg bw/d (600 ppm) based on diarrhea, vomiting, stiff gait, hunched posture and thymus atrophy. NO(A)EL: 6.5 mg/kg bw/d NOEL: 2 mg/kg bw/d based on reduced thymus weight
Reliability	2
Acceptability	Acceptable
Remarks	According to the reference list this document refers to section 6.4.1.2/01.

	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A 6.4.1.2-1: Group Mean Body Weights, both sexes

Group	♂♂	♀♀	♂♂+♀♀
Control	2.11 kg	2.22 kg	2.17 kg
I	2.78 kg	2.00 kg	2.39 kg
II	1.41 kg	2.02 kg	1.71 kg
III	2.08 kg	1.41 kg	1.75 kg

Table A 6.4.1.2-2: Group Mean Absolute and Relative Organ Weights (g), Both Sexes: Thymus

	Absolute	Relative
Control Group		
n	12	12
Maximum	8.4g	0.771g
Minimum	18.1g	1.760g
Mean	13.10g	1.225g
Standard Deviation	3.84	0.334
Group I 65 ppm		
n	12	12
Maximum	9.3g	0.865g
Minimum	23.0g	2.212g
Mean	14.10g	1.318g
Standard Deviation	4.19	0.364
Group II 200 ppm		
n	12	12
Maximum	6.2g	0.596g
Minimum	15.7g	1.653g
Mean	11.15g	1.110g
Standard Deviation	2.79	0.308
Group III 600 ppm		
n	12	12
Maximum	4.9g	0.537g
Minimum	16.6g	1.581g
Mean	8.95g	0.875g
Standard Deviation	3.39	0.276

CA Table 1: Group Mean Body Weight Gain, Comparison Week 1 to Week 26

Cyfluthrin	♂♂	♀♀	♂♂+♀♀
0 mg/kg bw/d	2.11 kg	2.22 kg	2.17 kg
1.6 mg/kg bw/d	2.78 kg	2.00 kg	2.39 kg
5 mg/kg bw/d	1.41 kg	2.02 kg	1.71 kg
15 mg/kg bw/d	2.08 kg	1.41 kg	1.75 kg

CA Table 2: Mean Thymus weight in ♂ and ♀: absolute (g) and relative (g/kg)

	Absolute thymus weight (g)		Relative thymus weight (g/kg)	
	♂	♀	♂	♀
Control	16.22	9.98	1.47	0.98
Group I 65 ppm	16.58	11.62	1.49	1.15
Group II, 200 ppm	**10.48**	11.82	**1.03**	1.09
Group III 600 ppm	**10.70**	**7.20**	**0.99**	**0.76**

Document IIIA/ Section 6.4.1.2/01 Chronic toxicity

12-Month Oral Toxicity, Dogs

BPD Data set IIA/ Annex Point VI.6.4

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1 REFERENCE

1.1	**Reference**	[redacted] (1983). FCR 1272 – Chronic toxicity to dogs on oral administration (12 months feeding study). [redacted] Unpublished Report No. 11983, Study No. T9 004 924. Report date: 3 August 1983 [BES Ref. : M-037410-01-1]
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes The study was performed and completed in accordance with the EPA Guidelines current at the time (Proposed Guidelines for Registering Pesticides in the US, Federal Register, Vol. 43, No. 163, August 22, 1978) and is compliant with OECD 452 and 87/302/EEC, part B.
2.2	**GLP**	No (not required, as study started before June 30 1988).
2.3	**Deviations**	Main deviations from the OECD Guideline for Testing Chemicals No. 452 concern the histopathology: trachea, ovaries were not studied; the intestine was studied as one organ, not its 6 constituent parts separately. Albumin, ornithine decarboxylase and gamma glutamyl transpeptidase were not determined. These deviations are not considered to compromise the validity of the study.

3 MATERIALS AND METHODS

3.1	**Test material**	FCR 1272 (cyfluthrin)
3.1.1	Lot/Batch number	Batch Nos. 16001/80, 16002/80, 16004/80, 16005/80, and 16006/80
3.1.2	Specification	50% premix (FCR 1272 + colloidal silicic acid (Wessalon S))

Document IIIA/ Section 6.4.1.2/01 Chronic toxicity

12-Month Oral Toxicity, Dogs

BPD Data set IIA/ Annex Point VI.6.4

3.1.2.1	Description	
3.1.2.2	Purity	51.0%; The active ingredient content was confirmed by analysis in the pre-mix before start of the study.
3.1.2.3	Stability	Tested at the beginning of the study; concentration in the diet was checked regularly over the entire study period.
3.2	**Test Animals**	
3.2.1	Species	Dog
3.2.2	Strain	Beagle
3.2.3	Source	[redacted]
3.2.4	Sex	Male and female
3.2.5	Age/weight at study initiation	Approximate age (week –1) 22 to 30 weeks old, weight 7.3 to 9.9 kg
3.2.6	Number of animals per group	6/sex/group
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	12 months
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	The last feeding time, and consequently last administration of the test substance, was not longer than 24 hours before autopsy in each case.
3.3.4	**Oral**	
3.3.4.1	Type	Diet
3.3.4.2	Concentration	Food consumption per day: each animal received 300 g daily from study weeks 1 to 5, 330 g daily for study weeks 6 to 8, 380 g daily for study weeks 9 to 21, 400 g daily for study weeks 22 to 26, and 430 g daily from the 27th study week until end of study.
3.3.4.3	Vehicle	ssniff-HH sole feed for dogs, double ground, mixed with hand-warm tap water in a ratio of 1:1 immediately before being given to the animals.
3.3.4.4	Concentration in vehicle	0, 40, 160 and 640 ppm, equivalent to 0, 1, 4 and 16 mg/kg b.w./day
3.3.4.5	Total volume applied	Not applicable, diet given ad libitum.
3.3.4.6	Controls	Plain diet
3.4	**Examinations**	
3.4.1	Observations	

Document IIIA/ Section 6.4.1.2/01 Chronic toxicity

12-Month Oral Toxicity, Dogs

BPD Data set IIA/ Annex Point VI.6.4

3.4.1.1	Clinical signs	Daily inspections; reflex tests given and body temperature measured before treatment and at 6, 13 26, 39 and 52 weeks after the start of treatment.
3.4.1.2	Mortality	Daily
3.4.2	Body weight	Weekly
3.4.3	Food consumption	Daily
3.4.4	Water consumption	The level of water in the dog's dish was observed as an indication of thirst, but not measured.
3.4.5	Ophthalmoscopic examination	Yes, all animals, before treatment and at 5, 13, 29, 39 and 52 weeks after start of treatment.
3.4.6	Haematology	The following parameters were measured: haematocrit, haemoglobin, erythrocyte count, leukocyte count, MCV, MCH, MCHC, thrombocyte count, reticulocyte count, thromboplastin time, blood sedimentation time, and differential blood count (all animals; before treatment and at 6, 13,26, 39 and 52 weeks after start of treatment).
3.4.7	Clinical Chemistry	The following parameters were measured: blood sugar, urea, creatinine, total protein, glutamate oxalacetate transaminase, glutamate pyruvate transaminase, alkaline phosphatase, bilirubin, cholesterol, glutamate dehydrogenase, sodium, potassium, calcium, and chloride (all animals; before treatment and at 6, 13, 26, 39, 52 weeks after start of treatment).
3.4.8	Urinalysis	The following parameters were measured: protein, glucose, blood, bilirubin, ketone bodies, pH-value and deposits (all animals; before treatment and at 6, 13, 26, 39, 52 weeks after start of treatment).
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	The following tissues were taken: heart, lungs, liver, kidneys, spleen, thyroid, adrenals, prostate, brain, pancreas, testicles, and ovaries.
3.5.2	Gross and histopathology	The following tissues were examined microscopically: heart, liver, lungs, spleen, kidneys, brain, adrenals, thyroid, pituitary, testicles, epididymes, prostate, uterus, parotid, oesophagus, stomach, intestines, pancreas, gallbladder, pancreas, skeletal muscle, urinary bladder, aorta, lymph nodes, thymus, mamma, eye, optic nerve, peripheral nerve, bone, and bone marrow. The bones were decalcified with EDTA. The organ material were fixed in Bouin's solution (or 4% aqueous formaldehyde for brain tissue), embedded in Paraplast and then approximately 15 µm thick sections were stained with HE or PAS. In addition, approx. 15 µm thick frozen liver sections were stained with Oil Red O for the fat demonstration. The bone marrow smears were stained with May-Gruenwald Giemsa.
3.5.3	Other examinations	
3.5.4	Statistics	The mean values of the treated groups were compared with those of the control values. Notable differences between control and treated animals were checked for statistical significance using Wilcoxon's non-parametric rank sum test.
3.6	**Further remarks**	

Document IIIA/ Section 6.4.1.2/01 **Chronic toxicity**

12-Month Oral Toxicity, Dogs

BPD Data set IIA/ Annex Point VI.6.4

4 RESULTS AND DISCUSSION

4.1	**Observations**	
4.1.1	Clinical signs	640 ppm: slightly abnormal movements in two animals (chiefly rear legs), higher incidence of vomiting and pasty to liquid faeces
4.1.2	Mortality	No mortalities at any dose
4.2	**Body weight gain**	640 ppm (males): mean body weights decreased
4.3	**Food consumption and compound intake**	No abnormalities detected
4.4	**Ophtalmoscopic examination**	No abnormalities detected
4.5	**Blood analysis**	
4.5.1	Haematology	No abnormalities detected
4.5.2	Clinical chemistry	No abnormalities detected
4.5.3	Urinalysis	No abnormalities detected
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	No abnormalities detected
4.6.2	Gross and histopathology	No abnormalities detected
4.7	**Other**	

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

In a chronic toxicity study with PCE 1272, groups of 6 male and 6 female beagles were treated for 12 months with the following concentrations of test substance in their feed:

Controls	0 ppm FCR 1272	0 mg/kg bw/day
Group I	40 ppm FCR 1272	1 mg/kg bw/day
Group II	160 ppm FCR 1272	4 mg/kg bw/day
Group III	640 ppm FCR 1272	16 mg/kg bw/day

The FCR 1272 was combined in the appropriate concentration with ssniff HH sole feed for dogs (except for the control group, for which only feed was used) and mixed in a 1:1 ratio with warm tap water to form a homogenous paste. The amount of feed given to the dogs increased throughout the experiment, and was measured by mass of dry feed before combination with the test material or water. Each animal received 300 g daily from study weeks 1 to 5, 330 g daily for study weeks 6 to 8, 380 g daily for study weeks 9 to 21, 400 g daily for study weeks 22 to 26, and 430 g daily from the 27th study week until the end of the study.

Document IIIA/ Section 6.4.1.2/01 **Chronic toxicity**

12-Month Oral Toxicity, Dogs

BPD Data set IIA/ Annex Point VI.6.4

All the animals were inspected daily. Each animal's individual feed consumption was recorded daily, and body weights weekly, always at intervals of 7 days. Individual nutritional states were appraised weekly and on the dates of the laboratory examinations. Before treatment and at 6, 13, 26, 39 and 52 weeks after the start of treatment, body temperature was recorded, the animals were given reflex tests, and haematological, clinical chemical and urine examinations took place. Before treatment and at 5, 13, 29, 39 and 52 weeks, ophthalmoscopic exams were given. After treatment, all the animals in the study were anaesthetised, exsanguinated, dissected and subjected to gross appraisal.

5.2 Results and discussion

Concentrations up to and including 640 ppm FCR 1272 were survived by all the animals, and had no influence on the animals' appearance.

After 640 ppm FCR 1272 (group III) slightly abnormal movements, especially in the area of the rear legs, were observed in the course of the 12 months treatment, in a total of two animals, once in each case.

The neurological examinations, reflexes, like the pathological anatomical and histopathological examinations of the nervous system, did not detect any deviations from the physiological norm in any animals.

The ophthalmoscopic examinations likewise provided no indication of treatment induced alterations to the eye.

The animals' nutritional state was not apparently affected by the treatment.

In regard to mean feed and water intake, there were no apparent differences between the animals in any of the groups.

In the group III animals, over the entire study, there was a higher incidence of vomiting and pasty to liquid faeces in comparison to the animals in the other groups.

Mean body weight gains were lower in the group III males than in the males in control group and groups I and II.

After concentrations up to and including 640 ppm FCR 1272 no indications of damage to the blood or impairment of coagulation were noted.

Neither the laboratory findings, nor the pathological anatomical and histopathological examinations and also the organ weight comparisons revealed damage to the liver up to and including 640 ppm FCR 1272.

After concentrations up to and including 640 ppm FCR 1272 no indication of damage to the kidneys were found.

5.3 Conclusion

5.3.1 LO(A)EL

The LOAEL of 640 ppm, equal to approximately 16 mg/bw kg/d, was based on increased incidence of vomiting and soft faeces, on reduction in body weight gain and impaired motility.

5.3.2 NO(A)EL

According to all the clinical examination results, the laboratory findings, the pathological anatomical and histopathological results, 160 ppm FCR 1272—equivalent to 4 mg/kg bw/day—was tolerated without effect by dogs treated for 12 months.

Document IIIA/ Section 6.4.1.2/01 Chronic toxicity

12-Month Oral Toxicity, Dogs

BPD Data set IIA/ Annex Point VI.6.4

5.3.3	Other	
5.3.4	Reliability	2 Study superseded by a guideline GLP study ([redacted] 1997 & 2000; Ref. M-044511-02-1, See Point 6.5/01)
5.3.5	Deficiencies	Main deviations from the OECD Guideline for Testing Chemicals No. 452 concern: – The clinical chemistry: albumine, ornithine decarboxylase and gamma glutamyl transpeptidase were not determined – The histopathology: trachea was not studied; the intestine was studied as one organ, not its 6 constituent parts separately.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/03/01
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is acceptable.
Conclusion	LO(A)EL: 23.5 mg/kg bw/d (640 ppm) NO(A)EL: 5.5 mg/kg bw/d (160 ppm)
Reliability	2 (reliable with restrictions)
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ... (specify)
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.4.1.2/02-1: Summary of Mean Body Weight Gain per Group

Group	Sex	Body Weight (kg)		Difference (Week -1 – Week 52) (kg)	Difference Both sexes (kg)
		Start Study (Week -1)	End Study (Week 52)		
Control (0 ppm)	Male	8.6	12.3	+3.7	+3.6
0 mg/kg bw/day	Female	8.4	11.8	+3.4	
Group I (40 ppm)	Male	8.6	12.8	+4.2	+3.8
1 mg/kg bw/day	Female	8.2	11.6	+3.4	
Group II (160 ppm)	Male	8.5	13.3	+4.8	+4.2
4 mg/kg bw/day	Female	8.2	11.8	+3.6	
Group III (640 ppm)	Male	8.5	11.1	+2.6	+3.2
16 mg/kg bw/day	Female	8.2	12.0	+3.8	

Document IIIA/ Section A6.4.2 **BPD Data set IIA/ Annex Point VI.6.4**	**Subchronic dermal toxicity test**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	In acute and sub-acute studies cyfluthrin is profoundly less toxic by dermal than oral exposure so additional studies are unwarranted.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2006-09-13	
Evaluation of applicant's justification	Since a 28-d-study repeated dose dermal toxicity was submitted it is justified to waive additional studies.	
Conclusion	The applicant's justification is acceptable.	
Remarks	-	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Document IIIA/ Section 6.4.3

Subchronic oral toxicity test

13-Week Inhalation Study, Rat

X

BPD Data set IIA/ Annex Point VI.6.4

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1984) FCR 1272 – Study for subchronic inhalative toxicity to the rat for 13 weeks (exposure 63 x 6 hours), [redacted] Bayer AG Report No.: 12436, BES Ref.: 037526-03-1 Report date: 1 February 1984 (Amended 30 July 1987) Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes, OECD Guideline for Testing of Chemicals No. 413	
2.2	**GLP**	No, when the study was performed, GLP was not compulsory (as study started before June 30 1988).	
2.3	**Deviations**	Main deviations from OECD No. 413 are: chloride, potassium, sodium, calcium, phosphate, ornithine decarboxylase, g-glutamyl transpeptidase, albumin, total protein, creatinine were not determined, and histopathology was not performed for thymus, sternum, uterus, bone marrow, pituitary.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	FCR 1272 (cyfluthrin)	
3.1.1	Lot/Batch number	Batch No. 816170019	
3.1.2	Specification	As given in sections 2	
3.1.2.1	Description	Not given	X
3.1.2.2	Purity	94.9%	
3.1.2.3	Stability	Guaranteed for the study duration	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Wistar rats [redacted]	
3.2.3	Source	[redacted]	
3.2.4	Sex	50 males and 50 females	
3.2.5	Age/weight at study initiation	No age provided, weight range approximately 160-200 grams for male and female.	X

Document IIIA/ Section 6.4.3

Subchronic oral toxicity test

13-Week Inhalation Study, Rat

X

BPD Data set IIA/ Annex Point VI.6.4

3.2.6	Number of animals per group	10/sex/group	
3.2.7	Control animals	One control group exposed to air, one control group to vehicle.	
3.3	**Administration/ Exposure**	Inhalation	
3.3.1	Duration of treatment	13 weeks	
3.3.2	Frequency of exposure	5 days per week, 6 hours/day	
3.3.3	Postexposure period	Not applicable	
3.3.4	**Inhalation**		
3.3.4.1	Concentrations	Nominal concentration	0 (air), 0 (vehicle), 0.5, 3.0, 20.0 mg/m³
		Analytical concentration	0 (air), 0 (vehicle), 0.09, 0.71, 4.52 mg/m³
3.3.4.2	Particle size	0 (vehicle) mg/m^3 MMAD = 2.7 µm (±1.8) 0.5 mg/m^3 MMAD = 2.6 µm (±1.8) 3 mg/m^3 MMAD = 2.5 µm (±1.8) 20 mg/m^3 MMAD = 2.5 µm (±1.9) Over 85 % of the particle mass was therefore respirable (particles <5 µm).	
3.3.4.3	Type or preparation of particles	Not applicable	
3.3.4.4	Type of exposure	Nose/head only	
3.3.4.5	Vehicle	The vehicle used was ethanol and Lutrol (polyethylene glycol 400) mixed 1:1.	
3.3.4.6	Concentration in vehicle	Concentration in wt./vol 0.0025% in Lu/EtOH corresponding to 0.5 mg FCR1272/m^3 air 0.015% in Lu/EtOH corresponding to 3.0 mg cyfluthrin/m^3 air 0.10% in Lu/EtOH corresponding to 20.0 mg cyfluthrin/m^3 air	
3.3.4.7	Duration of exposure	6 hours	
3.3.4.8	Controls	One group exposed to air, second group exposed to vehicle.	
3.4	**Examinations**		
3.4.1	Observations	Daily	
3.4.1.1	Clinical signs	Daily	
3.4.1.2	Mortality	Daily	
3.4.2	Body weight	Before first exposure, then weekly	
3.4.3	Food consumption	No	
3.4.4	Water consumption	No	
3.4.5	Ophthalmoscopic	No	

	examination	
3.4.6	Haematology	The following parameters were measured 6 weeks after study initiation and at study termination for all animals: haematocrit, haemoglobin, erythrocyte count, leukocyte count, reticulocyte count, MCV, MCHC, MCH, thrombocyte count, and differential blood count.
3.4.7	Clinical Chemisty	The following parameters were measured 6 weeks after study initiation and at study termination for all animals: glucose, urea, bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase.
3.4.8	Urinalysis	The following parameters were measured 6 weeks after study initiation and at study termination for all animals: glucose, blood, protein, pH, urobilinogen, bilirubin, and deposits.
3.5	**Sacrifice and pathology**	All surviving animals were sacrificed by exsanguination and grossly appraised.
3.5.1	Organ Weights	The following tissues were taken: heart, testicle, ovaries, liver, lungs, spleen, adrenals, kidneys, and thyroids.
3.5.2	Gross and histopathology	The following tissues were examined microscopically: aorta, intestine (stomach, duodenum, jejunum, ileum, colon), urinary bladder, hylus (lung) and cervical lymph nodes, heart, testicles, ovaries, uterus, head with eyes and nasal cavities, brain, scalp, lungs, liver, stomach, spleen, skeletal muscle, peripheral nerve, adrenals, kidneys, oesophagus, pancreas, trachea, larynx, oropharynx, and thyroid. Tissues were fixed in 10% buffered formaldehyde solution, embedded in Paraplast and stained with haemalum eosin (HE).
3.5.3	Other examinations	No
3.5.4	Statistics	Statistics include: means, standard deviation, confidence intervals (α = 95% and α = 99%). The values of the control groups were compared to the dosage groups by the Mann-Whitney-Wilcoxon-U-Test.
3.6	**Further remarks**	Chamber temperature recorded continuously
		4 RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical Signs	0.71 mg/m^3 (female): non-specific disturbed behaviour 4.5 mg/m^3 (male, female): non-specific disturbed behaviour, agitation, erected tail See Table A 6.4.3-1
4.1.2	Mortality	No mortalities at any dose
4.2	**Body weight gain**	> 0.71 mg/m^3 (male): decreased body weight (See Table A 6.4.3-2)
4.3	**Food consumption and compound intake**	Not conducted
4.4	**Ophtalmoscopic examination**	Not conducted

Document IIIA/ Section 6.4.3

BPD Data set IIA/ Annex Point VI.6.4

Subchronic oral toxicity test

13-Week Inhalation Study, Rat

X

4.5	**Blood analysis**	
4.5.1	Haematology	No abnormalities detected
4.5.2	Clinical chemistry	No abnormalities detected
4.5.3	Urinalysis	No abnormalities detected
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	The absolute and relative liver weights were reduced in the mid and high dose groups.
4.6.2	Gross and histopathology	No abnormalities detected
4.7	**Other**	Chamber temperature varied within one temperature interval of 23° C (± 3°).

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Ten male and ten female Wistar rats were head-nose exposed to the cyfluthrin-vehicle aerosol for 13 weeks (63 x 6 hours, five times per week) at concentrations of 0.09, 0.71 and 4.5 mg cyfluthrin per m^3 air. The rats exposed to cyfluthrin were compared with rats which had been exposed to air or the vehicle aerosol.

The tests were carried out in dynamic inhalation apparatus The solvent (vehicle) used was a mixture of Lutrol (polyethylene glycol 400) and ethanol, mixed in a ratio of 1:1. The test compound was sprayed with the vehicle by means of a jet, dynamically, into the inhalation chamber. Exposure was of the head-nose type; skin contact was largely prevented.

During the 13 weeks of treatment, body weights, signs and mortality were recorded and clinical chemical, haematological and urine examinations were made. At end of study gross pathological and histopathological examinations were carried out.

5.2 Results and discussion

The male and female rats exposed to the highest concentration showed non-specific disturbed behaviour with agitation at the end of study week 2. The female animals in the 0.71 mg cyfluthrin/m^3 group exhibited non-specific disturbed behaviour from study week 6 onwards.

A significant reduction in body weight gains was observed, in particular in the male rats exposed to the concentrations of 0.71 and 4.5 mg cyfluthrin/m^3 air. In the case of the females, a significant effect on the body weights was only observed in the animals exposed to 0.71 mg cyfluthrin/m^3 air.

There were no toxicologically significant or concentration related alterations in the clinical chemical and haematological parameters. The examination of the N,O-demethylases and cytochrome P-450 in the liver tissue did not detect any indication of enzyme induction. The absolute and relative liver weights were reduced in the mid and high dose groups.

The gross pathological and histopathological examinations did not detect indications of specific organ damage.

5.3 Conclusion

Document IIIA/ Section 6.4.3 **BPD Data set IIA/ Annex Point VI.6.4**	**Subchronic oral toxicity test** 13-Week Inhalation Study, Rat	X

5.3.1	LO(A)EL	0.71 mg/m^3 based on the decreased body weight in males and agitated behaviour in females.
5.3.2	NO(A)EL	The NOEL of 0.09 mg/m air was based on behavioural effects and reductions in growth of male animals exposed to 0.71 mg/m^3 air and above.
5.3.3	Other	
5.3.4	Reliability	1
5.3.5	Deficiencies	Main deviations from OECD No. 413 are: chloride, potassium, sodium, calcium, phosphate, ornithine decarboxylase, γ-glutamyl transpeptidase, albumin, total protein, and creatinine were not determined, and histopathology was not performed for thymus, sternum, uterus, bone marrow, pituitary. These deviations are not considered to compromise the validity of the study.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-09-08
Heading	Subchronic inhalation toxicity test
Materials and Methods	*3.1.2.1 Description:* Amber mass of oily to pasty consistency *3.2.5 Age/weight at study initiation:* Young adult, appr. 6-12 weeks
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A 6.4.3-1: Dynamic Exposure for 63 x 6 Hours

Analytical Concentration (mg/m^3 air)	Toxicological Result*	Length of Signs
Male Rats		
0 (air)	0/0/10	
0 (vehicle)	0/0/10	
0.09	0/0/10	
0.71	0/0/10	
4.52	0/10/10	13d-88d
Female Rats		
0 (air)	0/0/10	
0 (vehicle)	0/0/10	
0.09	0/0/10	
0.71	0/10/10	42d-86d
4.52	0/10/10	9d-86d

* Figures in the "Toxicological Result" column are interpreted:

First figure = number of animals dying

Second figure = number of animals with effects

Third figure = number of animals used

Table A 6.4.3-2: Mean Body Weights (g) by Group and Sex

	Week												
Male	0	1	2	3	4	5	6	7	8	9	10	11	12
Group 1	192	195	208	219	228	233	239	248	255	262	269	268	277
Group 2	191	194	209	222	237	239	246	255	263	264	269	270	276
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-	-	-	-	-	-
Group 3	191	191	203	215	224	229	235	241	243	246	251	249	258
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-	-	+	+	+	+
Group 4	186	188	198	210	221	224	233	237	243	244	247	246	253
TS 1%	-	-	+	+	-	-	-	-	-	+	+	+	+
TS 5%	-	+	+	+	+	+	-	+	-	+	+	+	+
Group 5	190	182	188	196	205	209	215	221	223	228	230	229	236
TS 1%	-	+	+	+	+	+	+	+	+	+	+	+	+
TS 5%	-	+	+	+	+	+	+	+	+	+	+	+	+
Female	0	1	2	3	4	5	6	7	8	9	10	11	12
Group 1	164	164	168	173	179	181	183	186	188	191	189	191	193
Group 2	162	161	163	168	172	174	177	181	181	183	183	183	185
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-	-	-	-	-	-
Group 3	159	159	162	167	171	173	176	179	182	182	183	184	185
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-	-	-	-	-	-
Group 4	157	158	157	159	163	168	170	176	177	176	178	179	178
TS 1%	-	-	+	+	+	-	-	-	-	+	-	-	+
TS 5%	-	-	+	+	+	+	+	-	+	+	+	+	-
Group 5	160	162	161	166	171	173	176	179	182	183	182	183	182
TS 1%	-	-	-	-	-	-	-	-	-	-	-	-	-
TS 5%	-	-	-	-	-	-	-	-	-	-	-	-	+

Nominal Concentrations/Analytical Concentrations:

Group 1 – 0 (air), Group 2 – 0 (vehicle), Group 3 – 0.5 mg/m^3/0.09 mg/m^3, Group 4 – 3.0 mg/m^3/0.71 mg/m^3, Group 5 – 20.0 mg/m^3/4.52 mg/m^3

TS 1%: Significance at $\alpha = 99\%$

TS 5%: Significance at $\alpha = 95\%$

Document IIIA/ Section A6.5/01

BPD Data Set IIA/ Annex Point VI.6.5

Chronic toxicity

12-Month Oral Toxicity, Dogs

Official use only

1 REFERENCE

1.1	**Reference**	*From addendum 2 of the monograph p35* [redacted] (1997) Technical grade Cyfluthrin (FCR 1272) - A chronic toxicity feeding study in the beagle dog. [redacted] Bayer AG Report No.: 108007 BES Ref.: M-044511-02-1 Report date: 20 November 1997 Unpublished Supplemental submission to AC No. 108007: [redacted] (2000) Technical grade Cyfluthrin (FCR 1272) - A chronic toxicity feeding study in the beagle dog. [redacted] Bayer AG Report No.: 108007-1 BES Ref.: M-044511-02-1 Report date: 20 July 2000 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes US-EPA-NFRA, Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Guideline 83-1, November 1984 US-EPA-TSCA, Health Testing Guidelines, 40 CFR Section 798.3320, revised July 1989 OECD Guidelines for Testing of Chemicals, Section 4, Guideline 453, May 1981 taken from study and pesticide summary Japan, Ministry of Agriculture, Forestry and Fisheries, Guidance on Toxicology Study Data for Application of Agricultural Chemical Registration, 59 NohSan No. 4200, January 1985 US-FDA Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food, Appendix II Guidelines for Toxicological Testing, October, 1982
2.2	**GLP**	Yes
2.3	**Deviations**	None that were considered to have compromised the validity of the study results.

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Chronic toxicity

12-Month Oral Toxicity, Dogs

3 MATERIALS AND METHODS

3.1	**Test material**	Test material:
3.1.1	Lot/Batch number	Technical grade cyfluthrin, purity: 94.8 - 95.1 %, batch no.: 4030059/BF9340-71
3.1.2	Specification	
3.1.2.1	Description	Based on analytical chemistry determinations, cyfluthrin in the feed was considered to be homogeneously distributed and stable.
3.1.2.2	Purity	
3.1.2.3	Stability	
3.2	**Test Animals**	
3.2.1	Species	Test animals :
3.2.2	Strain	Pure-bred male and female Beagle dogs; age at study initiation not greater than 25 wk.
3.2.3	Source	[redacted]
3.2.4	Sex	Technical grade cyfluthrin was administered in the diet to Beagle dogs (4 animals/sex/group) for 12 months at initial nominal concentrations of 0-50-100-360-640 ppm. The selection of doses was based on the results of two former dog studies (6-month study: 0-65-200-600 ppm, NOEL 65 ppm [see section 6.4.1/01] and 12-month study: 0-40-160-600 ppm, NOEL: 160 ppm [Hoffmann & Schilde (1983)]). The selected intermediate dosage of 360 ppm was expected to confirm a dose response relationship, while 640 ppm was expected to toxicologically stress the animals without influencing survival. However, the high-dose group began to demonstrate severe neurological symptoms in the first few weeks of the study, with one high-dose female requiring sacrifice following a severe seizure episode. Therefore, the high-dose was reduced to 500 ppm beginning on week 8 for the remainder of the study.
3.2.5	Age/weight at study initiation	
3.2.6	Number of animals per group	
3.2.7	Control animals	
3.3	**Administration/ Exposure**	
3.3.1	Duration of treatment	
3.3.2	Frequency of exposure	The test substance intake is summarised in table IIIA 6.5/01-1below.
3.3.3	Postexposure period	
3.3.4	**Oral**	
3.3.4.1	Type	
3.3.4.2	Concentration	
3.3.4.3	Vehicle	X
3.3.4.4	Concentration in vehicle	
3.3.4.5	Total volume applied	
3.3.4.6	Controls	X
3.4	**Examinations**	Study performed according to OECD Guideline No. 453, as stated in the addendum on the monograph from PPP dossier, no deviations from this guideline were noted.

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Chronic toxicity

12-Month Oral Toxicity, Dogs

3.5 Sacrifice and pathology

3.6 Further remarks

In addition to the routine guideline requirements, the study investigated potential cardiac and neurologic effects. Electrocardiography (ECG) and blood pressure (BP) measurements were performed. Neurological examinations, conducted on all animals at approx. 6 months after study start and just prior to study termination, included: peripheral and cranial reflex tests, task performance tests, gait and behavioural observations as well as rectal temperature measurements. At necropsy, the following organ weights were determined: adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testicles, thymus and thyroid with parathyroid. All tissues and gross lesions from all animals were histopathologically examined.

4 RESULTS AND DISCUSSION

4.1 Observations

4.1.1 Clinical signs

There were clinical neurology findings in this study related to chronic cyfluthrin administration. The 360 ppm and 640/500 ppm doses groups (both sexes) were affected. In the 360 and 640/500 ppm dose groups, principle findings included gait abnormalities (hypermetria, reluctance to walk) and postural reaction deficits (abnormal head placement during wheelbarrowing and abnormal foot placement during backward stepping, abnormal foot placement during lateral hopping, abnormal hemistanding posture). Gait abnormalities were found at the 6 month and pre-sacrifice examinations. Postural reaction deficits were found at the 6 month and pre-sacrifice examinations.

It appeared that the incidence of gait abnormalities and postural deficits was increased in the 640/500 ppm males and females at both the 6 month and the pre-sacrifice exam intervals when compared to the 360 ppm groups. It appeared that the severity of and extent of abnormalities and deficits was slightly increased in the 640/500 ppm males compared to the 360 ppm males. However, two high dose females (ZR4102 and ZR4103) that had a markedly more severe and extensive neurological syndrome than the 360 ppm females or the other 640/500 ppm females.

There were no changes in rectal body temperature related to chronic cyfluthrin administration, excluding hyperthermia secondary to convulsions. There were no other relevant clinical signs attributed to compound administration.

4.1.2 Mortality

Two control animals died in extremis during the study, a male (ZR0004) on day 318 and a female (ZR0102) on day 210. Necropsy was unremarkable in both animals. The animals had been asymptomatic to trained veterinary technicians prior to the clinical episode. Further investigations indicated that both dogs were genealogically predisposed to seizures and probably died suffering from idiopathic epilepsy. Another high-dose female (ZR4103) suffering from extreme neurological symptoms was sacrificed on day 56 due to animal welfare concerns.

4.2 Body weight gain

In evaluation of a possible treatment effect on body weight

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development, no clear dose response relationship could be established (see Table IIIA 6.5/01-2). However, there appeared to be a biologically relevant decrease in body weight gain over the 12-mo treatment period within the 640/500 ppm male (-55 %) and female (-54 %) dose groups when compared to concurrent controls that was considered to be compound-related.

4.3 Food consumption and compound intake

There was no compound-related effect on food consumption in any of the dose groups tested.

4.4 Ophthalmoscopic examination

There were no direct ophthalmological findings related to chronic cyfluthrin administration in this study that were not regarded as variants of normal. However, in one high-dose female, there was a neurological condition that contributed indirectly to ophthalmological findings of ptosis, deficits in direct and indirect pupillary responses and protrusion of the nictitating membrane.

4.5 Blood analysis

4.5.1 Haematology

4.5.2 Clinical chemistry

4.5.3 Urinalysis

There were no clinical chemistry, plasma cholinesterase, haematology or urinalysis findings that were considered treatment-related or toxicologically relevant.

4.6 Sacrifice and pathology

4.6.1 Organ weights

4.6.2 Gross and histopathology

There was a non-significant and somewhat inconsistent trend toward decreased terminal body weights in both sexes when compared with controls (see Table IIIA 6.5/01-3). Due to overlaps in individual weights, initial weight spreads, lack of dose relationship and of statistical significance, it can only be suggested that a treatment effect may be present in the 500 ppm group males, which were terminally 18 % lower than controls. Absolute ovary weights from all treated groups were significantly lower than control values, but no significant differences were evident for relative ovary weights.

There were no treatment-related microscopic lesions.

4.7 Other

There were no dose-related changes found in the ECG or BP parameters measured in this study.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Technical grade cyfluthrin was administered in the diet to Beagle dogs (4 animals per sex and treatment level) for 12 months at initial nominal concentrations of 0, 50, 100, 360 and 640 ppm of technical grade cyfluthrin. However, the high-dose group began to demonstrate severe neurological symptoms in the first few weeks of the study. Therefore, the high-dose was reduced to 500 ppm beginning on week 8 for the remainder of the study.

The average daily consumption of cyfluthrin active ingredient in the male dose groups was 0, 1.36, 2.43, 10.64 and 15.47 mg /kg bw/day and, in the female dose groups 0, 1.46, 3.61, 10.74 and 17.99 mg/kg bw/day.

5.2 Results and discussion

Clinical neurology findings, including gait abnormalities and postural reaction deficits, were observed in mid and high dose animals. Chronic

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cyfluthrin administration produced a reduced body weight gain in both males and females from the high dose group.

The statistically significant decreases in absolute ovary weight changes observed in all treatment groups were likely due to the differences in terminal body weights noted above, as the absolute weights tracked the respective group mean body weights in a near perfect manner. The death of a small control female animal caused the remaining three heavier control animals to bias the mean of the terminal body weight upward and likely caused also a statistical aberration in the absolute ovarian weights. A treatment-related effect on ovary weights was considered to be unlikely in the absence of statistically significant changes in the relative ovary weight, the lack of corresponding histopathological changes, and in the absence of any indication of treatment-related ovary effects from other dog or rodent studies.

5.3 Conclusion

5.3.1	LO(A)EL	The neurological findings noted at 360 ppm (10.64 mg/kg bw/day) demonstrated an intermediate level of toxicity based on findings of gait abnormalities and postural reaction deficits.
5.3.2	NO(A)EL	In the 12-month dietary dog study, the NOAEL was established at 100 ppm (equivalent to 2.4 mg/kg bw/d for males and 3.6 mg/kg bw/d for females), based on neurological findings noted at 360 ppm, which demonstrated an intermediate level of toxicity based on findings of gait abnormalities and postural reaction deficits. The MTD (maximum-tolerated-dose) was established at 500 ppm within the limits of animal welfare concerns. The severity of and extent of neurological abnormalities and deficits were increased in the 640/500 ppm dose groups compared to the 360 ppm dose groups.
5.3.3	Other	
5.3.4	Reliability	1
5.3.5	Deficiencies	None

Evaluation by Competent Authorities

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

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	2006-09-08
Materials and Methods	*3.3.4.3 Vehicle*: Corn oil/acetone *3.3.4.6 Controls:* Yes, vehicle only
Results and discussion	Applicant's version is adopted.
Conclusion	LO(A)EL: 10.7 mg/kg bw/d (360 ppm) based on neurological symptoms: gait and posture abnormalities NO(A)EL: 2.4/3.6 (M/F) mg/kg bw/d (100 ppm)

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Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A 6.5/01-1: Calculated test substance intake

Nominal Dose Levels (ppm)	Average Daily Consumption of cyfluthrin (mg/kg bw/d)	
	Males	Females
0	0.00	0.00
50	1.36	1.46
100	2.43	3.61
360	10.64	10.74
640/500*	15.47	17.99

*This calculation includes the 640 ppm concentration fed during weeks 1-7, since the high-dose was changed on week 8 of the study from 640 to 500 ppm. Therefore, the mean concentration for this level is a time-weighted average, calculated to be 523 ppm (105% of 500ppm).

Table A 6.5/01-2. Body weight gains

Time Period	Mean Bw Gain (g) During the Designated Study Periods									
	Male Dose Groups (ppm)					Female Dose Groups (ppm)				
	0	50	100	360	500/ 640	0	50	100	360	500/ 640
3 mo	3613.7 (100%)	3012.2 (83%)	3046.5 (84%)	3513.0 (97%)	1629.3 (45%)	2611.5 (100%)	1845.7 (71%)	2053.0 (79%)	1838.8 (70%)	920.0 (35%)
6 mo	4883.0 (100%)	3520.5 (72%)	4028.0 (82%)	4407.7 (90%)	2350.0 (48%)	3666.0 (100%)	1909.5 (52%)	2939.5 (80%)	2575.8 (70%)	1804.7 (49%)
12 mo	4864.4 (100%)	3488.2 (72%)	4404.3 (91%)	4579.0 (94%)	2199.8 (45%)	5220.7 (100%)	2514.0 (48%)	3054.3 (59%)	2775.0 (53%)	2379.0 (46%)

Bw gains were determined for 3 months (Day 0 – Day 91), 6 months (Day 0 – Day 182) and 12 months (Day 0 – Day 364).

Table A 6.5/01-3. Terminal body weight and organ weight changes

Parameter		Dose (ppm)				
		0	**50**	**100**	**360**	**640/500**
Males						
Terminal bw (g)		14037	13266	13695	14466	11434
		(100%)	(95%)	(98%)	(103%)	(81%)
Females						
Terminal bw (g)		13503	10383	11098	10495	10290
		(100%)	(77%)	(82%)	(78%)	(76%)
Ovary	abs. wt. (g)	1.940	0.889	1.217	1.034	0.789
		(100%)	(46%)	(63%)	(53%)	(41%)
	rel. wt. (%)	0.014±0.001	0.009±0.002	0.011±0.003	0.010±0.005	0.008±0.002
		(100%)	(64%)	(79%)	(71%)	(57%)

Statistics: ANOVA + Student's t-test (two-sided):*=p≤0.05#

RMS: These weights are statistically significantly lower than controls and should therefore be marked "*".

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Chronic toxicity

2-year Combined Chronic Toxicity / Oncogenicity in the rat

			Official use only
		1 REFERENCE	
1.1	**Reference**	*From addendum 2 of the monograph p41* [redacted] (1997) Technical grade cyfluthrin: a combined chronic toxicity/oncogenicity study in the rat. [redacted] Bayer AG Report No.: 107769 BES Ref.: M-044524-02-1 Report date: 20 November 1997 Unpublished [redacted] (2000). Supplemental Submission to Bayer Report No.: 107769 Bayer AG Report No.: BES Ref.: M-044524-02-1 Report date: Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	OECD Guideline No. 453	
2.2	**GLP**	Yes	
2.3	**Deviations**	None	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in section 2	
3.1.1	Lot/Batch number		
3.1.2	Specification	Test material:	

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Chronic toxicity

2-year Combined Chronic Toxicity / Oncogenicity in the rat

3.1.2.1	Description	
3.1.2.2	Purity	
3.1.2.3	Stability	
3.2	**Test Animals**	
3.2.1	Species	
3.2.2	Strain	
3.2.3	Source	
3.2.4	Sex	X
3.2.5	Age/weight at study initiation	
3.2.6	Number of animals per group	X
3.2.7	Control animals	X
3.3	**Administration/ Exposure**	
3.3.1	Duration of treatment	X
3.3.2	Frequency of exposure	
3.3.3	Postexposure period	
3.3.4	Oral	

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Chronic toxicity

2-year Combined Chronic Toxicity / Oncogenicity in the rat

3.3.4.1	Type	
3.3.4.2	Concentration	
3.3.4.3	Vehicle	
3.3.4.4	Concentration in vehicle	
3.3.4.5	Total volume applied	
3.3.4.6	Controls	
3.4	**Examinations**	Study performed according the OECD Guideline No. 453, as stated in the addendum on the monograph from PPP dossier, no deviations from this guideline were noted.
3.5	**Sacrifice and pathology**	
3.6	**Further remarks**	Haematological and clinical-chemistry examinations including urinalyses were performed on the first 20 surviving rats/sex/dose of the 2-yr sacrifice group. In all cases, blood was sampled via the orbital sinus following an overnight fast; to the extent possible, urine was collected on the same non-fasted animals the week prior to blood collection. In addition to the routine guideline requirements, ophthalmologic exams were conducted on all acclimatised animals prior to exposure, and then again on all surviving animals just prior to termination of the 1- and 2-yr segments of the study. At necropsy, the organ weights and organ/body weights were determined for the following tissues: adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen and testicles. All required tissues plus all gross lesions detected at necroscopy from all animals were histopathologically examined.

4 RESULTS AND DISCUSSION

4.1	**Observations**	
4.1.1	Clinical signs	With the exception of a statistically significantly increased frequency of alopecia noted in 450-ppm males and females (see Table 6.5/02-3), no clinical and/or cage-side observations toxicity attributable to exposure to the test substance were observed.
4.1.2	Mortality	Survival was unaffected by administration of the test substance as the incidence of mortality was comparable between treated and control animals of each sex. Overall, survival to the end of the 2-yr treatment period was in the range of 54-82 %.
4.2	**Body weight gain**	Data for body weight gain and terminal body weight are summarised in Table 6.5/02-2. Body weight gain remained unaffected in both sexes at the low dose level of 50 ppm. At the end of the treatment period, declines of 11 % and 10% body weight gain were noted in 225-ppm males and females, respectively, while at 450 ppm, body weight gains were reduced by 14 % and 21 % in males and females, respectively. Terminal body weights were statistically significantly decreased at 225 ppm and above in both

sexes.

4.3	**Food consumption and compound intake**	The mean test substance intake over the 2-yr treatment period is summarised in Table 6.5/02-1. Food consumption and utilisation was not influenced by treatment in both sexes at all doses tested.
4.4	**Ophtalmoscopic examination**	No ophthalmic toxicity attributable to exposure to the test substance was observed.
4.5	**Blood analysis**	
4.5.1	Haematology	Clinical chemistry findings included a slight albeit statistically significant decline in serum triglyceride concentration (and to a lesser extent serum cholesterol concentration) in 450-ppm males. No evidence of cyfluthrin-induced toxicity was observed in any other in-life parameter including haematology and urinalysis.
4.5.2	Clinical chemistry	
4.5.3	Urinalysis	
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	Statistically significant changes in absolute organ weights and organ/body weight ratios are summarised in Table 6.5/02-4. Decreased absolute weights were accompanied by increases in the respective relative organ weights, indicating that the organ weight changes observed in this study were secondary to cyfluthrin-induced decreases in body weight. This conclusion is supported by the lack of corresponding treatment-related histopathological tissue changes.
4.6.2	Gross and histopathology	There were no neoplastic or non-neoplastic microscopic alterations in the 24-month male and female rats that were considered to be compound-related. Only one neoplasm was marginally increased over the concurrent controls consisting of mammary gland adenocarcinomas in the 24-month 450 ppm female rats (see Table 6.5/02-5).
4.7	**Other**	None

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Cyfluthrin (purity 93-9-95.1%, batch No. 4030059/BF9340-71) was administered to separate 1-year and 2-year sacrifice groups of rats (Fischer-344rats [redacted], Age: 8 weeks at treatment initiation) at nominal dietary concentrations of 0, 50, 225 and 450 ppm. The 1-year sacrifice group consisted of 20 rats/sex in both the control and high groups and 10 rats/sex in both the low and intermediate dose levels. The 2-year sacrifice group consisted of 50 rats/sex in all 4 dose groups.
5.2	**Results and discussion**	The mean treatment concentrations remained within approx. 5 % of the nominal concentrations. Based on analytical chemistry determinations, cyfluthrin was considered to be homogeneously distributed and stable in the feed. Survival was unaffected by administration of the test substance as the incidence of mortality was comparable between treated and control animals of each sex. Overall, survival to the end of the 2-yr treatment period was in the range of 54-82 %. Body weight gain remained unaffected in both sexes at the low dose level of 50 ppm. At the end of the treatment period, declines of 11 % and 10% body weight gain were noted in 225-ppm males and females,

respectively, while at 450 ppm, body weight gains were reduced by 14 % and 21 % in males and females, respectively. Terminal body weights were statistically significantly decreased at 225 ppm and above in both sexes.

With the exception of a statistically significantly increased frequency of alopecia noted in 450-ppm males and females, no clinical and/or cage-side observations toxicity attributable to exposure to the test substance were observed.

Clinical chemistry findings included a slight albeit statistically significant decline in serum triglyceride concentration (and to a lesser extent serum cholesterol concentration) in 450-ppm males. No evidence of cyfluthrin-induced toxicity was observed in any other in-life parameter including haematology and urinalysis.

Decreased absolute weights were accompanied by increases in the respective relative organ weights, indicating that the organ weight changes observed in this study were secondary to cyfluthrin-induced decreases in body weight. This conclusion is supported by the lack of corresponding treatment-related histopathological tissue changes.

There were no neoplastic or non-neoplastic microscopic alterations in the 24-month male and female rats that were considered to be compound-related. Only one neoplasm was marginally increased over the concurrent controls consisting of mammary gland adenocarcinomas in the 24-month 450 ppm female rats.

Despite being out of range of in-house historical control data, the increased incidence of mammary gland adenocarcinomas was considered to be incidental for the following reasons:

1. The incidence was statistically comparable to the concurrent control animals.

2. There was no suggestion of compound-induced carcinogenicity due to cell proliferation based on the incidence of mammary gland hyperplasias, fibroadenomas, and a lack of mammary gland adenomas;

3. No dose-dependent increase incidence of all mammary gland tumours combined was found.

4. Additionally a complete battery of mutagenicity studies performed on the compound indicated it was non-genotoxic.

5. The time to tumour development between control and treated animals appeared to be comparable, as no proliferative lesions of any kind were seen in the mammary glands of the 12-month group in this study and all treated and control 24-month females that contained mammary gland adenocarcinomas were sacrificed at study termination.

6. Finally, there was no evidence of compound-induced carcinogenicity based on a previous two-year feeding study in the Wistar rat with technical grade cyfluthrin at doses identical to those used in this study.

5.3 Conclusion

Based on the lack of adverse compound-related effect in body weight gain at a dose of 50 ppm in males and females, a systemic chronic toxicity NOEL of 2.6 and 3.3 mg cyfluthrin/kg bw/d was established for male and female rats, respectively. No evidence for compound-induced

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Chronic toxicity

2-year Combined Chronic Toxicity / Oncogenicity in the rat

		neoplasia was found in this study.
5.3.1	LO(A)EL	
5.3.2	NO(A)EL	2.6 and 3.3 mg cyfluthrin/kg bw/d was established for male and female rats, respectively
5.3.3	Other	
5.3.4	Reliability	1
5.3.5	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	2006-09-05
Materials and Methods	*3.2.4 Sex:* M + F *3.2.6 Number of animals per group:* 2 yr-groups: 50 M/50 F, 1 yr-groups: 20 M/20 F (control/high dose), 10 M/10 F (medium doses) *3.2.7 Control animals:* Yes *3.3.1 1 Duration of treatment:* 1 yr/2 yr *3.3.4.1 Type:* Dietary *3.3.4.2 Concentration:* 0/0, 2.6/3.3, 11.6/14.4, 22.8/28.3 (M/F) mg/kg bw/d (0,50,225,450 ppm) *3.3.4.3 Vehicle:* Acetone/corn oil *3.3.4.6 Controls:* Vehicle only
Results and discussion	Applicant's version is adopted.
Conclusion	neoplastic LO(A)EL: > 22.8/28.3 mg/kg bw/d (M/F) non-neoplastic LO(A)EL: 11.6/14.4 mg/kg bw/d (M/F) based on decreased body weight gain neoplastic NO(A)EL: 22.8/28.3 mg/kg bw/d (M/F) non- neoplastic NO(A)EL: 2.6/3.3 mg/kg bw/d (M/F)
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*

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Chronic toxicity

2-year Combined Chronic Toxicity / Oncogenicity in the rat

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Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table 6.5/02-1: Rat 2-yr study: Calculated test substance intake

Nominal dose levels (ppm)	Average daily consumption of cyfluthrin (mg/kg bw/d)	
	Males	**Females**
0	0.0	0.0
50	2.6	3.3
225	11.6	14.4
450	22.8	28.3

Table 6.5/02-2: Rat 2-yr study: Body weight gain and terminal body weight

Time period	Mean bw gain (g) during the designated study periods							
	Male dose groups (ppm)				Female dose groups (ppm)			
	0	**50**	**225**	**450**	**0**	**50**	**225**	**450**
wk 1 - wk 13	140.5 (100%)	136.9 (97 %)	123.9 (88 %)	108.8 (77%)	54.7 (100%)	53.3 (97 %)	51.2 (94 %)	45.0 (82 %)
wk 1 - wk 26	181.4 (100%)	175.9 (97 %)	160.4 (88 %)	145.6 (80 %)	73.3 (100%)	71.8 (98 %)	68.3 (93 %)	58.3 (80 %)
wk 1 - wk 52	224.0 (100%)	217.8 (97 %)	196.9 (88 %)	173.3 (77 %)	92.0 (100%)	89.4 (97 %)	86.8 (94 %)	73.9 (80 %)
wk 1 -wk 104[a]	192.1 (100%)	180.8 (94 %)	171.9 (89 %)	165.0 (86 %)	149.9 (100%)	137.9 (92 %)	134.7 (90 %)	118.8 (79 %)
Terminal body weight (g)	366.7 (100%)	354.5 (97 %)	344.4* (94 %)	340.5* (93 %)	274.5 (100%)	263.8 (96 %)	256.2* (93 %)	236.3* (86 %)

[a] Last body weight determinations for females were performed during treatment week 103.
Statistics: Anova + Dunnett's test: * = $p < 0.05$

Table 6.5/02-3: Rat 2-yr study: Clinical observations

Group	Incidence of alopecia (skin, forelimb)							
	Male dose groups (ppm)				Female dose groups (ppm)			
	0	**50**	**225**	**450**	**0**	**50**	**225**	**450**

1-year group	0/20	0/10	1/10	2/20	2/20	0/10	1/10	5/20
2-year group	1/50	1/50	3/50	6/50	5/50	5/50	6/50	9/50

Table 6.5/02-4: Rat 2-yr study: Organ weight changes

Parameter	Dose (ppm)			
	0	50	225	450
Males				
Adrenals abs. wt (g)	0.088 (100%)	0.085 (97 %)	0.072[s] (82 %)	0.070[s] (80%)
rel. wt (%)	0.013 (100%)	0.013 (100%)	0.014 (108 %)	0.014* (108%)
Kidneys abs. wt (g)	3.587 (100%)	3.586 (100%)	3.341* (93 %)	3.287* (92 %)
rel. wt (%)	0.799 (100%)	0.830 (104%)	0.846* (106%)	0.873* (109 %)
Liver abs. wt (g)	18.29 (100%)	17.08 (93 %)	15.95* (87 %)	14.73" (81 %)
rel. wt (%)	3.778 (100%)	3.881 (103 %)	3.980 (105%)	4.096* (108%)
Females				
Liver abs. wt (g)	11.47 (100%)	11.32 (99%)	11.08 (97%)	10.05[s] (88 %)
rel. wt (%)	4.097 (100%)	4.119 (101%)	4.067 (99 %)	4.217 (103 %)

Statistics: Anova + Dunnett's test: * = p<0.05;

Kruskal-Wallis Anova + Mann- Whitney u-test: s = p < 0.05.

CA: in box "Liver abs. wt (g) of 450 ppm group "substitute " by *

Table 6.5/02-5: Rat 2-yr study: Findings in the female mammary gland

MAMMARY GLAND	Incidence of mammary gland lesions(animals with lesion / animals examined)					
	Dose level				Historical control data[a]	
	0	50	225	450	92-272-SC	91-272-LJ
Hyperplasia	0/50	1/50	0/50	2/50	0/50	0/50
Adenomas	0/50	0/50	0/50	0/50	0/50	1/50
Adenocarcinoma	1/50	0/50	0/50	4/50	0/50	1/50
Fibroadenoma	9/50	15/50	9/50	4/50	no data	no data
Total mammary gland tumours	10/50	15/50	9/50	8/50	no data	no data

[a] Historical control data was available from two 2-year studies conducted at the testing facility using the Fischer-344 rat (Study-No. 92-272-SC and 91-272-LJ)

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1 REFERENCE

1.1	**Reference**	[redacted] (1983) FCR 1272 (Cyfluthrin, the active ingredient of Baythroid) chronic study on rats. [redacted] Unpublished Bayer AG Report No.: 11949 Report date: 19 July 1983 [BES Ref.: M-039641-02-1] [redacted] (1994). Addendum to report No.: 11949 Unpublished Bayer AG Report No.: 11949A Report date: 26 October 1994 [BES Ref.: M-039641-02-1]
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No guideline in force at the time the study was conducted
2.2	**GLP**	No. When the study was performed, GLP was not compulsory.
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	As given in section 2
3.1.1	Lot/Batch number	batch no.: not specified
3.1.2	Specification	
3.1.2.1	Description	Cyfluthrin, 50 % pre-mix with colloidal silicic acid
3.1.2.2	Purity	purity: 49.7 to 51 %,
3.1.2.3	Stability	Homogeneity and stability checked (Study No. T9013140, included in Document BES Ref.: M-039641-02-1)
3.2	**Test Animals**	Non-entry field
3.2.1	Species	Rat

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3.2.2	Strain	[redacted] rats
3.2.3	Source	[redacted]
3.2.4	Sex	Males and females
3.2.5	Age/weight at study initiation	5 to 6 weeks at treatment initiation Mean initial weight: 80 g (males) and 82 g (females).
3.2.6	Number of animals per group	65/sex/group 5 animals per sex and dose level were used to determine microsomal enzyme activities after the first week of treatment, and 10 animals per sex and dose level were used for the interim autopsy after one year of treatment
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	2 years
3.3.2	Frequency of exposure	5 days per week, daily or other
3.3.3	Postexposure period	14 days, 4 weeks or other
3.3.4	**Oral**	
3.3.4.1	Type	in food
3.3.4.2	Concentration	0, 50, 150, and 450 ppm corresponding to 2.02, 6.19 or 19.20 mg/kg bw/d for males and 3.71, 8.15 or 25.47 mg/kg bw/d for females.
3.3.4.3	Vehicle	food
3.3.4.4	Concentration in vehicle	0, 50, 150, and 450 ppm
3.3.4.5	Total volume applied	Not applicable, diet given *ad libitum*
3.3.4.6	Controls	Plain diet
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Clinical signs were observed twice a day during the week and once during week-ends.
3.4.1.2	Mortality	
3.4.2	Body weight	Body weight was determined weekly from week 1 to 27 and every 14 days from week 27 to 74.
3.4.3	Food consumption	Food consumption was determined on a weekly basis.
3.4.4	Water consumption	Not reported, given *ad libitum*
3.4.5	Ophthalmoscopic examination	Not conducted

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3.4.6	Haematology	Yes Haematological and clinical-chemistry examinations including urinalyses were performed on 10 animals/sex/dose at 6, 12, 18 and 24 months after the start of treatment. Erythrocyte, leukocyte, and thrombocyte counts as well as MCV and hemoglobin concentration: measured with Coulter Counter Calculation of MCH, MCHC, and hematocrit Leukocyte differential counts: using smears (Wright's stain, modified method) Thromboplastin time at end of experiment
3.4.7	Clinical Chemistry	Yes Clinical laboratory tests were conducted on 10 males and 10 females from each test group at 6, 12, 18, and 24 months after the start of treatment. At 12 months, the serum protein was determined by electrophoresis. <u>Enzymes in Plasma:</u> Alkaline Phosphatase (ALP) , Glutamate oxalacetate transaminase (GOT), Glutamate pyruvate transaminase (GPT) <u>Substrates in Plasma::</u> Creatinine , urea , blood glucose ,cholesterol ,bilirubin , total protein <u>Determinations in Serum:</u> Protein electrophoresis, Na, K , Ca <u>Fluoride Determination:</u> At 12 and 24 months, the fluoride content was determined in bones and teeth of 5 males and 5 females randomly selected from each group.
3.4.8	Urinalysis	Yes <u>Semiquantitative:</u> Glucose, blood, protein, and pH, ketone bodies, bilirubin, urobilinogen Microscopic examination of the sediment after centrifuging the urine samples <u>Quantitative:</u> Protein, volume of urine
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	Yes Heart, testes, lungs, liver, spleen, kidneys, adrenals, and ovaries.
3.5.2	Gross and histopathology	Yes After 1 year of treatment, 5 randomly selected rats/sex/dose were sacrificed. After 1 year and 2 years of treatment, 5 rats/sex/dose were perfused with 10% buffered formaldehyde solution. All animals were dissected and grossly examined and organ weights (except for perfused animals) were determined. Histopathological examination was conducted on selected organs.

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3.5.3	Other examinations	After the initial week of the experiment, the activity of the N-demethylase (N-DEM) and of the O-demethylase (O-DEM) as well as the concentration of cytochrome P 450 was determined in the liver of 5 males and 5 females randomly selected from each group. The organs of these rats were not grossly examined and were not fixed.
3.5.4	Statistics	The following were calculated: – arithmetic means of the values of each group, standard deviation s, and upper and lower confidence limits at the confidence level 1 - alpha = 95% and 1 - alpha = 99%. – The. data for the test populations were compared with the control population by means of the significance test (U test) of MANN, WHITNEY, and WILCOXON at the significance level alpha = 5% and alpha = 1%. – The mortality rates of the test populations were compared with the control population by means of Fisher's exact test at the significance level alpha = 5% and alpha = 1
3.6	**Further remarks**	
		4 RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical signs	None in any dose group.
4.1.2	Mortality	Survival was unaffected by administration of the test substance as the incidence of mortality was comparable between treated and control animals of each sex.
4.2	**Body weight gain**	At 150 ppm a slight transient retardation of growth was observed, while at 450 ppm growth was clearly retarded for the entire experimental period. (See table A6.5/03-1)
4.3	**Food consumption and compound intake**	Food consumption was not affected by treatment. Compound intake was 2.02, 6.19 and 19.20 mg/kg bw/day in males and 2.71, 8.15 and 25.47 mg/kg bw/day in females.
4.4	**Ophtalmoscopic examination**	Not conducted.
4.5	**Blood analysis**	
4.5.1	Haematology	At 6 months, the leukocyte counts were significantly increased at 450 ppm in males and females, and at 150 ppm in females. At 18 months it was significantly lower in females at 450 ppm. At 24 months, it was decreased in males at all dosage groups. There was no clear dose relationship in this parameter. (See table A6.5/03-2)
4.5.2	Clinical chemistry	Significant increases over control in the blood glucose concentration were determined at 18 month for the male rats at all dosage levels. This parameter was not increased statistically at 12 and 24 months for males. Furthermore, the blood glucose concentration was not increased over the control for the females at 18 month. (See table A6.5/03-2) The fluoride content in teeth and bones of treated animals was similar to

		those of control values at month 12 of the study. Increased fluoride levels were noted in the teeth and bones of males receiving the high dose, and in the bones of males receiving the mid-dose and females receiving the high-dose level. (See table A6.5/03-2)
4.5.3	Urinalysis	Urinalysis measured parameters were not affected by treatment.
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	The absolute organ weights of the livers were decreased at 12 and 24 months. Additionally the relative organ weights of the adrenals were increased at 24 months in the highest dose group. (See table A6.5/03-3)
4.6.2	Gross and histopathology	The examined organs of the rats of all dose groups showed spontaneous inflammatory or degenerative changes. In female rats an increase of adrenal cortical hyperplastic nodules and of ovarial stromal hyperplasia were found. The adrenal glands of males showed an increased incidence of medullary hyperplasia. (See table A6.5/03-4) In every group the range of tumors found was normal for rats of the given age and conformed to the relevant experience with this strain. A slight increase in the combined incidence of medullary hyperplasia and pheochrompcytomas in the adrenals of male rats was observed. No evidence of oncogenicity of the substance at any dose could be derived from the type, localisation, incidence and latency of neoplasias found. (See table A6.5/03-5) Macroscopic-anatomical and histopathological examinations did not reveal any sign of damage to the liver or kidneys in any of the groups. Necropsies, macroscopic-anatomical examinations and histopathological examinations of dead animals, animals sacrificed in moribund condition as well as animals sacrificed in good health halfway through and at the end of the study did not yield any evidence of a specific organ-damaging effect of the test substance at doses up to and including 450 ppm. In all groups, the range of tumours reported was in the normal range for rats of the given age and strain.
4.7	**Other**	Enzyme induction assay: No differences were noted in N- or O-demethylase activities or cytochrome P450 levels in treated animals when compared to control values, except for a significant increase in N-demethylase activity in females receiving the high-dose. (See table A6.5/03-2)

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2-year Combined Chronic Toxicity / Oncogenicity in the rat

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Cyfluthrin, 50 % pre-mix with colloidal silicic acid (purity 49.7 to 51 %, batch No. not specified) was administered at dose levels of 0, 50, 150 and 450 ppm to [redacted] rats aged 5 to 6 weeks at treatment initiation. Each dose group was composed of 65 animals. Five animals of each sex and dose were used to determine microsomal enzyme activities. After 1 year of treatment, Ten randomly selected rats per sex per dose were sacrificed. At termination, all surviving animals were sacrificed, dissected and grossly examined. Histopathological examination was conducted on selected organs.

5.2 Results and discussion

Based on analytical chemistry determinations, cyfluthrin was considered to be homogeneously distributed and stable in the feed. The analytical results of the verification of all nominal concentrations demonstrated a good a good correspondence with the nominal concentrations.

In appearance, behaviour, food consumption and survival rate the animals treated with cyfluthrin did not differ from the controls. The dose of 150 ppm induced a slight transient retardation of growth, while at 450 ppm growth was clearly retarded for the entire experimental period.

Haematological examination did not reveal any evidence of toxic effects of cyfluthrin at doses up to and including 450 ppm. Clinical chemical analysis, macroscopic-anatomical and histopathological examinations and organ gravimetry did not reveal any signs of damage to the liver or kidneys in any of the groups. At necropsy, macroscopic-anatomical examinations and histopathological examinations of dead animals, animals sacrificed in moribund condition as well as animals sacrificed in good health halfway through and at the end of the study did not yield any evidence of a specific organ-damaging effect of the test substance at doses up to and including 450 ppm.

In all groups, the range of tumours reported was in the normal range for rats of the given age and strain. Cyfluthrin was not found to possess any oncogenic potential.

5.3 Conclusion

The no-observed-adverse-effect level was 50 ppm eq. to 2.02 and 2.71 mg/kg bw/day in males and females, respectively, based on a slight transient retardation in growth of rats at 150 ppm. No evidence for compound-induced neoplasia was found in this study.

A NOAEL was used, since some parameters were statistically significantly changed at the lowest dose level of 50 ppm (e.g. leukocyte counts, blood glucose), which are not considered as toxicologically significant by the rapporteur of the 91/414 Review

5.3.1 LO(A)EL — 150 ppm eq. to 6.19 and 8.15 mg/kg bw/day in males and females, respectively

5.3.2 NO(A)EL — 50 ppm eq. to 2.02 and 2.71 mg/kg bw/day in males and females, respectively

5.3.3 Other

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5.3.4	Reliability	2 Study superseded by a guideline GLP study ([redacted], 1997 BES Ref. M-044524-02-1, See Point 6.5/02)
5.3.5	Deficiencies	The number of animals per sex and dose group was 65 instead of 70, ophthalmological examinations were not performed, hematology was not performed after three months, ornithine decarboxylase and gamma glutamyl transpeptidase were not determined, the amount of albumin was only determined by protein electrophoresis after 12 months. The brain weight was not determined. The histopathological investigations did not include mammary gland. Additional investigations: The liver function (N-demethylase, O-demethylase, cytochrome P-450, alkaline phosphatase) and the concentration of fluoride in bones and teeth were determined 12 and 24 months after the start of the study. This study was considered as acceptable during the 91/414/EC Review

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Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007/03/02
Materials and Methods	Applicant's version is acceptable.
Results and discussion	*Table A6.5/03-1:* 12 month body weights of interim sacrificed animals only. See CA-Table 1 for body weights of all animals.
Conclusion	Differing from the applicant's version the NOAEL/LOAEL are as follows: LO(A)EL: 19/25 mg/kg bw/d based on a significant decreased body weight gain of 8-11% NO(A)EL: 6.2/8.2 mg/kg bw/d
Reliability	2 (reliable with restrictions)
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM (specify)
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.5/03-1: Mortality and body weight

Dose [ppm] Sex	0 M / F	50 M / F	150 M / F	450 M / F
Mortality (24 months) %	12 / 14	8 / 10	4 / 10	18 / 18
Body weight (12 months) [g]	435 / 234	418 / 235	385 / 247	371 / 208
± SD [g]	19 / 15	39 / 23	25 / 26	27 / 11
Significance #	-	-	** / -	** / *
Body weight (24 months) [g]	418 / 265	408 / 266	410 / 252	382 / 237
± SD [g]	46 / 26	37 / 29	48 / 33	34 / 25
Significance #	-	-	- / *	** / **

(# = * p<0.05 / ** p<0.01)

Table A6.5/03-2: Clinical laboratory tests and enzyme induction assay

Dose [ppm] **Sex**	**0** **M / F**	**50** **M / F**	**150** **M / F**	**450** **M / F**
Leukocytes (6 months) [giga/l]	9.1 / 6.8	8.9 / 7.7	9.3 / 8.0	11.8 / 7.9
± SD [giga/l]	1.1 / 1.0	1.6 / 1.8	1.1 / 1.5	2.9 / 0.9
Significance #	-	-	- / *	* / *
Leukocytes (18 months) [giga/l]	6.5 / 4.4	5.7 / 4.3	5.5 / 5.3	5.5 / 3.7
± SD [giga/l]	1.6 / 0.7	1.2 / 0.7	0.9 / 3.4	1.2 / 0.7
Significance #	-	-	-	- / *
Leukocytes (24 months) [giga/l]	7.3 / 5.7 (1)	5.6 / 4.4	5.8 / 5.3	5.8 / 4.8
± SD [giga/l]	1.0 / 4.4 (1)	0.9 / 0.6	0.8 / 1.9	1.7 / 0.9
Significance #	-	** / -	* / -	* / -
Glucose (18 months) [mmol/l]	4.46 / 4.95	5.18 / 4.78	5.25 / 5.29	5.42 / 5.30
± SD [mmol/l]	0.6 / 0.7	0.5 / 0.6	0.6 / 0.5	0.3 / 0.5
Significance #	-	* / -	* / -	* / -
N-demethylase (7 days) [nmol/g/min]	108 / 59	108 / 69	109 / 71	135 / 104
± SD [nmol/g/min]	12 / 6	13 / 14	33 / 9	37 / 14
Significance #	-	-	-	- / *

(# = * p<0.05 / ** p<0.01)

(1) One uncommon value of 18.1 giga/l at animal No.87

Table A6.5/03-3: Organs weights

Dose [ppm] **Sex**	**0** **M / F**	**50** **M / F**	**150** **M / F**	**450** **M / F**
Liver (abs. / 12 months) [mg]	14810 / 8361	14828 / 7311	13245 / 7506	12900 / 6781
± SD [mg]	1921 / 851	1648 / 1108	1775 / 1053	376 / 776
Significance #	-	-	-	** / **
Liver (abs. / 24 months) [mg]	14192 / 9332	14607 / 9156	14242 / 8508	12975 / 8330
± SD [mg]	1839 / 1060	1989 / 1196	2152 / 1117	1699 / 1158
Significance #	-	-	- / **	** / **
Adrenals (rel. / 24 months) [%]	10 / 25	11 / 24	11 / 25	16 / 29
± SD [%l]	2 / 12	2 / 7	3 / 7	26 / 14
Significance #	-	-	* / -	- / **

(# = * p<0.05 / ** p<0.01)

Table A6.5/03-4: Histopathology, non-neoplastic lesions

Dose [ppm] Sex	0 M / F	50 M / F	150 M / F	450 M / F
Ovaries	/ 50	/ 50	/ 50	/ 50
– Stromal hyperplasia	/ 3	/ 6	/ 9	/ 9
Adranal glands	48 / 50	48 / 49	49 / 50	50 / 49
– Cortic. hyp. nodule	10 / 4	21 / 9	14 / 11	20 / 18
– Medull. hyperplasia	4 / 5	8 / 9	8 / 1	14/ 4

Table A6.5/03-5: Histopathology, neoplastic lesions

Dose [ppm]	0	50	150	450
Sex	M / F	M / F	M / F	M / F
Adrenals [No.#]	48 / 50	48 / 49	49 / 50	50 / 49
– Cortical carcinoma (m)	0 / 1	0 / 0	0 / 0	0 / 0
– Pheochromocytoma (b/m)	4 / 0	3 / 2	5 / 1	6 / 1
Bones [No.#]	49 / 50	50 / 50	49 / 50	50 / 49
– Osteochondroma (b)	0 / 0	0 / 0	0 / 0	0 / 1
– Fibrosarcoma (m)	1 / 0	0 / 0	0 / 0	0 / 0
Brain [No.#]	49 / 50	50 / 50	49 / 50	50 / 49
– Meningioma (m)	0 / 0	1 / 0	0 / 0	0 / 0
– Astrocytoma (m)	0 / 2	1 / 0	0 / 1	0 / 0
Cutis and subcutis [No.#]	1 / 4	2 / 10	0 / 4	5 / 4
– Adenoma (b)	0 / 0	1 / 0	0 / 0	0 / 0
– Basal cell. carcinoma (m)	0 / 0	0 / 1	0 / 0	0 / 0
– Squam. cell. carcinoma (m)	0 / 0	0 / 1	0 / 1	0 / 0
– Lipoma (b)	0 / 0	1 / 0	0 / 0	0 / 1
– Malign. neurilemmoma (m)	0 / 0	0 / 1	0 / 0	0 / 0
– Fibrosarcoma (m)	0 / 0	0 / 2	0 / 1	2 / 0
– Fibroma (b)	1 / 0	0 / 0	0 / 0	1 / 0
Heart [No.#]	49 / 50	50 / 50	49 / 50	50 / 49
– Aortic body tumor (b)	0 / 0	1 / 0	0 / 0	0 / 0
– Endocardial tumor (b)	1 / 0	1 / 0	0 / 0	0 / 0
– Endocardial sarcoma (m)	0 / 0	0 / 0	0 / 0	0 / 1
Kidneys [No.#]	49 / 50	49 / 50	49 / 50	50 / 49
– Adenoma (b)	0 / 0	0 / 0	1 / 0	0 / 0
– Lipomatous tumor (b)	0 / 0	1 / 0	1 / 1	0 / 0
Liver [No.#]	49 / 50	50 / 50	49 / 50	50 / 49
– Carcinoma (m)	0 / 0	0 / 0	0 / 0	1 / 0
Lymph nodes [No.#]	49 / 50	49 / 47	46 / 48	50 / 49
– Hemangioma (b)	0 / 0	1 / 0	0 / 0	0 / 0
Mammary glands [No.#]	0 / 5	0 / 5	1 / 4	0 / 5
– Carcinoma (m)	0 / 1	0 / 1	0 / 0	0 / 0
– Fibroadonoma (b)	0 / 5	0 / 3	0 / 3	0 / 3
Ovaries [No.#]	0 / 50	0 / 50	0 /49	0 / 49
– Gran. Theca cell.	0 / 3	0 / 0	0 / 2	0 / 2
Pancreas [No.#]	48 / 50	48 / 50	49 / 49	50 / 49
– Islet cell tumor (b)	0 / 0	0 / 0	2 / 0	0 / 0
– Exocrine adenoma (b)	0 / 0	1 / 0	0 / 0	0 / 0
Parathyroids [No.#]	15 / 14	6 / 14	6 / 13	14 / 15
– Adenoma (b)	2 / 0	1 / 0	0 / 1	0 / 0
Pituitary [No.#]	47 /49	49 / 50	47 / 48	47 / 48
– Adenoma (b)	10 / 14	12 / 23	19 / 12	7 / 12
Reticuloend. tissue [No.#]	49 / 50	50 / 50	49 / 50	50 / 49
– Malignant lymphoma (m)	0 / 0	0 / 0	0 / 0	1 / 0
– Malignant hysticytoma (m)	0 / 0	1 / 1	0 / 0	2 / 0

Table A6.5/03-5: Histopathology, neoplastic lesions				
Dose [ppm] **Sex**	**0** **M / F**	**50** **M / F**	**150** **M / F**	**450** **M / F**
Spleen [No.#]	49 / 50	48 / 50	49 / 50	50 / 49
– Hemangioma (b)	0 / 0	0 / 0	1 / 0	0 / 0
Testes [No.#]	49 / 0	49 / 0	49 / 0	50 / 0
– Leydig's cell tumor (b)	3 / 0	5 / 0	5 / 0	4 / 0
– Mesothelioma (b)	2 / 0	0 / 0	0 / 0	4 / 0
Thymus [No.#]	0 / 0	0 / 0	1 / 0	0 / 0
– Squam. cell. carcinoma (m)	0 / 0	0 / 0	1 / 0	1 / 0
Thyroids [No.#]	49 / 49	48 / 48	47 / 49	48 / 47
– Adenoma (b)	4 / 2	2 / 1	2 / 1	1 / 0
– Carcinoma (m)	0 / 0	2 / 0	0 / 3	1 / 0
Urinary bladder [No.#]	48 / 50	48 / 49	49 / 48	50 / 49
– Papilloma (b)	0 / 0	0 / 0	0 / 0	0 / 3
Uterus [No.#]	0 / 50	0 / 50	0 / 50	0 / 49
– Adenocarcinoma (m)	0 / 5	0 / 4	0 / 4	0 / 3
– Polyp (b)	0 / 14	0 / 7	0 / 20	0 / 17

[(No# =]: Number of rats examined; (b): benign; (m): malignant

CA-Table 1 Body weight – week 53

Dose [ppm] **Sex**	**0** **M / F**	**50** **M / F**	**150** **M / F**	**450** **M / F**
Body weight [g]	399 / 239	398 / 238	388 / 232	369 / 222
± SD [g]	32 / 20	38 / 19	41 / 21	32 / 16
Significance #	-	-	-	**

(* $p<0.05$ / ** $p<0.01$)

Document IIIA/ Section 6.6.1

Genotoxicity in vitro

In Vitro Gene Mutation Study in Bacteria (*Salmonella typhimurium*)

BPD Data set IIA/ Annex Point VI.6.6

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1980). FCR 1272 – Salmonella/microsome test for detection of point-mutagenic effects. [redacted] Bayer AG Report No.: 9273 BES Ref.: M-039114-01-1 Report date: 27 June 1980 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes FCR 1272 was tested for mutagenicity by the Salmonella/ microsome test described by AMES et al. (1973, 1975), more commonly known as the Ames test.
2.2	**GLP**	No, when the study was performed, GLP was not compulsory (as study started before June 30 1988).
2.3	**Deviations**	The test was generally in compliance with the demands of Directive 92/69/EEC, part B, December 29, 1992. Main deviations concern the choice of positive control substances and the reporting of test results. These deviations do not affect the overall integrity of the study.

3 MATERIALS AND METHODS

3.1	**Test material**	FCR 1272 (cyfluthrin)
3.1.1	Lot/Batch number	Batch No. 16001/79
3.1.2	Specification	As given in sections 2 and 3 of Doc IIIA
3.1.2.1	Description	
3.1.2.2	Purity	83.6%
3.1.2.3	Stability	Not stated.
3.2	**Study Type**	Bacterial reverse mutation test (Ames test)
3.2.1	Organism/cell type	*Salmonella typhimurium* LT2 mutants TA 98, TA 100, TA 1535, TA 1537
3.2.2	Deficiencies / Proficiencies	Not applicable

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Genotoxicity in vitro

In Vitro Gene Mutation Study in Bacteria (*Salmonella typhimurium*)

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3.2.3	Metabolic activation system	S9 derived from adult male Sprague-Dawley rats. The homogenate was prepared by the performing laboratory. For enzyme induction, the animals received a single intraperitoneal injection of Aroclor 1254 (500 mg/kg b.w. dissolved in peanut oil) five days before sacrifice. The livers were excised and prepared by the procedure reported by AMES et al (1975) and the S-9 fraction was stored in 10ml portions at -80°C.
3.2.4	Positive control	Cyclophosphamide in the form of Endoxan® (Asta), Batch No. 8343 Trypaflavin (Roth), Batch No. 0282995
3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	FCR 1272, main test (with and without S9): 0 - 20 - 100 - 500 - 2500 - 12500 µg/plate in the main test, 0-3000-6000-12000 µg/plate in the first repeat test and 0-6000-12000-24000 µg/plate in further repeat tests with TA1535, TA100 or 0-1500-3000-6000-12000 µg/plate with TA1537 Controls (with and without S9): Cyclophosphamide, TA 100, TA 1535: 300 µg/plate Trypaflavin, TA 98, TA 1537: 200 µg/plate
3.3.2	Way of application	The solvents used were DMSO for FCR 1272 and trypaflavin, and demineralised water for Endoxan.
3.3.3	Pre-incubation time	Not applicable
3.3.4	Experimental Procedure	Four agar plates were used per substance and dose. To score the total number of bacteria, two plates were used in each group and a 10^{-6} dilution made. The bacterial suspensions used were from 24-hour nutrient broth cultures incubated at 37°C. They were added to the plates which already contained test-substance concentrations or the positive controls—S9 mix was added to half the plates in order to determine any possible detoxifications caused by metabolism. The plates were counted after incubation at 37°C for 48 hours.
3.4	**Examinations**	
3.4.1	Number of cells evaluated	To determine the number of mutants, four agar plates were used per substance and dose. To score the total number of bacteria, two plates were used in each group and a 10^{-6} dilution made. Total number of bacteria ranged from 15-408 x 10^8 bacteria/mL
3.4.2	Acceptance criteria	A reproducible dose-dependent increase in the number of mutants to a level about double that of the negative control, obtained with at least one strain, is considered to be a positive result.
3.4.3	Statistical analysis	Means, standard deviation

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Genotoxicity in vitro

In Vitro Gene Mutation Study in Bacteria (*Salmonella typhimurium*)

		4 RESULTS AND DISCUSSION	
4.1	**Genotoxicity**		
4.1.1	without metabolic activation	An increase in the numbers of mutants was noted in the first experiment, in comparison with the respective negative control, on each of the four strains used. Confirmation of the increase on Salmonella typhimurium TA1535, TA100 and TA98 was not obtained in two repeat tests, and therefore it is considered to have been incidental. The repeat test on Salmonella typhimurium TA1537 again resulted in doublings of mutant numbers as compared with the negative control. However, these doublings were not dose-related and therefore they are attributed to the low rate of mutants in the negative control. This was confirmed by the second repeat test which produced a completely negative result. See table A 6.6.1-1 to table A 6.6.1-3	
4.1.2	with metabolic activation	No real difference was seen between strains with and without S9. Results reported above are equally true in the presence of S9 activation. See table A 6.6.1-1 to table A 6.6.1-3	
4.2	**Cytotoxicity**	In the Salmonella/microsome test FCR 1272 tested at doses of up to and including 24000 µg/plate did not cause any bacteriotoxic effects. However, FCR 1272 precipitated at dose levels of 2500 µg/plate and above.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	FCR 1272 (batch no.: 16001/79, purity: 83.6 %) was tested for mutagenic effects in a Salmonella/ microsome test on four Salmonella typhimurium LT2 mutants, viz. the histidine-auxotrophic strains TA 1535, TA 100, TA 1537 and TA 98 at the following doses : 0-20-100-500-2500-12500 µg/plate in the main test, 0-3000-6000-12000 µg/plate in the first repeat test and 0-6000-12000-24000 µg/plate in further repeat tests with TA1535, TA100 or 0-1500-3000-6000-12000 µg/plate with TA1537 The test material was formulated in DMSO, which was also used as negative control compound. Positive controls were cyclophosphamide on TA100, TA1535 (300 µg/plate) and trypoflavin on TA98, TA1537 (200 µg/plate).	X
5.2	**Results and discussion**	<u>Cytotoxicity test;</u> Cyfluthrin tested at doses of up to and including 24000 pg/plate did not cause a bacteriotoxic effect (high concentration tested only with strain TA1535 and TA100). However, Cyfluthrin precipitated at dose levels of 2500 pg/plate and above. <u>Reverse mutation assay;</u> An increase in the numbers of mutants was noted in the first experiment, in comparison with the respective negative control, on each of the four strains used. Confirmation of the increase on Salmonella typhimurium TA1535, TA100 and TA98 was not obtained in a repeat test (two repeat tests on TA100), and therefore the increase was considered as incidental. The repeat test on Salmonella typhimurium TA1537 again resulted in doublings of mutant numbers as compared with the negative	

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In Vitro Gene Mutation Study in Bacteria (*Salmonella typhimurium*)

		control. However, these doublings were not dose-related and therefore they are attributed to the low rate of mutants in the negative control. This was confirmed by the second repeat test which produced a completely negative result. The positive controls (cyclophosphamide and trypoflavin) on the other hand, increased the number of mutants well over that recorded for the negative controls, and thus demonstrated the sensitivity of the system and the activity of the S-9 mix.
5.3	**Conclusion**	Taken the results of all the individual experiments together there was no indication of cyfluthrin having a mutagenic effect on the tester strains used in this study.
5.3.1	Reliability	2
5.3.2	Deficiencies	Yes Main deviations from 92/69/EEC B14: - Choice of positive controls (cyclophosphamide, trypaflavin) - Repeat tests did not include all concentrations - No individual plate data given in the report

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-29
Materials and Methods	pre-guideline study, similar to OECD No. 471 *5.1* FCR 1272 (batch no.: 16001/79, purity: 83.6 %) was tested for mutagenic effects in a Salmonella/ microsome test on four Salmonella typhimurium LT2 mutants, viz. the histidine-auxotrophic strains TA 1535, TA 100, TA 1537 and TA 98 at the following doses
Results and discussion	Table A 6.6.1-1: see note
Conclusion	Applicant's version is adopted.
Reliability	2
Acceptability	acceptable
Remarks	-

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Genotoxicity in vitro

In Vitro Gene Mutation Study in Bacteria (*Salmonella typhimurium*)

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	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading number and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A 6.6.1-1: Salmonella/Microsome Test with FCR 1272 on *Salmonella typhimurium* TA 1537

Dose in µg per Plate	Mutants/Plate (M/P)		Total No. of Bacteria per ml x 10^8	M/P Treatment / M/P Negative Control	
	+ S-9 mix	- S-9 Mix		+ S-9 mix	- S-9 Mix
12500	27.0	19.0	256.9	5.40	8.26
2500	6.8	2.0	287.7	136	0.87
500	5.0	2.5	281.0	1.00	1.09
100	8.5	3.8	250.0	1.70	1.65
20	4.5	3.5	251.1	0.90	1.52
Negative Control: 0	5.0	2.3	301.1	1.00	1.00
Positive Control Trypaflavin: 200	342.5	54.0	289.3	68.50*	23.48*

* Mutagenic effect

CAA 1.36

Table A 6.6.1-2: Repeat Test 1: Salmonella/Microsome Test with FCR 1272 on *Salmonella typhimurium* TA 1537

Dose in µg per Plate	Mutants/Plate (M/P)		Total No. of Bacteria per ml x 10^8	M/P Treatment M/P Negative Control	
	+ S-9 mix	- S-9 Mix		+ S-9 mix	- S-9 Mix
12000	22.0	11.0	96.8	2.75	2.44
6000	35.5	3.3	92.0	4.44	0.73
3000	28.0	12.3	104.8	3.50	2.73
Negative Control: 0	8.0	4.5	122.5	1.00	1.00
Positive Control Trypaflavin: 200	307.5	92.3	141.2	38.44*	20.51*

* Mutagenic effect

Table A 6.6.1-3: Repeat Test 2: Salmonella/Microsome Test with FCR 1272 on *Salmonella typhimurium* TA 1537

Dose in µg per Plate	Mutants/Plate (M/P)		Total No. of Bacteria per ml x 10^8	M/P Treatment M/P Negative Control	
	+ S-9 mix	- S-9 Mix		+ S-9 mix	- S-9 Mix
12000	13.5		339.5	0.65	
6000	12.3		352.0	0.59	
3000	10.3		341.8	0.50	
1500	12.3		329.4	0.59	
Negative Control: 0	20.8	6.0	395.5	1.00	1.00
Positive Control Trypaflavin: 200	373.8	133.8	372.2	17.97*	22.30*

* Mutagenic effect

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Genotoxicity in vitro

***In vitro Gene* Mutation Study in Bacteria (*Bacillus subtilis, Salmonella typhimurium, Escherichia coli*)**

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1 REFERENCE

1.1	**Reference**	[redacted] (1982). FCR 1272 – Mutagenicity Test on Bacterial System. [redacted] Report No.: 213; BES Ref.: M-044607-01-1 Report date: 19 January 1982 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Not applicable FCR 1272 was tested for mutagenicity by the Salmonella/ microsome test described by Ames et al. (1973, 1975)[1] [2] [3], more commonly known as the Ames test. Similar to OECD 471 or EC Method B.14 The rec-assay was performed according to Kada et al. [4] [5]
2.2	**GLP**	No, when the study was performed, GLP was not compulsory (as study started before June 30 1988).
2.3	**Deviations**	The test was generally in compliance with the demands of Directive 92/69/EEC, part B, December 29, 1992. Main deviations concern the choice of positive control substances and the reporting of test results. These deviations do not affect the overall integrity of the study.

3 MATERIALS AND METHODS

1 Ames B. N., F.D. Lee and W. E. Durston, An improved bacterial test system for the detection and classification of mutagens and carcinogens,Proc. Nat. Acad. Sci. U.S.A. 70, 782—786, 1973

[2] Ames B. N., W.E. Durston, E. Yamasaki and F.D. Lee, Carcinogens are mutagens : Simple test system combining liver homogenates for activation and bacteria for detection, Proc. Nat. Acad. Sci. U.S.A. 70, 2281—2285, 1973

[3] MacCann J., N. Spingarn, J. Kobori and B. Ames, Detection of carcinogens as mutagens : Bacterial tester strain with R factor plasinids, Proc. Nat. Acad. Sci. U.S.A. 72, 979—983, 1975

[4] Kada T.,K. Tsutikawa and Y. Sadaie, In vitro and hose-mediated "rec-assay" procedures for screening chemical mutagens ; And phloxine, a mutagenic red dye detected, Mutation Research, 16, 165—174, 1972.

[5] Kada, T. and Sadaie, Y. Improved procedures of the rec-assay for rapid detection of chemical mutagens, National Institute of Genetics (Japan) Annual Report No. 25, 49, 1974.

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Annex Point IIA VI.6.6

Genotoxicity in vitro

***In vitro Gene* Mutation Study in Bacteria (*Bacillus subtilis, Salmonella typhimurium, Escherichia coli*)**

3.1	**Test material**	FCR 1272 (cyfluthrin)
3.1.1	Lot/Batch number	Batch No. Eg.3/81
3.1.2	Specification	As given in sections 2 and 3 of Doc IIIA
3.1.2.1	Description	
3.1.2.2	Purity	95%
3.1.2.3	Stability	Not stated.
3.2	**Study Type**	Bacterial reverse mutation test (Ames test) Recombination assay with *Bacillus subtilis*
3.2.1	Organism/cell type	*Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538 *Escherichia coli:* B/r WP2 try$^-$ hcr$^-$ *Bacillus subtilis*: NIG 17 and NIG 45
3.2.2	Deficiencies / Proficiencies	*Bacillus subtilis*: NIG 45 is a recombinational repair deficient strain (rec$^+$)
3.2.3	Metabolic activation system	The supernatant (S-9) of liver homogenates at 9000xg centrifugation from rats tested with PCB was used for the metabolic activation.
3.2.4	Positive control	β-propiolactone: CAS No. 57-57-8 9-aminoacridine: CAS No. 90-45-9 2-nitrofluorene: CAS No. 607-57-8 furylfuramide (AF-2): CAS No. 3688-53-7 2-acetylaminofluorene: CAS No.53-96-3
3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	FCR 1272, main test (with and without S9): 0 - 5 – 10 - 100 - 500 - 1000 - 5000 µg/plate Controls (with and without S9): 2-acetylaminofluorene: TA 100, TA 98: 50 µg/plate Controls (without S9): furylfuramide, TA 100: 0.10 µg/plate TA 98: 0.05 µg/plate E. Coli: 0.2 µg/plate β-propiolactone: TA 1535: 200 µg/plate 9-aminoacridine: TA 1537: 50 µg/plate 2-nitrofluorene: TA 1538: 50 µg/plate
3.3.2	Way of application	All substance were dissolved in dimethylsulfoxide.

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Annex Point IIA VI.6.6

Genotoxicity in vitro

***In vitro Gene* Mutation Study in Bacteria (*Bacillus subtilis, Salmonella typhimurium, Escherichia coli*)**

3.3.3	Pre-incubation time	Not applicable, plate incorporation only
3.3.4	Experimental Procedure	Rec-assay: Overnight cultures of two strains of *Bacillus subtilis* were streaked on the surface of a solid agar plate. The paper disc which was immersed with test compound was put in a refrigerator and then at 37"C for overnight in a incubator. After incubation, length of growth inhibition was measured. AAC 2 was used as positive control in rec-assay Reversion assay: Solid agar, S-9 mixture and soft agar were prepared. A part of each frozen strain was inoculated in a test tube containing 5ml of Pennassay Broth made by Difco and then incubated at 37°C for overnight in a incubator. For the mutagenicity test without in vitro metabolic activation, 0.1 ml of overnight culture and 0.1 ml of test compound were added in a test tube containing 2ml of soft agar, mixed and then poured on the solid agar plate. In the case of in vitro metabolic activation, 0.1 ml of overnight culture and 0.1 ml of tested compound were added in a test tube containing 0.5 ml of S-9 mixture and then incubated at 37°C for minutes in a shaking incubator. After incubation, 2 ml of soft agar kept at 45°C were added into the incubated tube and then poured on the surface of a solid agar plated. These plates were kept at 37°C for 48 hours in a incubator and then revertant colonies were counted on the plates
3.4	**Examinations**	
3.4.1	Number of cells evaluated	Not reported Only revertant colonies were counted.
3.4.2	Acceptance criteria	Not reported
3.4.3	Statistical analysis	Not applicable, only replications

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	
4.1.1	without metabolic activation	Rec-assay: The growth of both strains of B. subtilis was not inhibited at the tested dose of FCR 1272, while the growth inhibition between NIG 17 and NIG 45 significantly different at 0.2 mg/disc of furylfuramide (See Table A6.6.1/02-1) Reversion assay: In reversion assay without *in vitro* metabolic activation, FCR 1272 did not show the killing effects at level of 5000 µg/plate against all tested strains, while there was no remarkable difference in incidence of revertant colonies between plates treated with FCR 1272 and those with no-drug in all tested strains. Since each tested strain showed remarkable increase of colonies against each positive substance, respectively it is suggested that all tested strains have those specific characters in reversion assay without *in vitro* metabolic activation. (See Table A6.6.1/02-2)

4.1.2	with metabolic activation	Reversion assay: In reversion assay with *in vitro* metabolic activation, similar results were observed as those without metabolic activation.
4.2	**Cytotoxicity**	No cytoxicity was observed with or without *in vitro* metabolic activation

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Rec-assay: Overnight cultures of two strains of *Bacillus subtilis* were streaked on the surface of a solid agar plate. The paper disc which was immersed with test compound was put in a refrigerator and then at 37"C for overnight in a incubator. After incubation, length of growth inhibition was measured. AF-2 was used as positive control in rec-assay Reversion assay: Solid agar, S-9 mixture and soft agar were prepared. A part of each frozen strain was inoculated in a test tube containing 5ml of Pennassay Broth made by Difco and then incubated at 37°C for overnight in a incubator. For the mutagenicity test without in vitro metabolic activation, 0.lml of overnight culture and 0.lml of tested compound were added in a test tube containing 2ml of soft agar, mixed and then poured on the solid agar plate. In the case of in vitro metabolic activation, 0.1 ml of overnight culture and 0.1 ml of test compound were added in a test tube containing 0.5 ml of S-9 mixture and then incubated at 37°C for minutes in a shaking incubator. After incubation, 2 ml of soft agar kept at 45°C were added into the incubated tube and then poured on the surface of a solid agar plated. These plates were kept at 37°C for 48 hours in a incubator and then revertant colonies were counted on the plates
5.2	**Results and discussion**	Rec-assay: The growth of both strains of *B. subtilis* was not inhibited at the tested dose of FCR 1272, while the growth inhibition between NIG 17 and NIG 45 significantly different at 0.2 mg/disc of furylfuramide Reversion assay: In reversion assay without *in vitro* metabolic activation, FCR 1272 did not show the killing effects at level of 5000 µg/plate against all tested strains, while there was no remarkable difference in incidence of revertant colonies between plates treated with FCR 1272 and those with no-drug in all tested strains. Since each tested strain showed remarkable increase of colonies against each positive substance, respectively it is suggested that all tested strains have those specific characters in reversion assay without *in vitro* metabolic activation.
5.3	**Conclusion**	Rec-assay: FCR 1272 has no DNA-damaging property to *B. subtilis*. Reversion assay: FCR 1272 was non-mutagenic in five strains of *Salmonella typhimurium*

Document IIIA/ Section 6.6.1/02	Genotoxicity in vitro
Annex Point IIA VI.6.6	*In vitro Gene* Mutation Study in Bacteria (*Bacillus subtilis, Salmonella typhimurium, Escherichia coli*)

		and *E. Coli* B/r WP2 try⁻ hcr⁻ (with or without metabolic activation)
5.3.1	Reliability	2
5.3.2	Deficiencies	Yes

Main deviations from 92/69/EEC B13/14:

- The strain of E. coli B/r WP2 try⁻hcr⁻ is used instead of WP2 uvrA and WP2 uvrA (pKM101).
- No information on quality of bacteria cultures
- PCB is used as enzyme-inducing agents to prepare the metabolic activation system. No information on the PCB mixture is provided
- Choice of positive controls (β-propiolactone for TA 1535, 2-acetylaminofluorene or furylfuramide for TA 100, TA 98)

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State	
Date	2012/10/29
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Reliability	2 (Deficiencies as reported by the applicant, reporting deficiency)
Acceptability	Acceptable
Remarks	
Comments from ...	
Date	Give date of comments submitted
Materials and Methods	Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state
Results and discussion	Discuss if deviating from view of rapporteur member state
Conclusion	Discuss if deviating from view of rapporteur member state
Reliability	Discuss if deviating from view of rapporteur member state
Acceptability	Discuss if deviating from view of rapporteur member state
Remarks	

Table A6.6.1/02-1. Rec-Assay with FCR 1272 on Bacillus subtilis strains (NIG 17 and NIG 45)

Substance (µg/plate)	Inhibition length (mm)		Difference (mm)
	NG 17	NG 45	
FCR 1272 (200.0)	0	0	0
Furylfuramide (0.2)	1	18	17

Table A6.6.1/02-2. Reversion Assay with FCR 1272 on Salmonella typhimurium strains (TA 98, TA 100, TA 1535, TA 1537, TA 1538) and E. coli B/r WP2 try⁻ hcr⁻

	Number of mutant colonies											
Concentration [µg/PLATE]	**TA 100**		**TA 1535**		**TA 98**		**TA 1537**		**TA 1538**			**E. coli**
	— S9	**+ S9**	**— S9**	**+ S9**	**— S9**	**+ S9**	**— S9**	**+ S9**	**— S9**	**+ S9**	**— S9**	**+ S9**
0	150 / 154	175 /183	28 / 13	26 / 17	15 / 22	25 / 28	3 / 8	5 / 3	12 / 5	10 / 20	30 / 37	8 / 12
5.0	97 / 128	152 / 156	30 / 22	17 / 17	24 / 28	20 / 29	5 / 8	5 / 4	4 / 8	10 / 11	30 / 36	15 / 9
10	129 / 125	188 / 177	26 / 5	9 / 12	21 / 20	30 / 34	3 / 8	4 / 14	12 / 17	10 / 18	30 / 16	15 / 12
100	131 / 145	201 / 210	8 / 5	9 / 8	17 / 16	24 / 26	4 / 5	5 / 4	14 / 8	20 / 18	26 / 37	11 / 14
500	132 / 159	193 / 196	5 / 20	10 / 15	26 / 23	29 / 30	1 / 4	9 / 4	18 / 12	14 / 16	32 / 23	13 / 8
1000	136 / 140	183 / 185	18 / 7	10 / 10	20 / 17	21 / 22	3 / 6	1 / 4	10 / 8	15 / 14	40 / 32	11 / 14
5000	150 / 123	192 / 200	17 / 18	19 / 7	37 / 24	21 / 21	5 / 5	6 / 4	12 / 23	12 / 11	19 / 28	9 / 9
Furylfuramide (0.05)	-	-	-	-	110 / 110	-	-	-	-	-	-	-
Furylfuramide (0.1)	1060 / 1044	-	--	-		-	-	-	-	-	-	-
Furylfuramide (0.2)	-	-	-	-	-	-	-	-	-	-	371 / 425	-
2-acetylaminofluorene (50)	127 / 106	840 / 832	-	-	18 / 9	1300 / 1160	-	-	-	-	-	-
β-propiolactone (200)	-	-	5400 / 5400		-	-	-	-	-	-	-	-
9-aminoacridine (50)	-	-	-	-	-	-	408 / 340	-	-	-	-	-
2-nitrofluorene (50)	-	-	-	-	-	-	-	-	4560 / 5400	-	-	-

Document IIIA/ Section 6.6.2

Genotoxicity in vitro

In Vitro Cytogenicity Study in Human Lymphocytes

BPD Data set IIA/ Annex Point VI.6.6

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1988) FCR 1272 (c.n. Cyfluthrin) - In vitro cytogenetic study with human lymphocytes for the detection of induced clastogenic effects, [redacted] Bayer AG Report No.: 17358 BES Ref.: M-038539-01-1 Report date: 11 November 1988 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes Directive 92/69/EEC (1992), part B FIFRA § 84-2
2.2	**GLP**	Yes
2.3	**Deviations**	Yes, only one preparation time was used after a cultivation period of 72 hours.

3 MATERIALS AND METHODS

3.1	**Test material**	FCR 1272 (cyfluthrin)
3.1.1	Lot/Batch number	Batch No. 233690489 = 3757
3.1.2	Specification	As given in sections 2 and 3 of Doc IIIA
3.1.2.1	Description	Brown viscous liquid
3.1.2.2	Purity	95.5% (analytical result dated April 27, 1987) - 95.1% (analytical result dated October 7, 1987)
3.1.2.3	Stability	The batch used was analytically examined prior to study initiation and was approved for use at least for the duration of the test period. A stability test in the solvent did not detect a relevant change in the percent active ingredient.
3.2	**Study Type**	In vitro mammalian chromosome aberration test
3.2.1	Organism/cell type	Lymphocytes
3.2.2	Deficiencies / Proficiencies	Not applicable
3.2.3	Metabolic activation system	S9 derived from adult male Sprague-Dawley rats. The homogenate was prepared by the performing laboratory. For enzyme induction, the animals received a single intraperitoneal injection of Aroclor 1256 (500 mg/kg b.w. dissolved in corn oil).

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BPD Data set IIA/ Annex Point VI.6.6

Genotoxicity in vitro

In Vitro Cytogenicity Study in Human Lymphocytes

3.2.4	Positive control	Positive Control without S9 mix: Mitomycin C Batch No.: 0574935, 2475835 Positive Control with S9 mix: Cyclophosphamide Batch No.: 105459,014435
3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	1st trial: 0, 500, 1000 and 5000 µg/ml (± S9 mix) 2nd trial: 0, 500, 1000 and 2000 µg/ml (± S9 mix) 3rd trial: 0, 1000, 2000 and 4000 µg/ml (± S9 mix)
3.3.2	Way of application	Dissolved in DMSO
3.3.3	Pre-incubation time	Cells were cultivated for 48 hours before application of compound.
3.3.4	Other modifications	Not applicable
3.4	**Examinations**	
3.4.1	Number of cells evaluated	1000 cells per culture, including spare cultures, for determination of mitotic index Approximately 200 metaphases per concentration, both with and without S9 mix, were examined for structural changes in the chromosomes, i.e. approximately 100 metaphases were evaluated per culture.
		4 RESULTS AND DISCUSSION
4.1	**Genotoxicity**	
4.1.1	Without metabolic activation	Aberration rates were noted, which differed statistically significantly from the negative control. These variations were, however, not concentration related. To check the relevance of these results, two additional experiments were performed. In the first of these, no statistically significant variations were noted in the parameters relevant for evaluation (metaphases with aberrations including or excluding gaps, and metaphases with exchanges). In the second additional experiment, a statistically significant increase in metaphases with aberrations including gaps was seen in the lowest concentration. However, in higher concentrations no statistically significant values were found. Therefore, the results of the first test were not judged to be biologically relevant. See table 6.6.2-1 and 6.6.2-2

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Genotoxicity in vitro

In Vitro Cytogenicity Study in Human Lymphocytes

4.1.2	With metabolic activation	Statistically significant rates of aberrations were observed. These statistical significances were, however, not concentration-dependent. In addition, with respect to the parameters relevant for evaluation (meta-phases with aberrations including or excluding gaps, and metaphases with exchanges), the statistically significant variations were not reproducible in two additional experiments. Therefore, the results of the first test were not judged to be biologically relevant. See table 6.6.2-1 and 6.6.2-2
4.2	**Cytotoxicity**	With and without S-9 mix, in comparison to the negative control, the treated cultures showed a concentration-related fall in mitosis rate from 500 µg/ml onwards. In addition, substance precipitation was noted, starting at 500 µg/ml. The positive controls CPP and MMC reduced the mitosis rate in a similar magnitude.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Human lymphocytes were exposed in two separate cultures to cyfluthrin (batch no.: 233690489 = 3757, purity: ca. 95 %) in concentrations of 0-500-1000-5000 µg/ml (1st trial, ± S-9 mix), 0-500-1000-2000 µg/ml (2nd trial, ±S-9 mix) and 0-1000-2000-4000 µg/ml (3rd trial, ± S-9 mix). Cyfluthrin and the positive control substances cyclophosphamide (CPP, 15 µg/ml, with S-9mix) as well as mitomycin C (MMC, 0,15 µg/ml without S-9 mix) were formulated in DMSO, which served also as negative control. After the cultivation of the cells for 48 hours, in the non-activated cultures the cells were exposed to cyfluthrin for 24 hours and in the activated cultures for 3 hours. In the second case, after 3 hours the medium was changed. All cells were prepared after 72 hours. For the activation experiments, S-9 mix was derived from adult male Sprague Dawley rats. For enzyme induction, the animals received a single intraperitoneal injection of Aroclor 1254 (500 mg/kg bw, dissolved in peanut oil) five days before sacrifice. The liver supernatant fluid was prepared and combined with an appropriate co-factor solution according to established procedures. The mitotic index was determined by counting 1000 cells per culture including the spare cultures. The numbers of mitotic and non-mitotic cells were noted. Approximately 200 metaphases per concentration, both with and without S9 mix, were examined for structural changes in the chromosomes, i.e. approximately 100 metaphases were evaluated per culture in each test group.

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In Vitro Cytogenicity Study in Human Lymphocytes

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5.2	**Results and discussion**	After in vitro treatment at concentrations of up to 5000 µg/ml cyfluthrin produced a fall in mitotic index (starting at 500 µg/ml) in human lymphocyte cultures both with and without S9 mix. In addition, substance precipitation was noted, starting at 500 µg/ml. The positive controls CCP and MMC reduced the mitosis rate in a similar magnitude Evaluation of the individual groups with respect to parameters relevant for evaluating clastogenicity detected no variations of biological relevance between the groups. The results for the positive controls mitomycin C and cyclophosphamide, indicated a clear clastogenic effect and documented the system's sensitivity.	X
5.3	**Conclusion**	All the individual runs taken together, cyfluthrin did not induce chromosome aberrations in human lymphocytes under the conditions used in this test.	
5.3.1	Reliability	1	
5.3.2	Deficiencies	Only one preparation time was used after a cultivation period of 72 hours. This is not considered to have compromised the validity of the test results.	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-29
Materials and Methods	Applicant's version is acceptable.
Results and discussion	*5.2:* Mitotic rates: see CA Table 1. Mitotic rates are decreased down to 40 % of negative controls. *Table A 6.6.2-2:* see note
Conclusion	Applicant's version is adopted.
Reliability	2
Acceptability	Acceptable
Remarks	-

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Genotoxicity in vitro

In Vitro Cytogenicity Study in Human Lymphocytes

BPD Data set IIA/ Annex Point VI.6.6

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A 6.6.2-1: Summary of Results without S9 Mix of Third Cytogenetic Experiment with Human Lymphocytes in Vitro

µg/ml	Evaluated metaphases	Metaphases with aberrations including gaps		Metaphases with aberrations excluding gaps		Metaphases with exchanges		Polyploid cells in x evaluated metaphases	
		n	%	n	%	n	%	n x	%
DMSO 0	200	6	3.0	2	1.0			0 400	0
1000	200	15*	7.5	6	3.0			0 400	0
2000	200	12	6.0	3	1.5			0 400	0
4000	200	10	5.0	5	2.5			0 400	0
MMC 0.15	200	104**	52.0	66**	33.0	17**	8.5	0 400	0

*P ≤ 0.05 in χ^2 test

** P ≤ 0.01 in χ^2 test

Table A 6.6.2-2: Summary of Results with S9 Mix of Third Cytogenetic Experiment with Human Lymphocytes in Vitro

g/ml	Eval-uated meta-phases	Metaphases with aberrations including gaps		Metaphases with aberrations excluding gaps		Metaphases with exchanges		Polyploid cells in x evaluated metaphases	
		n	%	n	%	n	%	n x	%
DMSO 0	200	8	4.0	2	1.0			0 400	0
1000	200	14	7.0	3	1.5			2 400	0.5
2000	200	13	6.5	6	3.0			0 400	0
4000	200	14	7.0	5	2.5	1	0.5	0 400	0
MMC 0.15	200	86*	43.0	57*	28.5	12*	6.0	1 400	0.3

*P ≤ 0.05 in χ^2 test

** P ≤ 0.01 in χ^2 test

RMS: *P ≤ 0.01 in χ^2 test

CA Table 1

Experimental groups	Concentration in µg/ml	Evaluated nuclei	Mitotic nuclei absolute		
			1. trial – S9 / +S9	2. trial – S9 / +S9	3. trial – S9 / +S9
Negative control	0	4000	137 / 154	200 / 209	171 / 187
Cyfluthrin	500	4000	59** / 74**	112** / 120**	
	1000	4000	45** / 54**	127** / 88**	62** / 55**
	2000	4000		81** / 106**	63** / 105**
	4000	4000			64** / 119**
	5000	4000	23** / 103**		
Positive control[1)]		4000	55** / 87**	182 / 175*	89** / 112**

* P < 0.05 in chi^2 test

** P < 0.01 in chi^2 test

[1)] + S9: 0.15 µg/ml mitomycin C,
- S9: 15 µg/ml cyclophasphamide

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Genotoxicity in vitro

***In vitro* Cytogenicity Study in Chine hamster Lung cells (HLC)**

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			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1986) Cyfluthrin: in vitro cytogenetics test, [redacted] BES Ref.: M-044602-01-1 Report date: 9 October 1986 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not stated Similar to OECD No. 473 or EC method B.10	
2.2	**GLP**	Yes	
2.3	**Deviations**	The test was generally in compliance with the demands of OECD No.473. Main deviations concern the duration of exposure to test substance and the reporting of test results. In the first experiment, cells were exposed to the test substance without metabolic activation for 48 hours These deviations do not affect the overall integrity of the study.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Cyfluthrin	
3.1.1	Lot/Batch number	Batch No. 233 590 478	
3.1.2	Specification	As given in sections 2	
3.1.2.1	Description	Yellowish-brown mass of oily to pasty consistency	
3.1.2.2	Purity	93.7%	
3.1.2.3	Stability	Stable in conventional condition. Kept in dark at romm temperature	
3.2	**Study Type**	In vitro mammalian chromosome aberration test	
3.2.1	Organism/cell type	Lung cells. The cells were obtained [redacted] on January 12, 1984. The cells were not contaminated by mycoplasma when it was tested before initiation of the experiment	x

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Genotoxicity in vitro

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3.2.2	Deficiencies / Proficiencies	Not applicable
3.2.3	Metabolic activation system	For the preparation of S-9 fraction, 4 Sprague-Dawley male rats (7 weeks old; average body weight, 253g, Charles River Japan Inc.) were given a single intraperitoneal injection of a polychlorinated biphenyl mixture (Aroclor 1254) at a dosage of 500 mg/kg. The animals were fasted overnight on the fifth night after the injection. On the next day the animals were killed by cervical dislocation and the livers were removed immediately. The livers were perfused with chilled 0.15 M KCl solution and homogenized in three volumes of the same solution (3 ml/g wet liver). The homogenate was centrifuged for 10 min. at 9000 x g. All the steps were performed below 5°C with cold and sterile solutions and glassware. The 9000 x g supernatant (S-9 fraction) was stored at - 80°C. The S-9 fraction prepared on Feburary 20, 1985 (Lot No. 59; protein content, 27.1 mg/ml) was used in this experiment.
3.2.4	Positive control	Positive Control without S9 mix: Mitomycin C (MMC, Kyowa Hakko Kogyo Co.), dissolved in Hank's Balanced Salt Solution Positive Control with S9 mix: Benzo(a)pyrene (BaP, Sigma Chemical Inc.) dissolved in DMSO
3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	The highest concentration of the test compound for the cytogenetics test was determined by the results from a preliminary growth test. Preliminary growth test: 1.0 x 10^{-2} M, 3.3 x 10^{-3} M, 1.0 x 10^{-3} M and 3.3 x 10^{-4} M (± S9 mix) Cytogenetic test: 3.3 x 10^{-3} M, 1.0 x 10^{-3} M, 3.3 x 10^{-4} M, 1.0 x 10^{-4} M and 3.3 x 10^{-5} M (± S9 mix)
3.3.2	Way of application	Test compound was dissolved in DMSO Preliminary growth test: At the density of 2.5 x 10^5 cells/6cm-dish, CHL cells were seeded in culture dishes. The test compound was added 24 hours after the sub-culture. In a direct method, cell densities were measured by Monocellater (Olympus Optical Corporation, Tokyo) after a treatment with Cyfluthrin for 48 hours. In a metabolic activation method, cells were treated with the test compound in the presence of S-9 mix for 6 hours, and then the treatment medium was replaced by a fresh medium. Eighteen hours after the medium change, cell densities were measured. Two independent cultures were used for each experimental point. In a metabolic activation method, toxicity of Cyfluthrin was too weak to determine a concentration which suppressed cell growth by approximately 50%. A technically limited concentration (3.3 x 10 M) was employed as the highest concentration. Cytogenetic tests: 1/ Direct method:

		At the density of 1 x 10^6 cells/l0cm-dish, CHL cells were seeded in culture dishes and the test compound was added 24 hours after the sub-culture. After a treatment for 24 or 48 hours, mitotic preparations were prepared by air drying method. Two hours prior to harvesting, cells were treated with colchicine at 0.5 µg/ml to accumulate cells in c-metaphase. Both a solvent control treated with DMSO at 0.5% and a positive control treated with MMC at 6.0 x 10^{-7} M were included in the experiment. Two independent cultures were used for each experimental point. 2/ Metabolic activation method At the density of 1 x 10^6 cells/l0cm dish, CHL cells were seeded in culture dishes and the test compound was added with S-9 mix 24 hours after the sub-culture. Cells were treated with the test compound in the presence of S-9 mix for 6 hours, and treatment medium was changed to a fresh medium. Twelve and 18 hours after the medium change, mitotic preparations were prepared by air drying method. Colchicine treatment (0.5 µg/ml) was performed two hours prior to harvesting. Both a solvent control treated with DMSO at 0.5% and a positive control treated with BaP at 1.5 x 10^{-4} M were included in the experiment. Two independent cultures were used for each experimental point.	
3.3.3	Pre-incubation time	Not applicable	
3.3.4	Other modifications	Not applicable	
3.4	**Examinations**		
3.4.1	Number of cells evaluated	200 cells (metaphases) per concentration, both with and without S9 mix, were examined for structural changes in the chromosomes. Only good metaphases which satisfying the karyotype of CHL cell were analyzed and structural chromosome aberrations were recorded and classified. The number of chromosomes was not counted. The number of cells analyzed was 200 per experimental point. Metaphase containing at least one chromosome aberration was considered as an aberrant metaphase. Judgement of results are given in Table Table A6.6.2/02-1: Mitotic indices were calculated as the number of metaphases per 1000 cells.	
		4 RESULTS AND DISCUSSION	
4.1	**Genotoxicity**		
4.1.1	Without metabolic activation	<u>Preliminary growth test:</u> At 1.0 x 10^{-2} M the test compound was rapidly separated as an oily substance from the culture medium. Some little oily substance and heavy yellow turbidity were observed immediately after the addition of the test compound to the culture medium at 3.3 x 10^{-3} M. Yellow turbidity was observed immediately after the addition of the test compound to the culture medium at 1.0 x 10^{-3} and 3.3 x 10^{-4} M. Cell growth was 47.5% of solvent control after a treatment for 48 hours at 3.3 x 10^{-3} M, which revealed approximately 50% suppression of cell growth. No suppression of cell growth was observed at lower concentrations. Based on the above results, experiments were carried out at the following 5 concentrations including the concentrations at which turbidity was observed: 3.3 x 10^{-3} M, 1.0 x 10^{-3} M,	x

3.3 x 10^{-4} M, 1.0 x 10^{-4} M, 3.3 x 10^{-5} M.

Cytogenetic tests:

The results of the cytogenetic test by the direct method are shown in Table A6.6.2/02-2 (24-hr treatment) and Table A6.6.2/02-3 (48-hr treatment). The aberrant metaphase frequencies were less than 5% at any sampling time and concentration. On the other hand, Mitomycin C used as a positive control induced marked increases in the incidence of aberrant metaphases.

4.1.2 With metabolic activation

Preliminary growth test:

At 1.0 x 10 M the test compound was rapidly separated as an oily substance from the culture medium. Some little oily substance and heavy yellow turbidity were observed immediately after the addition of the test compound to the culture medium at 3.3 x 10^{-3} M. Yellow turbidity was observed immediately after the addition of the test compound to the culture medium at 1.0 x 10^{-3} and 3.3 x 10^{-4} M. However, suppression of cell growth was not observed at any concentrations. Based on the above results, experiments were carried out at the following 5 concentrations including the concentrations at which turbidity was observed: 3.3 x 10^{-3} M, 1.0 x 10^{-3} M, 3.3 x 1^{0-4} M, 1.0 x 10^{-4} M, 3.3 x 10^{-5} M.

Cytogenetic tests:

The results of the cytogenetic test with the metabolic activation method are shown in Table A6.6.2/02-4 (prepared 12 hours after medium change) and Table A6.6.2/02-5 (prepared 18 hours after medium change). The aberrant metaphase frequencies were less than 5% at any sampling time and concentration.

On the other hand, Benzo(a) pyrene used as a positive control induced marked increases in the incidence of aberrant metaphases.

4.2 Cytotoxicity

In the preliminary test without metabolic activation, cell growth was 47.5% of solvent control after a treatment for 48 hours at 3.3 x 10^{-3} M, which revealed approximately 50% suppression of cell growth. No suppression of cell growth was observed at lower concentrations.

With metabolic activation, suppression of cell growth was not observed at any concentrations.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

CHL Chinese hamster lung cells were exposed in two separate cultures to cyfluthrin to evaluate the clastogenic potential of test compound for cultured mammalian cells.

In a direct method, mitotic preparations were prepared after single treatment with Cyfluthrin at 3.3 x 10^{-3} to 3.3 x 10^{-5} M for 24 and 48 hours. In a metabolic activation method, cells were treated with Cyfluthrin at 3.3 x 10^{-3} to 3.3 x 10^{-5} M in the presence of S-9 mix for 6 hours, and then the treatment medium was replaced by a fresh medium. Twelve and 18 hours after the medium change, mitotic preparations were prepared.

Cyfluthrin and the substance Benzo(a)pyrene (BaP, 1.5 x 10^{-4} M, with S-9mix) were formulated in DMSO. Mitomycin C (MMC, 6.9 x 10^{-7} M) served as positive control in experiment without S-9 mix. DMSO at 0.5% was also used as negative control.

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Genotoxicity in vitro

***In vitro* Cytogenicity Study in Chine hamster Lung cells (HLC)**

		For the activation experiments, S-9 mix was derived from adult male Sprague Dawley rats. For enzyme induction, the animals received a single intraperitoneal injection of Aroclor 1254 (500 mg/kg bw) five days before sacrifice. The liver supernatant fluid was prepared and combined with an appropriate co-factor solution according to established procedures. The final concentration of S-9 fraction in the medium was 5% The number of cells analyzed was 200 per experimental point. Metaphase containing at least one chromosome aberration was considered as an aberrant metaphase. Mitotic indices were calculated as the number of metaphases per 1000 cells.
5.2	**Results and discussion**	Some little oily substance and heavy yellow turbidity were observed immediately after the addition of the test compound to the culture medium at 3.3×10^{-3} M. Yellow turbidity was observed immediately after the addition of the test compound to the culture medium at 1.0×10^{-3} and 3.3×10^{-4} M. Cell growth was 47.5% of solvent control after a treatment for 48 hours at 3.3×10^{-3} M, which revealed approximately 50% suppression of cell growth. No suppression of cell growth was observed at lower concentrations. With metabolic activation , suppression of cell growth was not observed at any concentrations. Evaluation of the individual groups with respect to parameters relevant for evaluating clastogenicity detected no variations of biological relevance between the groups. The aberrant metaphase frequencies were less than 5% at any sampling time and concentration. The results for the positive controls mitomycin C and benzo(a)pyrene, indicated a clear clastogenic effect and documented the system's sensitivity Results are summarised in Table from A6.6.2/02-2 to A6.6.2/02-5.
5.3	**Conclusion**	The aberrant metaphase frequencies were less than 5% at any sampling time and concentration either in the absence or presence of the metabolic activation enzymes. From these results, it is concluded that Cyfluthrin did not induce chromosome aberrations in CHL cells, either in the absence or presence of the metabolic activation enzymes, under the conditions used in this test.
5.3.1	Reliability	1
5.3.2	Deficiencies	None reported

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Genotoxicity in vitro

***In vitro* Cytogenicity Study in Chine hamster Lung cells (HLC)**

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	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	Evaluation by Rapporteur Member State
Date	2012/12/04
Materials and Methods	3.2.1 Organism/cell type: No justification for choice of the cell line. Lack of information on cell cycle length.
Results and discussion	4.1.1 Without metabolic activation: The applicant claims that cell growth was influenced only after treatment with 3.3 x 10^{-3} M cyfluthrin. However, mitotic index was reduced after treatment with all concentrations of cyfluthrin applied in the study. Mitotic index of 50% was reached after treatment with 3.3 x 10^{-4} M cyfluthrin.
Conclusion	
Reliability	2
Acceptability	acceptable
Remarks	
	Comments from ...
Date	Give date of comments submitted
Materials and Methods	Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state
Results and discussion	Discuss if deviating from view of rapporteur member state
Conclusion	Discuss if deviating from view of rapporteur member state
Reliability	Discuss if deviating from view of rapporteur member state
Acceptability	Discuss if deviating from view of rapporteur member state
Remarks	

Table 6.6.2/02-1: Evaluation criteria

Aberrant metaphase frequency (%)	Judgment
10% or more	Positive
5 - 10%	Inconclusive
less than 5%	Negative

Table A 6.6.2/02-2: Aberrant metaphase frequency in the absence of metabolic activation system (%)t with Hamster Lung Cells in vitro - Prepared 24 hours after treatment

Compound	Concentration (M)	No. of observed metaphase	Cell with (%)		Mitotic index	Comment
			Chromosome aberration	Gaps only		
Cyfluthrin	3.3×10^{-3} *)	100	0	0	1.1	
	3.3×10^{-3} *)	100	1	0	2.1	Chromatid aberration (1 ctb)
	Mean		0.5	0	1.6	
Cyfluthrin	1.0×10^{-3} **)	100	0	0	2.5	
	1.0×10^{-3} **)	100	0	0	1.5	
	Mean		0	0	2.0	
Cyfluthrin	3.3×10^{-4} **)	100	0	0	1.4	
	3.3×10^{-4} **)	100	0	0	2.1	
	Mean		0	0	1.8	
Cyfluthrin	1.0×10^{-4}	100	0	0	2.1	
	1.0×10^{-4}	100	0	0	2.3	
	Mean		0	0	2.2	
Cyfluthrin	3.3×10^{-5}	100	0	0	3.6	
	3.3×10^{-5}	100	0	0	2.6	
	Mean			0	3.1	
Mitomycin C	6.0×10^{-7}	50	50	2	1.8	Chromatid aberration (14 ctg; 34 ctb; 22 cte) Chromosome aberration (4 itcg; 2 itcb; 2 poc; 8 ring; 4 ace)
	6.0×10^{-7}	50	62	4	2.3	Chromatid aberration (10 ctg; 38 ctb; 30 cte) Chromosome aberration (6 ring; 12 ace)
	Mean		56	3	2.1	
Solvent control	0	100	0	0	3.4	
	0	100	0	0	3.6	
	Mean		0	0	3.5	
Non-treated	0	100	0	0	3.8	
	0	100	0	0	4.8	
	Mean		0	0	4.3	

*) Yellow turbidity and oily substance in the culture medium were observed immediately after addition of the test compound to the culture medium

**) Yellow turbidity in the culture medium were observed immediately after addition of the test compound to the culture medium

Table A 6.6.2/02-3: Aberrant metaphase frequency in the absence of metabolic activation system (%)t with Hamster Lung Cells in vitro- Prepared 48 hours after treatment

Compound	Concentration (M)	No. of observed metaphase	Cell with (%)		Mitotic index	Comment
			Chromosome aberration	Gaps only		
Cyfluthrin	3.3×10^{-3} *)	100	0	0	0.6	
	3.3×10^{-3} *)	100	0	0	1.0	
	Mean		0	0	0.8	
Cyfluthrin	1.0×10^{-3} **)	100	2	0	1.3	Chromosome aberration (1 ictb; 1 ace)
	1.0×10^{-3} **)	100	0	0	1.5	
	Mean		1	0	1.4	
Cyfluthrin	3.3×10^{-4} **)	100	1	0	1.1	Chromosome aberration (1 ace)
	3.3×10^{-4} **)	100	0	0	1.4	
	Mean		0.5	0	1.3	
Cyfluthrin	1.0×10^{-4}	100	0	0	1.4	
	1.0×10^{-4}	100	0	0	1.9	
	Mean		0	0	1.7	
Cyfluthrin	3.3×10^{-5}	100	0	0	2.5	
	3.3×10^{-5}	100	1	1	4.2	Chromatid aberration (1 ctg)
	Mean		0.5	0.5	3.4	
Mitomycin C	6.0×10^{-7}	50	72	2	1.1	Chromatid aberration (4 ctg; 26 ctb; 26 cte) Chromosome aberration (10 ring; 26 ace; 2 pvz)
	6.0×10^{-7}	50	70	6	1.0	Chromatid aberration (8 ctg; 38 ctb; 36 cte) Chromosome aberration (12 ring; 20 ace)
	Mean		71.0	4.0	1.1	
Solvent control	0	100	0	0	1.0	
	0	100	0	0	2.0	
	Mean		0	0	1.5	
Non-treated	0	100	0	0	1.0	
	0	100	0	0	2.1	
	Mean		0	0	1.6	

*) Yellow turbidity and oily substance in the culture medium were observed immediately after addition of the test compound to the culture medium

**) Yellow turbidity in the culture medium were observed immediately after addition of the test compound to the culture medium

Table A 6.6.2/02-4: Aberrant metaphase frequency in the presence of metabolic activation system (%)t with Hamster Lung Cells in vitro- Prepared 12 hours after medium change

Compound	Concentration (M)	No. of observed metaphase	Cell with (%)		Mitotic index	Comment
			Chromosome aberration	Gaps only		
Cyfluthrin	3.3×10^{-3} *)	100	2	2	1.1	Chromatid aberration (2 ctg)
	3.3×10^{-3} *)	100	0	0	2.1	
	Mean		1	1	1.6	
Cyfluthrin	1.0×10^{-3} **)	100	0	0	1.2	
	1.0×10^{-3} **)	100	1	1	1.5	Chromatid aberration (1 ctg)
	Mean		0.5	0.5	1.4	
Cyfluthrin	3.3×10^{-4} **)	100	0	0	1.7	
	3.3×10^{-4} **)	100	1	1	1.5	Chromatid aberration (1 ctg)
	Mean		0.5	0.5	1.6	
Cyfluthrin	1.0×10^{-4}	100	0	0	1.5	
	1.0×10^{-4}	100	0	0	1.5	
	Mean		0	0	1.5	
Cyfluthrin	3.3×10^{-5}	100	0	0	1.8	
	3.3×10^{-5}	100	1	1	1.4	Chromatid aberration (1 ctg)
	Mean		0.5	0.5	1.6	
Benzo(a)pyrene	1.5×10^{-4}	50	38	2	0.9	Chromatid aberration (4 ctg; 12 ctb; 34 cte) Chromosome aberration (2 ace)
	1.5×10^{-4}	50	44	0	1.8	Chromatid aberration (2 ctg; 24 ctb; 28 cte) Chromosome aberration (4 ring; 8 ace)
	Mean		41.0	1.0	1. 4	
Solvent control	0	100	0	0	1.8	
	0	100	0	0	1.3	
	Mean		0	0	1.6	
Non-treated	0	100	0	0	2.6	
	0	100	0	0	2.6	
	Mean		0	0	2.6	

*) Yellow turbidity and oily substance in the culture medium were observed immediately after addition of the test compound to the culture medium

**) Yellow turbidity in the culture medium were observed immediately after addition of the test compound to the culture medium

Table A 6.6.2/02-5: Aberrant metaphase frequency in the presence of metabolic activation system (%)t with Hamster Lung Cells in vitro- Prepared 18 hours after medium change

Compound	Concentration (M)	No. of observed metaphase	Cell with (%)		Mitotic index	Comment
			Chromosome aberration	Gaps only		
Cyfluthrin	3.3×10^{-3} *)	100	0	0	3.6	
	3.3×10^{-3} *)	100	2	2	3.7	Chromatid aberration (2 ctg)
	Mean		1	1	3.7	
Cyfluthrin	1.0×10^{-3} **)	100	0	0	3.7	
	1.0×10^{-3} **)	100	0	0	4.2	
	Mean		0	0	4.0	
Cyfluthrin	3.3×10^{-4} **)	100	0	0	4.1	
	3.3×10^{-4} **)	100	0	0	2.5	
	Mean		0	0	3.3	
Cyfluthrin	1.0×10^{-4}	100	0	0	3.4	
	1.0×10^{-4}	100	0	0	3.9	
	Mean		0	0	3.7	
Cyfluthrin	3.3×10^{-5}	100	0	0	4.4	
	3.3×10^{-5}	100	0	0	4.1	
	Mean		0	0	4.3	
Benzo(a)pyrene	1.5×10^{-4}	50	40	4	1.2	Chromatid aberration (6 ctg; 12 ctb; 30 cte) Chromosome aberration (4 poc; 4 ring; 14 ace)
	1.5×10^{-4}	50	54	2	1.4	Chromatid aberration (8 ctg; 12 ctb; 38 cte) Chromosome aberration (2 poc; 10 ring; 14 ace; 2 oth)
	Mean		46.0	3.0	1.3	
Solvent control	0	100	0	0	5.3	
	0	100	0	0	5.4	
	Mean		0	0	5.4	
Non-treated	0	100	0	0	3.6	
	0	100	0	0	4.6	
	Mean		0	0	4.1	

*) Yellow turbidity and oily substance in the culture medium were observed immediately after addition of the test compound to the culture medium

**) Yellow turbidity in the culture medium were observed immediately after addition of the test compound to the culture medium

Document IIIA/ Section A6.6.3

Genotoxicity in vitro

In Vitro Gene Mutation Assay

BPD Data set IIA/ Annex Point VI.6.VI.6.3

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1985). CHO/HGPRT mutation assay in the presence and absence of exogenous metabolic activation. [redacted] Report no: BC694 BES Ref: M-039037-01-1 Report date 1985 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2	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**	None cited, however, study is compliant with: Directive 87/302/EEC B.17 Mutagenicity—In vitro mammalian cell gene mutation test OECD 476 In vitro mammalian cell gene mutation test
2.2	**GLP**	Yes
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	FCR 1272 (cyfluthrin)
3.1.1	Lot/Batch number	Batch No.: 3-03-0143
3.1.2	Specification	As given in sections 2 and 3 of Doc IIIA
3.1.2.1	Description	Dark Amber Colour, Viscous Liquid
3.1.2.2	Purity	94.7%
3.1.2.3	Stability	Stability in acetone: given for 21 days
3.2	**Study Type**	
3.2.1	Organism/cell type	Chinese hamster ovary cells [redacted]
3.2.2	Deficiencies / Proficiencies	HGPRT deficient
3.2.3	Metabolic activation system	S-9 prepared from adult male Fischer rats treated with Aroclor 1254 2 days prior to sacrifice and frozen until use. Immediately prior to use, S-9 was mixed with the following reagents and stored on ice until used.

Final Concentration	Reagent
100 µL/mL total	S-9
4 mM	NADP

Document IIIA/ Section A6.6.3
BPD Data set IIA/ Annex Point VI.6.VI.6.3

Genotoxicity in vitro

In Vitro Gene Mutation Assay

		5 mM	Glucose-6-phosphate
		30 mM	KCl
		10 mM	CaCl2
		10 mM	MgCl2
		50 mM	Sodium phosphate buffer, pH 8.0
3.2.4	Positive control	Ethylmethane sulfonate (EMS) 0.2 µL/mLwas used as the positive control in non-activated (-S9) assays. Benzo[a]pyrene (BaP) 4 µg/mL was used as positive control in activated (+S9) assays.	
3.3	**Administration / Exposure; Application of test substance**		
3.3.1	Concentrations	Preliminary cytotoxicity assay (± S9): 0, 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10 µl/ml Mutation assay and concurrent cytotoxicity assay (± S9): 0, 3, 5, 7, 9, 10 µl/ml	
3.3.2	Way of application	Exponentially growing CHO-K_1-BH_4 cells were plated in F12FBS5 at a density of 5 x 10^5 cells/25 cm^2 flask and were incubated at 37 ± l°C in a humidified atmosphere of 5% CO_2 in air for 18-24 hours. The time of initiation of chemical treatment was designated as day 0. Test article was pre-warmed to 60°C in a water bath. Cells were exposed in duplicate to five concentrations of the test article for 5 hours at 37±l°C. The treatment medium consisted of 4 ml media containing various concentrations of test article, and 1 ml S9 reaction mixture for the activated study, and 5 ml media containing various concentrations of test article for the non-activated study. After the treatment period, all media were aspirated, the cells washed with saline and cultured in media for an additional 18-24 hours at 37 ± l°C. At this time, the cells were subcultured to assess cytotoxicity and to initiate the phenotypic expression period. For evaluation of cytotoxicity, the replicates from each treatment condition were pooled and subcultured in media, in triplicate, at a density of 100 cells/60 mm dish. After 7-10 days incubation, the colonies were fixed with methanol, stained with 10% aqueous Giemsa, and counted. For expression of the mutant phenotype, the replicates from each treatment condition were pooled and subcultured in media in duplicate, at a density no greater than 10^6 cells/100 mm dish. Subculture as above at 2-3 day intervals was employed for the 7-9 day expression period. At this time, selection for the mutant phenotype was performed. For selection of the TG-resistant phenotype, the replicates from each treatment condition were pooled and replated, in quintuplicate, at a density of 2 x 10^5 cells/100 mm dish in hypoxanthine deficient media containing 10 µM TG. For cloning efficiency determinations, at the time of selection, 100 cells/60 mm dish were plated in triplicate. After 7-10 days of incubation, the colonies were fixed, stained and counted for both	

Document IIIA/ Section A6.6.3

BPD Data set IIA/ Annex Point VI.6.VI.6.3

Genotoxicity in vitro

In Vitro Gene Mutation Assay

		cloning efficiency and mutant selection.	
3.3.3	Pre-incubation time		
3.3.4	Other modifications	None	
3.4	**Examinations**		
3.4.1	Number of cells evaluated	Cytotoxicity: 100 cells/dish Mutation:2 x 10^5 cells/dish	
		4 RESULTS AND DISCUSSION	
4.1	Cytotoxicity	Results are shown in tables A6.6.3-1 and A6.6.3-2 below. Cytotoxicity test (with S-9 mix); In the concurrent toxicity test, the survival relative to the solvent control (relative cloning efficiency) was 95 %, 106 %, 94 %, 100 % and 95 % at 10, 9, 7, 5 and 3 ug/ml, respectively. Cytotoxicity test (without S-9 mix); In the concurrent toxicity test, the survival relative to the solvent control (relative cloning efficiency) was 88 %, 94 %, 82 %, 93 % and 108 % at 10, 9, 7, 5 and 3 ul/ml, respectively.	
4.2	Mutation	Results are shown in tables A6.6.3-1 and A6.6.3-2 below. CHO/HGPRT mutation assay (with S-9 mix); The mutation frequency was 11.5 per 10 clonable cells in the untreated control group and <1.9 per 10 clonable cells in the solvent (acetone) control group. In none of the test article treated groups mutagenicity frequency was increased more than two fold above the untreated control. BaP induced a mutation frequency of 342.4 mutants per 10 clonable cells. CHO/HGPRT mutation assay (without S-9 mix); The nonactivated portion of the mutation assay was performed twice. In the first test, the mutation frequency was 3.7 per 10 clonable cells in the untreated control group and 3.9 per 10 clonable cells in the solvent (acetone) control group. At dose levels of 10, 9, 7, 5 and 3 ul/ml, the mutation frequency was 18.3, 6.4, 1.4, 3.2, 11.3 per 10 clonable cells. The mutation frequency at the highest dose was significantly increased compared to the solvent control. However, this mutation frequency was less than 20 mutants per 10 clonable cells, which is within the acceptable variation of the spontaneous mutant frequencies of the untreated and solvent control groups. In the repeat test the mutation frequencies of the test article treated groups were comparable to the control values (mutation frequencies: untreated control: 1.5 per 10 clonable cells, solvent control: 18.6 per 10 clonable cells, treated groups: 2.1, 5.0, 10.5, 5.9 and 5.7 per 10 clonable cells at dose levels of 10, 9, 7, 5 and 3 ul/ml). The positive control, EMS, induced mutation frequencies of 297.3 mutants per 10 clonable cells (first experiment) and of 500 mutants per 10 clonable cells (second experiment).	X
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The mutagenicity frequency at the hypoxanthine-guanine-phosphoribosyltransferase (HGPRT) locus of Chinese hamster ovary cells (CHO-K1-BH4) was examined in the absence and presence of metabolic	X

Document IIIA/ Section A6.6.3

BPD Data set IIA/ Annex Point VI.6.VI.6.3

Genotoxicity in vitro

In Vitro Gene Mutation Assay

		activation (S-9 mix) under exposure of cyfluthrin (batch no: 3-03-0143, purity: 94.7 %). Cyfluthrin was dissolved in acetone. The CHO cells were exposed to the test compound for 5 hours at concentrations of 0-3-5-7-9-10 ul/ml (5 plates per experiment). These dose levels were established on the basis of a preliminary toxicity test with concentrations of 0.001-10 ul/ml with and without metabolic activation. Additionally a concurrent cytotoxicity test was performed. The positive control substances were: Ethylmethanesulfonate (EMS, 0.2 ug/ml without S-9 mix) and Benzo(a)pyrene (BaP, 4 ug/ml, with S-9 mix). For the activation experiments, S-9 mix was derived from adult male Fisher rats. For enzyme induction, the animals received a single intraperitoneal injection of Arochlor 1254 (500 mg/kg bw) two days prior to sacrifice. The liver supernatant fluid was prepared and combined with an appropriate cofactor solution according to established procedures. Evaluation criteria: The assay is considered positive in the event a dose dependent increase in mutation frequency is observed with one or more of the five concentrations tested. A mutation frequency must be induced, which is at least twice that of the solvent control, and which is also increased above that of the solvent control by at least 8.7 mutants per 10 clonable cells. The assay is considered suspect if there is no dose response but one or more doses induce a mutation frequency, which is considered significant. The assay is considered negative if none of the doses tested induce a mutation frequency, which is considered significant. The test is valid if the cloning efficiency of the solvent and untreated controls is ≥50 %. The spontaneous mutation frequency in the solvent and untreated controls must fall within the range of 0 - 20 mutants per 10 clonable cells. The positive control must induce a mutation frequency at least three times that of the solvent control.
5.2	**Results and discussion**	In the S9 treated cells, survival was ± 6% of solvent control. Mutation frequency was not increased more than two-fold above the untreated control in any test group. The positive and negative control showed appropriate responses. In non-activated cells, survival varied between 79% and 113% of solvent control. This assay was performed twice: in the first assay, the mutation frequency at the highest concentration (10µg/ml) was significantly increased compared to controls, However, this was within acceptable variation for spontaneous mutation; and the assay was thus repeated. In the second assay, none of the test groups showed significant responses. In both assays, positive and negative controls behaved appropriately. In non-activated cells, survival varied between 79% and 113% of solvent control.
5.3	**Conclusion**	Cyfluthrin was negative in the CHO/HGPRT mutation assay.
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Document IIIA/ Section A6.6.3

Genotoxicity in vitro

In Vitro Gene Mutation Assay

BPD Data set IIA/ Annex Point VI.6.VI.6.3

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-29
Materials and Methods	Applicant's version is acceptable
Results and discussion	*4.2/5.1*: It should read: 10^6 clonable cells instead of 10 clonable cells throughout the paragraph.
Conclusion	Applicant's version is adopted.
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.6.3-1: CHO/HGPRT ASSAY – Activation (with S-9 mix)

Test condition	Survival (Cytotoxicity)		Cloning Efficiency at Selection	Total mutant colonies	Mutation frequency
	Cloning Efficiency	Relative Cloning Efficiency (%)			
Negative control	0.73	84	0.52	6	11.5
Vehicle control	0.87	100	0.52	0	<1.9
Positive control (BaP 4 µg/ml)	0.44	51	0.33	113	342.4
10 µl/ml	0.83	95	c	4	c
9 µl/ml	0.92	106	0.4	0	<2.1
7 µl/ml	0.82	94	0.5	5	20
5 µl/ml	0.87	100	0.45	1	2.2
3 µl/ml	0.83	95	0.55	5	9.1

C = dish lost to contamination

Cloning efficiency for survival calculated as total colonies counted/100 cells x number of replicates

Cloning efficiency at selection calculated as total counted/dishes counted x 100 cells/dish

Mutation frequency = Mutants/10^6 clonable cells calculated as total mutant colonies/number selection dishes x cloning efficiency x 2 x10^5 cells

Table A6.6.3-2: CHO/HGPRT ASSAY – Without Activation (without S-9 mix)

Test condition	Survival (Cytotoxicity)		Cloning Efficiency at Selection	Total mutant colonies	Mutation frequency
	Cloning Efficiency	Relative Cloning Efficiency (%)			
Negative control	0.68	89	0.82	3	3.7a
	0.95	112	1.36	2	1.5b
Vehicle control	0.76	100	0.76	3	3.9a
	0.85	100	1.02	19	18.6b
Positive control (EMS 0.2 µl/ml))	0.22	29	0.75	223	297.3a
	0.19	22	0.77	385	500b
10 µl/ml	0.67	88	0.6	11	18.3a
	0.8	94	0.96	2	2.1b
9 µl/ml	0.63	94	0.78	5	6.4a
	0.96	113	1.01	5	5.0b
7 µl/ml	0.62	82	0.69	1	1.4a
	0.71	84	1.05	11	10.5b
5 µl/ml	0.71	93	0.94	3	3.2a
	0.75	88	1.01	6	5.9b
3 µl/ml	0.82	108	0.80	9	11.3a
	0.67	79	1.06	6	5.7b

a: first assay

b: repeated assay

Cloning efficiency for survival calculated as total colonies counted/100 cells x number of replicates

Cloning efficiency at selection calculated as total counted/dishes counted x 100 cells/dish

Mutation frequency = Mutants/10^6 clonable cells calculated as total mutant colonies/number selection dishes x cloning efficiency x 2 x 10^6 cells

Document IIIA/ Section A6.6.4 **BPD Data set IIA/ Annex Point VI.6.VI.6.4**	**Genotoxicity in-vivo**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	According to the technical guidance document in support of directive 98/8/EC, *in vivo* genotoxicity assays will be required if a positive result is seen *in vitro* genotoxicity assays. As shown in sections A6.6.1 to A6.6.3, cyfluthrin is not genotoxic *in vitro*. Further tests on this compound are therefore not considered necessary.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
Date	**EVALUATION BY RAPPORTEUR MEMBER STATE** 2013-07-30	
Evaluation of applicant's justification	**A6.6.4: 1) in vivo mutagenicity study** There are two studies adressing in vivo mutagenicity [redacted] (1980, 1988). Both studies were submitted for PPP assessment and were classified “acceptable”. Cyfluthrin was tested in a dose range of 0-80 mg/kg bw (cyfluthrin: 0; 7.5; 15 mg/kg bw; beta-cyfluthrin 0, 80 mg/kg bw) and it did not show any clastogenic potential. The positive controls induced significant increase in the number of mironuclei. The ratios of polychromatic to normochromatic erythrocytes were unaffected. The study summaries are provided below. [redacted] Micronucleus test on the mouse to evaluate cyfluthrin for mutagenic potential - Report no.: 9435 (September 22, 1980); [redacted] (Dates of exp. work: June 23, 1980 to July 28, 1980). *“A micronucleus test was conducted on male and female mice to evaluate FCR 1272 for potential mutagenic effects on the chromosomes of bone marrow erythroblasts. The known mutagen and former cytostatic Trenimon was used as the reference substance.* *The oral applications were made at an interval of 24 hours, and the femoral marrow was prepared 6 hours after the second application. The FCR 1272 doses were 2 x 7.5 mg/kg and 2 x 15.0 mg/kg body weight, and the Trenimon positive control doses were 2 x 0.125 mg/kg. The test substance was applied orally and the positive control substance was applied by the intraperitoneal route. The treated mice did not show any symptoms of toxic effects and they all survived until test termination, apart from two but there was no evidence of their death being related to test compound administration.*	

Document IIIA/ Section A6.6.4	Genotoxicity in-vivo
BPD Data set IIA/ Annex Point VI.6.VI.6.4	
	The test provided no indication of FCR 1272 having a mutagenic effect at doses of up to and including 2 x 15.0 mg/kg body weight per os. Erythrocyte production , measured against the ratio of polychromatic to normochromatic erythrocytes also was not adversely affected. *Trenimon, the positive control, had a marked mutagenic effect manifested by a biologically relevant increase in the incidence of polychromatic erythrocytes with micronuclei. It was not seen to depress erythropoiesis."* [redacted] Micronucleus test on the mouse to evaluate for clastogenic effects - Report no.: 16557 (March 24, 1988); [redacted]. *"Beta-cyfluthrin (FCR 4545) was investigated in male and female mice foe a possible clastogenic effect on the chromosomes of bone marrow erythroblasts by means of the micronucleus test. Cyclophosphamide, served as a positive control.* *Treated animals received a single oral administration of either FCR 4545 or cyclophosphamide. 24, 48 and 72 hours after the administration the femoral marrow of the FCR 4545 – treated groups was prepared. Negative and positive controls were sacrificed after 24 hours only. The doses of FCR 4545 and positive control phosphamide were 80 mg/kg body weight and 20 mg/kg, respectively.* *The animals treated with FCR 4545 showed lasting symptoms of toxicity for up to 24 hours after administration. All animals survived until the end of the test.* *The ratio of polychromatic to normochromatic erythrocytes was not altered.* *No indications of a clastogenic effect of FCR 4545 were found after a single treatment with 80mg/kg per os.* *Cyclophosphamide had a clear clastogenic effect as is shown by the biologically relevant increase in polychromatic erythrocytes with micronuclei. The ratio of polychromatic to normochromatic erythrocytes was not altered."*
Conclusion	Cyfluthrin was not mutagenic in mouse micronucleous assay in vivo.
Remarks	-
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.6.5 BPD Data set IIA/ Annex Point VI.6.VI.6.5	Genotoxicity in-vivo	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	According to the technical guidance document in support of directive 98/8/EC, *in vivo* genotoxicity assays will be required if a positive result is seen *in vitro* genotoxicity assays. As shown in sections A6.6.1 to A6.6.3, cyfluthrin is not genotoxic *in vitro*. Further tests on this compound are therefore not necessary.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2006-09-13	
Evaluation of applicant's justification	**A6.6.5: 2nd in vivo mutagenicity study** Since there is no second in vivo study available and an in vivo test (not submitted) and in vitro tests do not show any genotoxic potential of cyfluthrin further testing is not necessary according to the technical guidance document in support of directive 98/8/EC.	
Conclusion	Applicant's justification is acceptable.	
Remarks	-	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Document IIIA/ Section A6.6.6 **BPD Data set IIA/ Annex Point VI.6.VI.6.6**	**Genotoxicity in-vivo**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	According to the technical guidance document in support of directive 98/8/EC, *in vivo* genotoxicity assays will be required if a positive result is seen *in vitro* genotoxicity assays. As shown in sections A6.6.1 to A6.6.3, cyfluthrin is not genotoxic *in vitro*. Further tests on this compound are therefore not necessary.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2006-09-13	
Evaluation of applicant's justification	**A6.6.6: Germ cell effects** There is a dominant lethal test in mouse germ cells available: [redacted] (1981). This study was submitted for PPP assessment and was classified "acceptable". However, submission of this study would not alter the current risk assessment. Therefore, the study is regarded dispensable. [redacted]**.:** Dominant lethal test on male mouse to evaluate cyfluthrin for mutagenic potential - Report no.: 9678 (January 07, 1981); [redacted] (Dates of exp. work: January 14, 1980 to March 14, 1980; July 07, 1980 to August 01, 1980)	
Conclusion	Non-submission of the study of germ cell effects is acceptable.	
Remarks	-	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	

Document IIIA/ Section A6.6.6	Genotoxicity in-vivo
BPD Data set IIA/ Annex Point VI.6.VI.6.6	
Remarks	

Document IIIA/ Section A6.6.7 **BPD Data set IIA/ Annex Point III-0§**	**Genotoxicity in-vivo**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	According to the technical guidance document in support of directive 98/8/EC, if *in vitro* assays are negative, further testing is only required if metabolites of concern are formed in mammals. The results from cyfluthrin in vitro genotoxicity testing are negative for the three tests 6.6.1, 6.6.2 and 6.6.3 and no metabolite of concern is formed in mammals. Metabolites formed in mammals are assessed in all mammalian toxicity studies performed with cyfluthrin or beta-cyfluthrin. Additionally, no evidence of carcinogenicity has been seen in long-term studies with cyfluthrin. Further tests on this compound are therefore unnecessary and unwarranted.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2006/09/13	
Evaluation of applicant's justification	No metabolites of concern are formed. Thus, further testing of metabolites is not required.	
Conclusion	The applicant's justification is acceptable.	
Remarks	-	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Document IIIA/ Section 6.7/01

BPD Data set IIA/ Annex Point VI. 6.7

Carcinogenicity

2-year Combined Chronic Toxicity / Oncogenicity in the rat

			Official use only
		1 REFERENCE	
1.1	**Reference**	*From addendum 2 of the monograph p41* [redacted] (1997) Technical grade cyfluthrin: a combined chronic toxicity/oncogenicity study in the rat. [redacted] Bayer AG Report No.: 107769 BES Ref.: M-044524-02-1 Report date: 20 November 1997 Unpublished [redacted] (2000). Supplemental Submission to Bayer Report No.: 107769 BES Ref.: M-044524-02-1 Report date: 19 July 2000 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	OECD Guideline No. 453	
2.2	**GLP**	Yes	
2.3	**Deviations**	None	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in section 2	
3.1.1	Lot/Batch number		
3.1.2	Specification	Test material:	
3.1.2.1	Description	Technical grade cyfluthrin,	
3.1.2.2	Purity	purity: 93.9-95.1 %, batch no.: 4030059/BF9340-71	
3.1.2.3	Stability	The mean treatment concentrations remained within approx. 5 % of the nominal concentrations. Based on analytical chemistry	
3.2	**Test Animals**		

Document IIIA/ Section 6.7/01

BPD Data set IIA/ Annex Point VI. 6.7

Carcinogenicity

2-year Combined Chronic Toxicity / Oncogenicity in the rat

3.2.1 Species	determinations, cyfluthrin was considered to be homogeneously distributed and stable in the feed.	
3.2.2 Strain	Test animals:	
3.2.3 Source		
3.2.4 Sex	Fischer-344 rats [redacted]	X
3.2.5 Age/weight at study initiation	age: 8 wk at treatment initiation	
3.2.6 Number of animals per group	[redacted]	X
3.2.7 Control animals		X
3.3 Administration/ Exposure	Technical grade cyfluthrin was administered to separate 1-yr and 2-yr sacrifice groups of Fischer 344 rats at nominal dietary concentrations of 0-50-225-450 ppm. The 1-yr sacrifice group consisted of 40 animals (20 males and 20 females) in both the control and high-dose groups and 20 animals (10 males and 10 females) in both the low and intermediate dose levels for a total of 120 animals. The 2-yr sacrifice group consisted of 100 animals (50 males and 50 females) in all 4 dose groups for a total of 400 animals.	
3.3.1 Duration of treatment		X
3.3.2 Frequency of exposure		
3.3.3 Postexposure period		
3.3.4 Oral		
3.3.4.1 Type		X
3.3.4.2 Concentration		X
3.3.4.3 Vehicle		X
3.3.4.4 Concentration in vehicle		
3.3.4.5 Total volume applied		
3.3.4.6 Controls		X
3.4 Examinations	Study performed according the OECD Guideline No. 453, as stated in the addendum on the monograph from PPP dossier, no deviations from this guideline were noted.	
3.5 Sacrifice and pathology		

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3.6	**Further remarks**	Haematological and clinical-chemistry examinations including urinalyses were performed on the first 20 surviving rats/sex/dose of the 2-yr sacrifice group. In all cases, blood was sampled via the orbital sinus following an overnight fast; to the extent possible, urine was collected on the same non-fasted animals the week prior to blood collection. In addition to the routine guideline requirements, ophthalmologic exams were conducted on all acclimatised animals prior to exposure, and then again on all surviving animals just prior to termination of the 1- and 2-yr segments of the study. At necropsy, the organ weights and organ/body weights were determined for the following tissues: adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen and testicles. All required tissues plus all gross lesions detected at necroscopy from all animals were histopathologically examined.
		4 RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical signs	With the exception of an statistically significantly increased frequency alopecia noted in 450-ppm males and females (see Table 6.7/01-3), no clinical and/or cage-side observations toxicity attributable to exposure to the test substance were observed.
4.1.2	Mortality	Survival was unaffected by administration of the test substance as the incidence of mortality was comparable between treated and control animals of each sex. Overall, survival to the end of the 2-yr treatment period was in the range of 54-82 %.
4.2	**Body weight gain**	Data for body weight gain and terminal body weight are summarised in Table 6.7/01-2. Body weight gain remained unaffected in both sexes at the low dose level of 50 ppm. At the end of the treatment period, declines of 11 % and 10% body weight gain were noted in 225-ppm males and females, respectively, while at 450 ppm, body weight gains were reduced by 14 % and 21 % in males and females, respectively. Terminal body weights were statistically significantly decreased at 225 ppm and above in both sexes.
4.3	**Food consumption and compound intake**	The mean test substance intake over the 2-yr treatment period is summarised in Table 6.7/01-1. Food consumption and utilisation was not influenced by treatment in both sexes at all doses tested.
4.4	**Ophtalmoscopic examination**	No ophthalmic toxicity attributable to exposure to the test substance was observed.
4.5	**Blood analysis**	
4.5.1	Haematology	Clinical chemistry findings included a slight albeit statistically significant decline in serum triglyceride concentration (and to a lesser extent serum cholesterol concentration) in 450-ppm males. No evidence of cyfluthrin-induced toxicity was observed in any other in-life parameter including haematology and urinalysis.
4.5.2	Clinical chemistry	
4.5.3	Urinalysis	

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4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	Statistically significant changes in absolute organ weights and organ/body weight ratios are summarised in Table 6.7/01-4. Decreased absolute weights were accompanied by increases in the respective relative organ weights, indicating that the organ weight changes observed in this study were secondary to cyfluthrin-induced decreases in body weight. This conclusion is supported by the lack of corresponding treatment-related histopathological tissue changes.
4.6.2	Gross and histopathology	There were no neoplastic or non-neoplastic microscopic alterations in the 24-month male and female rats that were considered to be compound-related. Only one neoplasm was marginally increased over the concurrent controls consisting of mammary gland adenocarcinomas in the 24-month 450 ppm female rats (see Table 6.7/01-5).
4.7	**Other**	None

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Cyfluthrin (purity 93-9-95.1%, batch No. 4030059/BF9340-71) was administered to separate 1-year and 2-year sacrifice groups of rats (Fischer-344rats [redacted], Age: 8 weeks at treatment initiation) at nominal dietary concentrations of 0, 50, 225 and 450 ppm. The 1-year sacrifice group consisted of 20 rats/sex in both the control and high groups and 10 rats/sex in both the low and intermediate dose levels. The 2-year sacrifice group consisted of 50 rats/sex in all 4 dose groups.
5.2	**Results and discussion**	The mean treatment concentrations remained within approx. 5 % of the nominal concentrations. Based on analytical chemistry determinations, cyfluthrin was considered to be homogeneously distributed and stable in the feed. Survival was unaffected by administration of the test substance as the incidence of mortality was comparable between treated and control animals of each sex. Overall, survival to the end of the 2-yr treatment period was in the range of 54-82 %. Body weight gain remained unaffected in both sexes at the low dose level of 50 ppm. At the end of the treatment period, declines of 11 % and 10% body weight gain were noted in 225-ppm males and females, respectively, while at 450 ppm, body weight gains were reduced by 14 % and 21 % in males and females, respectively. Terminal body weights were statistically significantly decreased at 225 ppm and above in both sexes. With the exception of a statistically significantly increased frequency of alopecia noted in 450-ppm males and females, no clinical and/or cage-side observations toxicity attributable to exposure to the test substance were observed. Clinical chemistry findings included a slight albeit statistically significant decline in serum triglyceride concentration (and to a lesser extent serum cholesterol concentration) in 450-ppm males. No evidence of cyfluthrin-induced toxicity was observed in any other in-life parameter including haematology and urinalysis.

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Decreased absolute weights were accompanied by increases in the respective relative organ weights, indicating that the organ weight changes observed in this study were secondary to cyfluthrin-induced decreases in body weight. This conclusion is supported by the lack of corresponding treatment-related histopathological tissue changes.

There were no neoplastic or non-neoplastic microscopic alterations in the 24-month male and female rats that were considered to be compound-related. Only one neoplasm was marginally increased over the concurrent controls consisting of mammary gland adenocarcinomas in the 24-month 450 ppm female rats.

Despite being out of range of in-house historical control data, the increased incidence of mammary gland adenocarcinomas was considered to be incidental for the following reasons:

1. The incidence was statistically comparable to the concurrent control animals.

2. There was no suggestion of compound-induced carcinogenicity due to cell proliferation based on the incidence of mammary gland hyperplasias, fibroadenomas, and a lack of mammary gland adenomas;

3. No dose-dependent increase incidence of all mammary gland tumours combined was found.

4. Additionally a complete battery of mutagenicity studies performed on the compound indicated it was non-genotoxic.

5. The time to tumour development between control and treated animals appeared to be comparable, as no proliferative lesions of any kind were seen in the mammary glands of the 12-month group in this study and all treated and control 24-month females that contained mammary gland adenocarcinomas were sacrificed at study termination.

6. Finally, there was no evidence of compound-induced carcinogenicity based on a previous two-year feeding study in the Wistar rat with technical grade cyfluthrin at doses identical to those used in this study.

5.3	**Conclusion**	Based on the lack of adverse compound-related effect in body weight gain at a dose of 50 ppm in males and females, a systemic chronic toxicity NOEL of 2.6 and 3.3 mg cyfluthrin/kg bw/d was established for male and female rats, respectively. No evidence for compound-induced neoplasia was found in this study.
5.3.1	LO(A)EL	
5.3.2	NO(A)EL	2.6 and 3.3 mg cyfluthrin/kg bw/d was established for male and female rats, respectively
5.3.3	Other	
5.3.4	Reliability	1
5.3.5	Deficiencies	No

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Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006/09/05
Materials and Methods	*3.2.4 Sex:* M + F *3.2.6 Number of animals per group:* 2 yr-groups: 50 M/50 F 1 yr-groups: 20 M/20 F (control/high dose), 10 M/10 F (medium doses) *3.2.7 Control animals:* Yes *3.3.1 Duration of treatment:* 1 yr/2 yr *3.3.4.1 Type:* Dietary *3.3.4.2 Concentration:* 0/0, 2.6/3.3, 11.6/14.4, 22.8/28.3 (♂/♀) mg/kg bw/d (0, 50, 225, 450 ppm) *3.3.4.3 Vehicle:* Acetone/corn oil *3.3.4.6 Controls:* Vehicle
Results and discussion	Applicant's version is adopted.
Conclusion	Neoplastic LO(A)EL: > 22.8/28.3 mg/kg bw/d (M/F) Non-neoplastic LO(A)EL: 11.6/14.4 mg/kg bw/d (M/F) based on decreased body weight gain Neoplastic NO(A)EL: 22.8/28.3 mg/kg bw/d (M/F) Non- neoplastic NO(A)EL: 2.6/3.3 mg/kg bw/d (M/F)
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table 6.7/01-1: Rat 2-yr study: Calculated test substance intake

Nominal dose levels (ppm)	Average daily consumption of cyfluthrin (mg/kg bw/d)	
	Males	Females
0	0.0	0.0
50	2.6	3.3
225	11.6	14.4
450	22.8	28.3

Table 6.7/01-2: Rat 2-yr study: Body weight gain and terminal body weight

Time period	Mean bw gain (g) during the designated study periods							
	Male dose groups (ppm)				Female dose groups (ppm)			
	0	50	225	450	0	50	225	450
wk 1 - wk 13	140.5 (100%)	136.9 (97 %)	123.9 (88 %)	108.8 (77%)	54.7 (100%)	53.3 (97 %)	51.2 (94 %)	45.0 (82 %)
wk 1 - wk 26	181.4 (100%)	175.9 (97 %)	160.4 (88 %)	145.6 (80 %)	73.3 (100%)	71.8 (98 %)	68.3 (93 %)	58.3 (80 %)
wk 1 - wk 52	224.0 (100%)	217.8 (97 %)	196.9 (88 %)	173.1 (77 %)	92.0 (100%)	89.4 (97 %)	86.8 (94 %)	73.9 (80 %)
wk 1 -wk 104[a]	192.1 (100%)	180.8 (94 %)	171.9 (89 %)	165.0 (86 %)	149.9 (100%)	137.9 (92 %)	134.7 (90 %)	118.8 (79 %)
Terminal body weight (g)	366.7 (100%)	354.5 (97 %)	344.4* (94 %)	340.5* (93 %)	274.5 (100%)	263.8 (96 %)	256.2* (93 %)	236.3* (86 %)

[a] Last body weight determinations for females were performed during treatment week 103.
Statistics: Anova + Dunnett's test: * = $p < 0.05$

Table 6.7/01-3: Rat 2-yr study: Clinical observations

Group	Incidence of alopecia (skin, forelimb)							
	Male dose groups (ppm)				Female dose groups (ppm)			
	0	50	225	450	0	50	225	450
1-year group	0/20	0/10	1/10	2/20	2/20	0/10	1/10	5/20
2-year group	1/50	1/50	3/50	6/50	5/50	5/50	6/50	9/50

Table 6.7/01-4: Rat 2-yr study: Organ weight changes

Parameter	Dose (ppm)			
	0	50	225	450
Males				
Adrenals abs. wt (g)	0.088 (100%)	0.085 (97 %)	0.072[s] (82 %)	0.070 [s] (80%)
rel. wt (%)	0.013 (100%)	0.013 (100%)	0.014 (108 %)	0.014* (108%)
Kidneys abs. wt (g)	3.587 (100%)	3.586 (100%)	3.341* (93 %)	3.287* (92 %)
rel. wt (%)	0.799 (100%)	0.830 (104%)	0.846* (106%)	0.873* (109 %)
Liver abs. wt (g)	18.29 (100%)	17.08 (93 %)	15.95* (87 %)	14.83" (81 %)
rel. wt (%)	3.778 (100%)	3.881 (103 %)	3.980 (105%)	4.096* (108%)
Females				
Liver abs. wt (g)	11.47 (100%)	11.32 (99%)	11.08 (97%)	10.05 [s] (88 %)
rel. wt (%)	4.097 (100%)	4.119 (101%)	4.067 (99 %)	4.217 (103 %)

Statistics: Anova + Dunnett's test: * = $p<0.05$;

Kruskal-Wallis Anova + Mann- Whitney u-test: s = $p < 0.05$.

Table 6.7/01-5: Rat 2-yr study: Findings in the female mammary gland

MAMMARY GLAND	Incidence of mammary gland lesions(animals with lesion / animals examined)					
	Dose level				Historical control data[a]	
	0	50	225	450	92-272-SC	91-272-LJ
Hyperplasia	0/50	1/50	0/50	2/50	0/50	0/50
Adenomas	0/50	0/50	0/50	0/50	0/50	1/50
Adenocarcinoma	1/50	0/50	0/50	4/50	0/50	1/50
Fibroadenoma	9/50	15/50	9/50	4/50	no data	no data
Total mammary gland tumours	10/50	15/50	9/50	8/50	no data	no data

[a] Historical control data was available from two 2-year studies conducted at the testing facility using the Fischer-344 rat (Study-No. 92-272-SC and 91-272-LJ)

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Official use only

1 REFERENCE

1.1	**Reference**	*From addendum 2 of the monograph p45* [redacted] (1998) Technical grade cyfluthrin: An oncogenicity study in the mouse [redacted] Bayer AG Report No.: 108041 BES Ref.: M-027231-02-0 Report date: 28 May 1998 Unpublished [redacted] (2000). Supplemental Submission to Bayer AG Report No. 108041-1. [redacted] Bayer AG Report No.: 108041-1 BES Ref.: M-027231-02-1 Report date: 6 September 2000 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	OECD Guideline No. 451
2.2	**GLP**	Yes
2.3	**Deviations**	None

3 MATERIALS AND METHODS

3.1	**Test material**	Test material:
3.1.1	Lot/Batch number	Cyfluthrin, purity 93-9-95.1%,
3.1.2	Specification	batch No. 4030059/BF9340-71
3.1.2.1	Description	Test animals:
3.1.2.2	Purity	CD-1 mice: age and bw (Day 0): approx. 8 wk.,
3.1.2.3	Stability	males: 28.7 g, females: 24.3 g
3.2	**Test Animals**	[redacted]
3.2.1	Species	

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3.2.2 Strain 3.2.3 Source 3.2.4 Age/weight at study initiation 3.2.5 Number of animals/group 3.2.6 Control animals	Cyfluthrin was administered in the diet to 50 CD-1 mice/sex/dose for approximately 18 months. Nominal doses were 0, 200, 750, 1400/1600 ppm (male/female), equivalent to 0, 31.9, 114.8, 232.7 mg/kg bw/d for males and 0, 38.4, 140.6, 309.7 mg/kg bw/d for females. Test and control diets were available *ad libitum* at all time; Homogeneity and stability of cyfluthrin in the diet mixture were confirmed.	
3.3 Administration/ **3.4 Exposure** 3.4.1 Duration of treatment 3.4.2 Frequency of exposure 3.4.3 Post exposure period 3.4.4 Oral 3.4.4.1 Type 3.4.4.2 Concentration 3.4.4.3 Vehicle 3.4.4.4 Concentration in vehicle 3.4.4.5 Total volume 3.4.4.6 Controls	Study performed according the OECD Guideline No. 453, as stated in the addendum on the monogragh from PPP dossier, no deviation to this guideline were noted.	X
3.5 Examinations	Body weight and food consumption were determined weekly for 17 months and once during the last month of the study. Detailed examinations of each animal were conducted weekly throughout the study. Standard haematological and differential leukocyte analyses were performed on blood from non-fasted animals at approximately 12 and 18 months of study. All animals were subjected to a post-mortem examination, which included documenting and saving all gross lesions, weighing adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, spleen and testes; and collecting representative tissues for histopathological evaluation.	
3.6 Sacrifice and pathology **3.7 Further remarks**		
	4 RESULTS AND DISCUSSION	
4.1 Observations		
4.1.1 Clinical signs	Clinical observations attributable to exposure included rough coat noted in 1400/1600 ppm males and females, hunched back, lesion redness and lesion scabs observed in 1600 ppm females. The redness and scabs were generally associated with the ear pinnae of one or both ears.	

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4.1.2	Mortality	Survival was unaffected by treatment.
4.2	**Body weight gain**	Decreased body weight gains were observed over the 18-month treatment period in all treated female groups and high dose males. See Table A6.7/02-1 for details.
4.3	**Food consumption and compound intake**	Food consumption and food utilization were unaffected by treatment in both sexes at all doses tested. Compound intake for the nominal doses of 0, 200, 750, 1400/1600 ppm (male/female) were equivalent to 0, 31.9, 114.8, and 232.7 mg/kg bw/d for males, and 0, 38.4, 140.6, and 309.7 mg/kg bw/day for females.
4.4	**Ophthalmoscopic examination**	Not evaluated
4.5	**Blood analysis**	
4.5.1	Haematology	Unaffected by treatment
4.5.2	Clinical chemistry	Not evaluated
4.5.3	Urinalysis	Not evaluated
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	There were numerous changes in organ weights in both sexes, which are likely due to decreases in body weight gain. This conclusion is supported by the lack of microscopic evidence of a direct toxicological insult by cyfluthrin on any tissue examined in this study. See Table A6.7/02-2 and A6.7/02-3 for details.
4.6.2	Gross and histopathology	Histopathological considerations were limited to the skin of the ear (gross lesions only) which included increased incidences of acanthosis, chronic active inflammation, inflammation (all types), ulcer and debris which corresponded to the increased incidence of "crusty zones" found at the tip of the ears upon gross necropsy examination, generally noted in 750 ppm males and 1400/1600 ppm males and females. The "skin ear" (tip of ear) lesions appear to have resulted from cyfluthrin-induced paresthesia. There was no evidence of a treatment-related neoplastic response in any tissue examined.
4.7	**Other**	None

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Technical grade cyfluthrin (purity 93-9-95.1%, batch No. 4030059/BF9340-71) was administered in the diet to 50 CD-1 mice/sex/dose for approximately 18 months. Nominal doses were 0, 200, 750, 1400/1600 ppm (male/female), equivalent to 0, 31.9, 114.8, 232.7 mg/kg bw/d for males and 0, 38.4, 140.6, 309.7 mg/kg bw/d for females. All test diets were available for ad libitum consumption at all

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		times; Homogeneity and stability of cyfluthrin in the diet mixture were confirmed. Body weight and food consumption were determined weekly for 17 months, and once during the last month of the study. Detailed examinations of each animal were conducted weekly throughout the study. Standard haematological and differential leukocyte analyses were performed on blood from non-fasted animals at approximately 12 and 18 months of study. All animals were subjected to a post-mortem examination, which included documenting and saving all gross lesions, weighing adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, spleen and testes; and collecting representative tissues for histopathological evaluation.
5.2	**Results and discussion**	Decreased body weight gains over the 18-month treatment were observed in all female treatment groups and in high-dose-group males. Food consumption and utilisation remained unaffected in both sexes at all doses tested. At sacrifice, female terminal body weights were statistically significantly decreased compared to controls at all dose levels tested, while male terminal body weight was statistically significantly decreased only at 1400 ppm. Clinical observations attributable to exposure included rough coat in the 1400/1600 ppm males and females, and hunched back, lesion redness, and lesion scab observed in the 1600 ppm females. The redness and scabs were generally associated with the ear pinnae of one or both ears. No evidence of a cyfluthrin-induced toxicity was observed in any other in-life parameter including survival and haematology. Gross pathological observations attributable to exposure included rough coat in 1400/1600 ppm males and females, crusty zones of the skin of the ear in 750 ppm males and the 1400/1600 ppm males and females, and wet/stained ventrum in 1400 ppm males. Numerous declines in absolute organ weight were observed especially in female treatment groups. Evaluation of organ/body weight ratios suggest that organ weight changes observed in this study were likely secondary to cyfluthrin-induced decreases in body weight gain. This conclusion is supported by the lack of microscopic evidence of a direct toxicological insult by cyfluthrin on any tissue examined in this study. Microscopic lesions associated with exposure to the test substance observed in this study occurred in a gross lesion involving the skin of the ear and included acanthosis, chronic active inflammation, inflammation-all types, ulcer, and debris, which corresponded to the increased incidence of "crusty zones" found at the tip of the ears upon gross necropsy examination. The incidences were generally elevated in 750-ppm males and 1400/1600-ppm males and females. In general, the affected ears at the time of necropsy were ulcerated (parts of pinnae missing) and red with crust and debris. The "skin ear" (tip of ear) lesions appear to have resulted from cyfluthrin-induced paresthesia.

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		The body weight profile which emerged through approx. 18 months of continuous and repeated dietary exposure to the test substance suggests that at the highest dose tested, the MTD for cyfluthrin in the male mouse was established (1400 ppm), while in the female mouse, the MTD was clearly exceeded (1600 ppm). No evidence of a compound-induced neoplastic response was observed in any tissue examined.
5.3	**Conclusion**	Under the conditions of the this study, cyfluthrin showed no evidence of a carcinogenic potential in mice after 18-month continuous dietary exposure of up to 1400 ppm in males and 1600 ppm in females, the highest dose tested.
5.3.1	LO(A)EL	The LOEL was the lowest dose tested, (200 ppm equivalent to 31.9 and 38.4 mg/kg bw/day for males and females respectively)
5.3.2	NO(A)EL	A NOAEL for systemic toxicity could not be derived because female body weights were slightly albeit statistically significantly decreased already at 200 ppm, the lowest dose level tested. In males, a NOAEL for systemic toxicity of 200 ppm (31.9 mg/kg bw/d) was based on increased incidences of crusty ear lesions at and above 750 ppm (115 mg/kg bw/d). NOEL (Mouse 18-mo carcinogenicity): 1400 ppm (233 mg/kg bw/d)
5.3.3	Other	None
5.3.4	Reliability	1
5.3.5	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	2006-09-05
Materials and Methods	Study performed according to OECD Guideline No. 451 (as correctly stated under 2.1). The study design is not in accordance with OECD Guideline No. 453.
Results and discussion	Applicant's version is adopted.
Conclusion	neoplastic LO(A)EL: > 233/>310 mg/kg bw/d *(♂/♀)* neoplastic NO(A)EL: 233/310 mg/kg bw/d *(♂/♀)* non-neoplastic LO(A)EL: 115/38.4 mg/kg bw/d *(♂/♀)* based on ear lesions in males and decreased body weight gain in females. non-neoplastic NO(A)EL: 31.9/ - mg/kg bw/d *(♂/♀)*
Reliability	1
Acceptability	Acceptable

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Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6-7/02-1. Body weight gains

	Males				Females			
Dose	**0**	**200**	**750**	**1400**	**0**	**200**	**750**	**1600**
BW gain (g) 0-18 mo	11.3 (100%)	10.9 (96%)	10.4 (92%)	8.5 (75%)	13.2 (100%)	11.8 (89%)	10.4 (79%)	6.1 (46%)
Terminal bw (g)	39.3 (100%)	38.7 (98%)	37.6 (96%)	35.8 (91%)*	36.4 (100%)	34.0* (93%)	33.1* (91%)	29.8* (82%)

*Statistically significant (Anova + Dunnett's Test): $p \leq 0.05$

Table A6-7/02-2. Male organ weight changes (absolute and relative) and terminal body weights

Organ	ppm		0	200	750	1400
	Terminal bw (g)		39.3 (100%)	38.7 (98%)	37.6 (96%)	35.8* (91%)
males	Brain	abs. wt (g)	0.517 (100%)	0.511 (99%)	0.514 (99%)	0.512 (99%)
		rel wt (%)	1.331 (100%)	1.333 (100%)	1.376 (103%)	1.442* (108%)
	Heart	abs. wt (g)	0.232 (100%)	0.235 (101%)	0.241 (104%)	0.235 (101%)
		rel wt (%)	0.596 (100%)	0.610 (102%)	0.643 (108%)	0.656 (110%)
	Kidney	abs. wt (g)	0.924 (100%)	0.875 (95%)	0.907 (98%)	0.903 (98%)
		rel wt (%)	2.353 (100%)	2.272 (97%)	2.413 (103%)	2.527* (107%)
	Liver	abs. wt (g)	2.371 (100%)	2.294 (97%)	2.253 (95%)	2.245 (95%)
		rel wt (%)	6.059 (100%)	5.940 (98%)	5.996 (99%)	6.318$ (104%)
	Spleen	abs. wt (g)	0.145 (100%)	0.124 (86%)	0.113 (78%)	0.106$ (73%)
		rel wt (%)	0.372 (100%)	0.322 (87%)	0.303 (81%)	0.296 (80%)
	Testes	abs. wt (g)	0.226 (100%)	0.223 (99%)	0.239 (106%)	0.226 (100%)
		rel wt (%)	0.576 (100%)	0.582 (101%)	0.637* (111%)	0.637 (111%)

* Anova + Dunnett's test: $p < 0.05$

$ Kruskal-Wallis Anova + Mann-Whitney u-test: $p < 0.05$

Table A6-7/02-3. Female organ weight changes (absolute and relative)

Organ	ppm		0	200	750	1600
	Terminal bw (g)		36.4 (100%)	34.0* (93%)	33.1* (91%)	29.8* (82%)
Females	Brain	abs. wt (g)	0.529 (100%)	0.527 (100%)	0.530 (100%)	0.512* (97%)
		rel wt (%)	1.464 (100%)	1.563* (107%)	1.612* (110%)	1.742* (119%)
	Heart	abs. wt (g)	0.201 (100%)	0.192 (96%)	0.197 (98%)	0.171* (85%)
		rel wt (%)	0.555 (100%)	0.567 (102%)	0.594 (107%)	0.582 (105%)
	Kidney	abs. wt (g)	0.669 (100%)	0.606 (91%)	0.630 (94%)	0.597 (87%)
		rel wt (%)	0.810 (100%)	0.810 (100%)	0.877$ (108%)	0.877$ (108%)
	Liver	abs. wt (g)	2.171 (100%)	1.971* (91%)	2.112 (97%)	1.938* (89%)
		rel wt (%)	5.946 (100%)	5.796 (97%)	6.350 (107%)	6.520* (110%)
	Lung	abs. wt (g)	0.295 (100%)	0.275 (93%)	0.291 (99%)	0.260 (88%)
		rel wt (%)	0.810 (100%)	0.810 (100%)	0.877$ (108%)	0.877$ (108%)
	Ovaries	abs. wt (g)	0.163 (100%)	0.214 (131%)	0.182 (112%)	0.122$ (75%)
		rel wt (%)	0.442 (100%)	0.650 (147%)	0.562 (127%)	0.372$ (84%)
	Spleen	abs. wt (g)	0.205 (100%)	0.152$ (74%)	0.141 (69%)	0.128$ (62%)
		rel wt (%)	0.554 (100%)	0.448 (81%)	0.423 (76%)	0.429 (77%)

* Anova + Dunnett's test: $p < 0.05$

$ Kruskal-Wallis Anova + Mann-Whitney u-test: $p < 0.05$

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Reproductive toxicity

Inhalation developmental toxicity study in rats

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		1 REFERENCE
1.1	**Reference**	[redacted] (1993) Inhalation study for embryotoxic effects in rats, [redacted] Bayer AG Report No.: 22581 BES Ref.: M-038947-01-1 Report date: 5 October 1993 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	Yes OECD Guidelines for Testing of Chemicals, Section 4, Guideline 414, (adopted 12 May 1981) The inhalation part of the study was conducted according to the OECD Guideline no. 412 which complies to Directive 92/69 EEC method B8. US EPA Subdivision F guidelines, Series 83-3, revised November 1984.
2.2	**GLP**	Yes
2.3	**Deviations**	No
		3 MATERIALS AND METHODS
3.1	**Test Material**	Technical grade cyfluthrin
3.1.1	Lot/batch number	Batch No. 238005176.
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Crystallized yellow-brown mass;
3.1.2.2	Purity	Purity: 96.2%, Stability was assured throughout the study period
3.2	**Test Animals**	
3.2.1	Species	Wistar rats
3.2.2	Strain	[redacted]
3.2.3	Source	[redacted]
3.2.4	Sex	Male and female

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3.2.5	Age/weight at study initiation	Males more than 300 g at time of mating females ranged from 186-244 g on day 0 p.c.
3.2.6	Number of animals/group	25 inseminated Wistar rats/group
3.2.7	Control animals	Yes, exposed to air and to the vehicle.
3.3	**Administration/Exposure**	Technical grade cyfluthrin (formulated in ethanol/polyethylene glycol E 400) was administered by head/nose only under dynamic conditions for 6 hours/day from day 6 to 15 of gestation to 25 inseminated Wistar rats/group. The nominal concentrations were 0 (air), 0 (vehicle), 0.5, 2.5, 12.5 mg/m^3 air corresponding to analytical concentrations of 0.46, 2.55, 11.9 mg/m^3 air (See table 6.8.1/01-1). An additional group was exposed to 12.5 mg/m^3 air (analytical conc. 12.8 mg/m^3 air) supplemented with 40% oxygen.
3.3.1	Duration of treatment	
3.3.2	Frequency of exposure	
3.4	**Examinations**	For every concentration a satellite group with 5 pregnant rats was established and exposed for eight days (day 0 to day 7 corresponding to day 6 to 13 of gestation). In this group parameters of maternal toxicity (including some specific parameters) were determined: mortality, clinical signs, body weight and food intake day 0 to day 7, lung function parameters day 0, reflexes and rectal temperature day 0 and day 6, plasma levels of cyfluthrin and pathological examination day 7.
3.5	**Sacrifice and pathology**	Lung function tests: Five pregnant rats per dose (satellite animals) were exposed to cyfluthrin in a plethysmograph for 4-5 hours. To achieve a total exposure time of 6 hours the rats were exposed thereafter in the "normal" head-nose only inhalation chamber. The following lung function parameters were evaluated: Peak expiratory flow, tidal volume, breaths per minute, respiratory minute volume, inspiratory time and expiratory time.
3.6	**Further remarks**	

4 RESULTS AND DISCUSSION

4.1	**Observations: Exposure**	Stable and reproducible conditions of exposure were achieved. The aerosol had a mean mass media aerodynamic diameter (MMAD) of about 1.1 µm. More than 98% of the aerosol mass may be regarded as readily respirable (particles ≤ 3 µm).
4.1.1	Clinical observations	Clinical signs (bloody snout, unkempt fur and piloerection) were apparent in the dams at 2.55 mg/m³ air and above. Respiratory disturbances and hypoactivity were noted at 11.9 and 12.8 mg/m³ air, and a high-stepping gait and salivation at 11.9 mg/m³ air only. The satellite groups exhibited a concentration-dependent hypother-mia and bradypnoea (hypoventilation) at concentrations of 0.46 mg/m³ air and above.
4.1.2	Survival	Mortality was unaffected by treatment.

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4.2	**Body weight gain**	Body weight development was decreased at levels of 0.46 mg/m^3 air and above (Table A6.8.1/01-2). In the satellite groups concentrations up to 2.55 mg/m3 air were tolerated without an effect on body weight gain.	
4.3	**Food consumption**	Food consumption was decreased at levels of 0.46 mg/m^3 and above (Table 6.8.1/01-2).	
4.4	**Sacrifice and pathology**	No test substance-related gross pathological findings were ascertained at necropsy of any of the dose groups.	
4.5	**Embryo/**		
4.6	**Foetotoxicity**		
4.6.1 Embryo implantation/resorption		Fertility rate (percentage of inseminated animals with implantations), gestation rate, resorption rate and mean number of fetuses, sex ratio foetal weights, numbers of corpora lutea did not differ from those in the control groups. Placental weights were lower and foetuses showed signs of retarded development (reduction of foetal weights)	
4.6.2 Foetal skeletal and visceral findings		Statistically significant instances of retarded ossification (phalanges, metacarpals and metatarsals except in the 2.55 mg/m^3 group- sternebrae, vertebrae, pelvis or the skull-Table 6.8.1/01-3), which were less frequent in the 2.55 mg/m3 group than in either of the high dose groups, were evident in most cases when the calculations were made on individual foetal or litter basis. An increased incidence of malformations was also observed at levels of 2.55 mg/m3 air and above. However, the nature of the malformations, which with one exception were comparable to those of controls of this or previous studies, did not indicate a specific teratogenic potential of cyfluthrin inhalation. With oxygen supplement the embryotoxic findings in the high dose were less pronounced.	X

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Technical grade cyfluthrin, (Purity: 96.2%, Batch No. 238005176), formulated in ethanol/polyethylene glycol E 400 was administered by head/nose only under dynamic conditions 6 hours/day from day 6 to 15 of gestation to groups of 25 inseminated Wistar rats [redacted] he nominal concentrations were 0 (air), 0 (vehicle), 0.5, 2.5, 12.5 mg/m^3 air corresponding to analytical concentrations of 0.46, 2.55, 11.9 mg/m^3 air. An additional group was exposed to 12.5 mg/m^3 air (analytical conc. 12.8 mg/m^3 air) supplemented with 40% oxygen. For every concentration a satellite group with 5 pregnant rats was established and exposed for eight days (day 0 to day 7 corresponding to day 6 to 13 of gestation). In this group parameters of maternal toxicity (including some specific parameters) were determined: mortality, clinical signs, body weight and food intake day 0 to day 7, lung function parameters day 0, reflexes and rectal temperature day 0 and day 6,

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Inhalation developmental toxicity study in rats

plasma levels of cyfluthrin and pathological examination day 7.

Lung function tests: Five pregnant rats per dose (satellite animals) were exposed to cyfluthrin in a plethysmograph for 4-5 hours. To achieve a total exposure time of 6 hours the rats were exposed thereafter in the "normal" head-nose only inhalation chamber. The following lung function parameters were evaluated: Peak expiratory flow, tidal volume, breaths per minute, respiratory minute volume, inspiratory time and expiratory time.

5.2 Results and discussion

In the dams of the main group, food intake and body weight development were decreased at levels of 0.46 mg/m^3 air and above. Clinical signs (bloody snout, unkempt fur and piloerection) were apparent in the dams at 2.55 mg/m^3 air and above. Respiratory disturbances and hypoactivity were noted at 11.9 mg/m^3 air and 12.8 mg/m^3 air (plus oxygen), and a high-stepping gait and salivation at 11.9 mg/m^3 air only. No gross pathological findings were recorded at necropsy of any dose group (including the satellite groups).

The satellite groups exhibited a concentration-dependent hypothermia and bradypnoea (hypoventilation) after the 1st exposure to levels of 0.46 mg/m^3 air and above. After the eight exposures this hypothermia could still be determined in the high dose groups only, being less severe in the group with oxygen substitution. In the satellite groups concentrations up to 2.55 mg/m^3 air were tolerated without an effect on body weight gain. No signs of toxicologically significant neurological or sensorimotor changes (reflex tests) were seen. Comparing the findings from the groups with and without oxygen substitution permits the conclusion that the increase in the partial pressure of oxygen in the inhalation chamber produced an attenuation of the maternal toxic effects.

There were no significant differences in the plasma cyfluthrin levels in the groups with and without oxygen substitution. Placental weights were lower and fetuses showed signs of retarded development (reduction of fetal weight).

At 2.55 mg/m^3 air and above, fetuses exhibited signs of retarded ossification of the phalanges, metacarpals and metatarsals (except in the 2.55 mg/m^3 group), sternebrae, vertebrae, pelvis or the skull.

Statistically significant instances of retarded ossification, which were less frequent in the 2.55 mg/m^3 group than in either of the high dose groups, were evident in most cases when the calculations were made on individual fetal or litter basis. An increased incidence of malformations was also observed at levels of 2.55 mg/m^3 air and above. However, the nature of the malformations, which with one exception were comparable to those in the controls of this or previous studies, did not indicate a specific teratogenic potential of cyfluthrin inhalation. With oxygen supplement the embryotoxic findings in the high dose group were less pronounced. X

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Reproductive toxicity

Inhalation developmental toxicity study in rats

5.3	**Conclusion**	The embryotoxicity of cyfluthrin after inhalation exposure is caused by a physiological maternal compensation mechanism (hypothermia with respiratory alkalosis) following reflex bradypnoea after sensory irritation.	X
5.3.1	LO(A)EL	Maternal: 2.55 mg/m^3 Based on transient, marginal changes (reduced food intake during pregnancy in the main group, hypothermia and reflexively induced bradypnea in the satellite group) were already observed at the lower dose. However, these transient effects were not regarded as toxicologically relevant. Foetal: 2.55 mg/m^3 - based on reduced food consumption and body weight development of dams during pregnancy and on reduced placental weights and retardation of development.	
5.3.2	NO(A)EL	The NOAEL of 0.46 mg/m^3 air for maternal toxicity and the NOEL of 0.46 mg/m^3 air for fetotoxicity was based on reduced food consumption and bodyweight development of dams during pregnancy and on reduced placental weights and retardation of development. NOAEL: Maternal: 0.46 mg/m^3 NOEL: Foetal: 0.46 mg/m^3	
5.3.3	Other		
5.3.4	Reliability	1	
5.3.5	Deficiencies	None	

Evaluation by Competent Authorities	
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2013-07-17
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted except for *4.6.2 and 5.2 Malformations:* Eye malformations (microphthalmia/anophthalmia) were specifically increased at levels of 11.9 mg/m^3 air and above (CA-Table 1). As this type of abnormality occurs spontaneously in this strain of rats the increase indicates that inhalation exposure to cyfluthrin may aggravate a pre-existing genetic condition.

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Reproductive toxicity

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Conclusion	LO(A)EL(maternal): 0.46 µg/L NO(A)EL(maternal): 0.46 µg/L LO(A)EL(developmental): 2.55 µg/L NO(A)EL(developmental): 0.46 µg/L Other conclusions: The maternal NOAEL and LOAEL corresponded to an inhaled dose of 0.2 and 1.0 mg/kg bw/day based on the respiratory volume determined in the satellite groups (CA-Table 1). No proof was provided that the embryotoxicity was caused by the maternal toxicity which was clearly present at embryotoxic dose levels. Nevertheless, cyfluthrin is considered to be not selectively toxic for the developing embryo when compared with the maternal organism.
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.8.1/01-1 Target concentrations of cyfluthrin

	Nominal concentration in mg/m^3 air	Mean analytical concentration in mg/m^3 air
Control (air)	0	0
Control (vehicle)	0	0
Group 1	0.5	0.46
Group 2	2.5	2.55
Group 3	12.5	11.9
Group 4	12.5 + approx. 40% O_2	12.8 + 39% O_2

Table A.6.8.1/01-2 General examinations (parental data)

Dose (mg/m^3 air)	0a.	0v.	0.46	2.55	11.9	12.8 + O_2
Number of inseminated rats	25	25	25	25	25	25
Dams with viable fetuses	21	22	23	23	23	23
Number of implantations	12.3	12.8	11.3	11.4	11.3	11.3
Food intake, pregnancy	19.9	20.0	19.1**	18.7**	17.7**	17.4**
Weight gain, pregnancy (g)	83.6	88.8	76.8	74.7**	58.7**	62.3**
Corrected weight gain (g)	20.0	23.0	19.8	19.3**	13.6**	12.5**
Number of live fetuses	11.6	12.0	10.7	10.9	10.4*	10.4*
Mean weight of fetuses (g)	3.41	3.50	3.48	3.13**	2.48**	2.83**
Mean placenta weight (g)	0.61	0.60	0.62	0.56*	0.46**	0.51**

a = air; v = vehicle control
* = $p < 0.05$, ** - $p < 0.01$ compared with air and vehicle controls

Table A6.8.1/01- 3 Anomalies (% foetuses)

Dose (mg/m^3 air)	0a.	0v.	0.46	2.55	11.9	12.8 + O_2
Malformations (all)	1.24	1.14	0.82	3.19	8.79**	4.17
Microphthalmia	0.4	0.6	0.4	1.2	5.4**	2.9
Anophthalmia	0	0	0	0	0.4	0.4
Bone malformations	0	0	0	0	2.9	0

a = air; v = vehicle control
* = $p < 0.05$, ** - $p < 0.01$ compared with air and vehicle controls

Evaluation by Rapporteur Member State, CA-Tables

CA-Table 1 Inhalation embryotoxicity study with cyfluthrin in rats – Litter data

Dose (mg/m^3 air)	**0[a]**	**0[v]**	**0.46**	**2.55**	**11.9**	**12.8 + O_2**
Respiratory vol. (mL/min/kg) [c]	1524	1682	1202	1099	706	650
Internal dose (mg/kg bw/d) [d]	0	0	0.2	1.0	3.0	3.0
Plasma levels (ng/mL) [e]	-	-	-	-	8.5-38.5	4.0-8.0
Number of inseminated rats	25	25	25	25	25	25
Dams with viable fetuses	21	22	23	23	23	23
Food intake, pregnancy	19.9	20.0	19.1**	18.7**	17.7**	17.4**
Weight gain, pregnancy (g)	83.6	88.8	76.8	74.7**	58.7**	62.3**
Corrected weight gain (g)	20.0	23.0	19.8	19.3*	13.6**	12.5**
Number of corpora lutea	14.3	14.2	13.6	13.7	13.9	13.5
Number of implantations	12.3	12.8	11.3	11.4	11.3	11.3
Number of live foetuses	11.6	12.0	10.7	10.9	10.4*	10.4*
Mean foetal weight (g)	3.41	3.50	3.48	3.13**	2.48**	2.83**
Mean placental weight (g)	0.61	0.60	0.62	0.56*	0.46**	0.51**
Malformations (all) [litters(foetuses)]	2 (3)	3(3)	2(2)	4(8)	10(21)	7(10)
Eye malformations	1(1)	2(2)	1(1)	2(3)	9(14)	5(7)

a = air; v = vehicle control; c = measured in satellite groups; d = calculated from respiratory volume (mL/min/kg) measured in satellite groups; e = measured in satellite groups on day 13 of pregnancy immediately post-exposure

* = $p < 0.05$, ** - $p < 0.01$ compared with air and vehicle controls

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BPD Data set IIA Annex Point VI.6.8.1 Oral developmental toxicity study in rats

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1 REFERENCE

From addendum 2 of the monograph p54

1.1	**Reference**	[redacted] (1996) A developmental toxicity study with FCR 4545 Technical in the Wistar Rat. [redacted] Bayer AG Report No.: 107453 BES Ref.:M-136592-01-1 Report date: 4 September 1996 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2	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 Guidelines for Testing of Chemicals, Section 4, Guideline 414, (adopted 12 May 1981)
2.2	**GLP**	Yes
2.3	**Deviations**	None that compromised the validity of the study results

3 MATERIALS AND METHODS

3.1	**Test Material**	As given in section 2
3.1.1	Lot/batch number	Beta-cyfluthrin technical ("FCR 4545 Technical"),
3.1.2	Specification	purity: 96.5-97.3 %,
3.1.2.1	Description	batch-no.: 3030125, suspended in 1 % aqueous Cremophor
3.1.2.2	Purity	
3.2	**Test Animals**	

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3.2.1	Species/Strain	Female Wistar rats,	X
3.2.2	Source	age at start of treatment: approx. 12-15 weeks.	
3.2.3	Sex	[redacted],	
3.2.4	Age/weight at study initiation	[redacted]	
3.2.5	Number of animals/group		
3.2.6	Control animals		
3.3	**Administration / Exposure**		X
	Oral (gavage)		
3.3.1	Duration of treatment	Technical grade Beta-cyfluthrin was administered via gavage to 20 sperm-positive female Wistar rats/group at nominal doses of 0, 3, 10, or 40 mg beta-cyfluthrin/kg bw/day on days 6 through 15 of gestation.	
3.3.2	Frequency of exposure		
3.3.3	Type		
3.3.4	Concentration		
3.3.5	Vehicle		
3.3.6	Concentration in vehicle		
3.3.7	Total volume applied		
3.3.8	Controls		
3.4	**Examinations**	Maternal toxicity, as demonstrated by clinical signs and changes in body weight gain and food consumption during gestation, was characterized.	

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3.5 Sacrifice and pathology	All dams were sacrificed on gestation day 20, at which time the foetuses were removed by caesarean section and gross maternal necropsy was performed. All foetuses were sexed, weighed, and evaluated for external anomalies. Approximately half of each litter was examined for visceral effects, the other half underwent a skeletal examination.	
3.6 Further remarks	Study performed according the OECD Guideline No. 453, as stated in the addendum on the monograph from PPP dossier, no deviations to this guideline were noted.	

4 RESULTS AND DISCUSSION

4.1	**Observations**		
4.1.1	Clinical observations	Clinical findings in the dams were confined to the high dose, where there was an increased incidence of mortality, hypoactivity, locomotor incoordination, and salivation (see Table A6.8.1/02-1)	
4.1.2	Mortality	3 dams died in the high dose group (40 mg/kg bw/day).	
4.2	**Body weight gain**	Statistically significantly decreased body weight gain of dams was observed at 40 mg/kg bw/day (See Table A6.8.1/02-2). In the 10 mg/kg bw/day dose group, evidence of toxicity was limited to slightly decreased body weight gain during the period of beta-cyfluthrin gavage administration, which reached statistical significance during gestational day 7-8.	X
4.3	**Food consumption**	Statistically significantly decreased food consumption that was considered treatment-related was observed in the mid- and high-dose group (see Table A6.8.1/02-2).	
4.4	**Sacrifice and pathology**	There were no remarkable necropsy findings in the dams at any dose level. The mean net body weight change was significantly decreased in the mid and high dose groups by 14% and 32% respectively relative to controls (See Table A6.8.1/02-2).	
4.5	**Reproductive parameters**	No treatment related effects on fertility, mating and gestation indices were observed. An adequate number of litters was available for evaluation in all treatment and control groups.	
4.6	**Embryo/Foetotoxicity**		
4.6.1	Embryo implantation/ resorption	There were no test compound-related effects on any reproductive indices or any embryological endpoints, including pre/post-implantation loss and resorptions.	

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4.6.2	Litter effects	There were no statistically significant effects on litter size or the number of viable foetuses per litter. The sole test compound-related litter finding, a statistically significant decrease in foetal weight (male: -8 %, female: -9 %, and combined: -9 % relative to control; $p < 0.01$) was observed in the 40 mg/kg bw/d dose group.	
4.6.3	Foetal external and visceral findings	No test compound-related foetal external or visceral malformations or variations were observed in any dose group.	
4.6.4	Foetal skeletal findings	No statistically significant increases in the incidences of specific or total skeletal malformations were observed at any dose level. Skeletal variations observed that were considered treatment-related are summarised in Table A6.8.1/02-3. Significantly increased foetal incidences of enlarged anterior fontanel and ossification disorders of frontal bones, sacral and caudal arches, metacarpals, sternebrae segments and xiphoid were observed at the highest dose level of 40 mg/kg bw/d. Corresponding litters incidence were increased in most cases, albeit none to a statistically significant degree. Although test compound-related, these findings are considered secondary to the severe maternal toxicity (which included mortality) and the resultant retardation in foetal development, as evidenced by the statistically significantly decreased foetal weight, observed at this dose level. No effect on the foetal or litter incidence of total skeletal variations was observed.	x

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Technical grade beta-cyfluthrin (purity: 96.5-97.3%, Batch No. 3030125) was administered via gavage to 20 sperm-positive 12-15 week old female Wistar rats/group at nominal doses of 0, 3, 10, or 40 mg beta-cyfluthrin/kg bw/day on days 6 through 15 of gestation. Maternal toxicity, as demonstrated by clinical signs and changes in body weight gain and food consumption during gestation, was characterized. All dams were sacrificed on gestation day 20, at which time the foetuses were removed by caesarean section and gross maternal necropsy was performed. All foetuses were sexed, weighed, and evaluated for external anomalies. Approximately half of each litter was examined for visceral effects; the other half underwent a skeletal examination.	
5.2	**Results and discussion**	Beta-cyfluthrin technical, administered as described in this study, produced maternal toxicity at doses of 10 and 40 mg/kg bw/d. The 3 mg/kg bw/d dose was free of test compound-related maternal effects. Developmental effects: reduced foetal weight and increased foetal skeletal variations were observed in the 40 mg/kg bw/day dose group. No other dose groups exhibited test compound-related developmental effects and no embryotoxicity was observed at any dose level.	

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5.3	**Conclusion**	Based on the observation of developmental effects only at a dose level that produced maternal lethality, the developmental findings are considered secondary to maternal toxicity. Therefore, beta-cyfluthrin technical is not considered a primary developmental toxicant.	X
5.3.1	LO(A)EL	Maternal LOEL: 40 mg/kg bw/d based on mortality, clinical findings and decreased body weights. Developmental LOEL 40 mg/kg bw/d based on reduced foetal weight and increased foetal skeletal variations.	
5.3.2	NO(A)EL	Maternal NOAEL: 10 mg/kg bw/day Developmental NOAEL :10 mg/kg bw/d	
5.3.3	Other	None	
5.3.4	Reliability	1	
5.3.5	Deficiencies	None	

Doc IIIA/Section 6.8.1/02 Reproductive toxicity

BPD Data set IIA Annex Point VI.6.8.1 Oral developmental toxicity study in rats

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-08-31
Materials and Methods	*3.2.5 Number of animals/group*: 30 sperm-positive females/group, resulting in 27, 24, 21, and 26 pregnant females at 0, 3, 10, and 40 mg/kg bw/d, respectively *3.3.7 Total volume applied*: 10 mL/kg bw *3.6 Further remarks*: The study is compatible with OECD Guideline No. 414; it is not compatible with OECD 453 and never was intended to be. The statement of the applicant regarding the lack of deviations to this guideline (OECD 453) is incorrect.
Results and discussion	*4.6.2 Litter effects:* Litter data are summarised in CA-Table 1. *4.6.4 Foetal skeletal findings:* No proof was provided that reduced foetal body weights and associated skeletal findings were causally related to maternal toxicity. It is just unlikely that maternal and embryofoetal toxicity are elicited in a similar dose range.
Conclusion	LO(A)EL(maternal): 10 mg/kg bw/day NO(A)EL(maternal): 3 mg/kg bw/day LO(A)EL(developmental): 40 mg/kg bw/day NO(A)EL(developmental): 10 mg/kg bw/day Other conclusions: Beta-cyfluthrin induced embryofoetal toxicity only at a dose level that produced maternal lethality and signs of intoxication in surviving dams. According to the limited results of this embryotoxicity study, beta-cyfluthrin is not selectively toxic for the developing embryo.
Reliability	1
Acceptability	Acceptable
Remarks	The RMS reviewer had to restructure part of the applicant's Material and Methods section by copy and paste to the appropriate boxes in order for all the text in this format to be readable.
	Comments from ... (specify)
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

Doc IIIA/Section 6.8.1/02	**Reproductive toxicity**
BPD Data set IIA Annex Point VI.6.8.1	Oral developmental toxicity study in rats

Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.8.1/02-1 Dam Clinical signs and mortality

Clinical findings	Incidence of clinical findings during gestation days 6-15 in the dose groups			
mg/kg bw/day	**0**	**3**	**10**	**40**
Mortality	0	0	0	3
Hypoactivity	0/27	0/24	0/21	26/26
Locomotor incoordination	0/27	0/24	0/21	26/26
Salivation	0/27	0/24	0/21	25/26

Table A6.8.1/02-2 Body weight gain and food consumption

Mean body weight gain (g)				
mg/kg bw/day **Treatment period**	**0**	**3**	**10**	**40**
Day 6-16	38.4 (100%)	36.3 (95%)	34.8 (91%)	17.2** (45%)
Day 0-20	100.6 (100%)	98.0 (97%)	98.2 (98%)	83.6** (83%)
Net body weight change[a]	44.9 (100%)	40.1 (89%)	38.5* (86%)	30.5** (68%)
Mean food consumption (g/kg bw/day)b				
Treatment period	**0**	**3**	**10**	**40**
Day 6-16	86.3 (100%)	82.1 (95%)	75.8 (88%)	60.0 (70%)
Day 0-20	85.4 (100%)	82.5 (97%)	78.6 (92%)	74.0 (87%)

* = $p \leq 0.05$; ** = $p \leq 0.01$

[a] = Net body weight change = [body weight (day 20) minus weight of gravid uterus] minus body weight (day 0)

[b] = No statistical evaluations were performed for the overall time frames day 6-16 and 0-20

Table A6.8.1/02-3 Foetal skeletal findings

Incidence of foetal skeletal findings				
Finding	**Dose group (mg/kg bw/day)**			
	0	**3**	**10**	**40**
Foetuses evaluated	27	24	21	23
Litters evaluated	152	145	127	133
Frontal bones, incompletely ossified				
- foetal incidence (%)	57.2	50.3	57.5	72.9*
- litter incidence (%)	96.3	87.5	95.2	100
Anterior fontanel, enlarged				
- foetal incidence (%)	59.9	50.3	61.4	74.4*
- litter incidence (%)	100	87.5	95.2	100
Ribs, presence of ossification centres				
- foetal incidence (%)	27.6	21.0	28.3	14.3*
- litter incidence (%)	66.7	79.2	76.2	52.2
Sacral arches, incompletely ossified				
- foetal incidence (%)	58.6	55.9	60.6	88.0**
- litter incidence (%)	92.6	87.5	95.2	100
Caudal arches, unossified				
- foetal incidence (%)	41.4	44.1	40.2	63.9**
- litter incidence (%)	77.8	83.3	76.2	100
Metacarpals, incompletely ossified				
- foetal incidence (%)	26.3	18.6	29.9	39.8*
- litter incidence (%)	63.0	62.5	66.7	91.3
Sternebrae segment 3, incompletely ossified				
- foetal incidence (%)	13.2	11.7	18.9	25.6*
- litter incidence (%)	48.1	37.5	52.4	60.9
Sternebrae segment 5, unossified				
- foetal incidence (%)	10.5	4.8	16.5	27.8**
- litter incidence (%)	40.7	29.2	42.9	73.9
Xiphoid, unossified				
- foetal incidence (%)	2.0	1.4	3.9	11.3**
- litter incidence (%)	11.1	8.3	19.0	34.8

* = $p \leq 0.05$; ** = $p \leq 0.01$

Evaluation by Rapporteur Member State, CA-Tables

CA-Table 1 Oral embryotoxicity study with beta-cyfluthrin in rats – Litter data

Dose (mg/kg bw/day)	0	3	10	40
Litters evaluated	27	24	21	23
Corpora lutea (mean/dam)	14.0	13.7	13.4	13.9
Implantation sites (mean/dam)	11.5	12.1	12.2	12.3
Live foetuses (mean/dam)	10.7	11.4	11.6	11.1
Males (%)	47	44	52	51
Foetal weight (g)	3.5	3.5	3.5	3.2*
Placental weight (g)	0.48	0.47	0.50	0.45

* statistically different from control, $p < 0.01$

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Annex Point VI.6.8.1

Reproductive toxicity

Oral developmental toxicity study in rabbits

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1 REFERENCE

1.1	**Reference**	[redacted] (1992) Embryotoxicity study (including teratogenicity) with FCR 1272 in the rabbit. [redacted] Report No.: R5770, Project 309914 BES Ref.: M-039695-01-1 Report date: 3 December 1992 Unpublished
1.2	**Data protection**	Yes
1.2.3	Data owner	Bayer CropScience AG
1.2.4	Companies with letter of access	
1.2.5	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 Guidelines for Testing of Chemicals, Section 4, Guideline 414, which complies with Directive 87/303/EEC, part B. The test followed the OECD principles of GLP
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	Technical grade cyfluthrin
3.1.3	Lot/Batch number	Batch No. 238005176, formulated in corn oil
3.1.4	Specification	As given in section 2
3.1.4.0	Description	
3.1.4.1	Purity	Purity:96.1-96.0%,
3.1.4.2	Stability	Expiration date: 19.08.92 (according Certificate of re-analysis dated 25.02.92) Stability in the vehicle(Corn oil) was determined during the first dose range finding study (RCC Project 309903) and confirmed during this study
3.2	**Test Animals**	

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Reproductive toxicity

Oral developmental toxicity study in rabbits

BPD Data set IIA
Annex Point VI.6.8.1

3.2.3	Species	Chinchilla rabbits
3.2.4	Strain	[redacted]
3.2.5	Source	[redacted]
3.2.6	Sex	Female
3.2.7	Age/weight at study initiation	16-27 weeks old, weighing 3189-4626 g
3.2.8	Number of animals per group	16/group
3.2.9	Control animals	Yes
3.2.10	Mating period	The day of mating was designated day 0 post coitum.
3.3	**Administration/ Exposure**	Oral
3.3.3	Duration of exposure	days 6 through 18 of gestation
3.3.4	Postexposure period	10 day
		Oral
3.3.5	Type	Gavage
3.3.6	Concentration	nominal doses of 0, 20, 60 or 180 mg/kg bw/day
3.3.7	Vehicle	corn oil
3.3.8	Concentration in vehicle	2 ml/kg bw
3.3.9	Total volume applied	
3.3.10	Controls	Vehicle
3.4	**Examinations**	
3.4.3	Body weight	Yes, body weights were recorded daily from day 0 until day 28 post coitum

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Reproductive toxicity

Oral developmental toxicity study in rabbits

3.4.4	Food consumption	Yes, food consumption was recorded for the following periods: days 0-6, 6-11, 11-15, 15-19, 19-24 and 24-28 post coitum
3.4.5	Clinical signs	The animals were observed at least twice dally for signs of reaction to treatment and/or symptoms of health.
3.4.6	Examination of uterine content	Post mortem examination, including gross macroscopic examination of all internal organs, with emphasis on the uterus, uterine contents, position of fetuses in the uterus and number of corpora lutea, was performed and the data recorded.
3.4.7	Examination of foetuses	
3.4.7.0	General	All foetuses were sexed, weighed, and evaluated for external anomalies. At dissection, the internal organs were examined and any abnormalities noted. Half of the fetal heads were evaluated by the Wilson technique (Wilson, 1965), the other half by the Dawson technique (Dawson, 1926). All fetal trunks were evaluated by the Dawson technique for the appraisal of thoracic and abdominal organs and of the skeletal system. Approximately half of each litter was examined for visceral effects; the other half underwent a skeletal examination.
3.4.7.1	Skeleton	Yes
3.4.7.2	Soft tissue	Yes
3.5	**Further remarks**	
		4 RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.3	Clinical observations	There were no clinical signs associated with FCR 1272 administration
4.1.4	Survival	No deaths occurred on test.
4.2	**Body weight gain**	Statistically significantly decreased body weight gain of dams was observed at 60 mg/kg bw/day (See Table A6.8.1/03-1) and above. No test article-related differences in body weight were noted at 20 mg/kg/day.
4.3	**Food consumption**	Statistically significantly decreased food consumption that was considered treatment-related was observed in the 60 and 180 mg/kg. (see Table A6.8.1/03-1). In these two groups, statistically significantly increased mean food consumption was noted during the last recording period (Days 24-28). This finding was considered to be a compensatory reaction to the previous reduction in food consumption.
4.4	**Sacrifice and pathology**	There were no abnormal, treatment related necropsy findings in the dams at any dose level.

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Reproductive toxicity

Oral developmental toxicity study in rabbits

4.5	**Embryo/Foetotoxicity**		
4.5.3	Embryo implantation/resorption	There was a dose-related increase in post-implantation loss as seen at 60 and 180 mg/kg/day. The number of fetuses in percentage of implantation sites was reduced. In the lowest dose group of 20 mg/kg bw a reduced number of pregnant rabbits and a decreased number of implantation sites were observed. From 60 mg/kg/day an increase in the number of post implantative resorption was the only observed change interpretable as a sign of reproduction toxicity. (Table A6.8.1/03-2)	X
4.5.4	Litter effects	There were no statistically significant effects on litter size or the number of viable fetuses per litter. In addition, there were no treatment-related differences in sex ratio of the fetuses and no adverse effects on fetal body weights.	X
4.5.5	Fetal external and visceral findings	No test compound-related fetal external or visceral malformations or variations were observed in any dose group.	
4.5.6	Fetal skeletal findings	No statistically significant increases in the incidence of specific or total skeletal malformations were observed at any dose level.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Technical grade cyfluthrin, Purity:96.1-96.0%, Batch No. 238005176, formulated in corn oil was administered via gavage to 16 sperm-positive female Chinchilla rabbits [redacted] at nominal doses of 0, 20, 60 or 180 mg/kg bw/day on days 6 through 18 of gestation in a volume of 2 ml/kg bw. Maternal toxicity, as demonstrated by clinical signs and changes in body weight gain and food consumption during gestation, was characterized. All dams were sacrificed on gestation day 28, at which time the foetuses were removed by caesarean section and gross maternal necropsy was performed. All foetuses were sexed, weighed, and evaluated for external anomalies. Approximately half of each litter was examined for visceral effects; the other half underwent a skeletal examination.	X

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Reproductive toxicity

Oral developmental toxicity study in rabbits

5.2	**Results and discussion**	The evaluation of the food consumption data resulted in a dose-related reduced mean food consumption during the treatment period at 60 and 180 mg/kg bw. In these two groups, statistically significantly increased mean food consumption was noted during the last recording period (24 - 28. day). This finding was considered to be a compensatory reaction to the previous reduction in food consumption. The development of the mean body weight correlated with the reduced food consumption and showed a dose-related, statistically significant body weight loss in group 3 (60 mg/kg bw) and group 4 (180 mg/kg bw) during the treatment period. The corrected body weight gain has not shown any changes, related to the substance administration. No deaths ensued. No deviations from the physiological norm were revealed by clinical observation and at necropsy. In the lowest dose group of 20 mg/kg bw a reduced number of pregnant rats and a decreased number of implantation sites were observed. From 60 mg/kg bw an increase in the number of post-implantative resorptions was the only observed change interpretable as a sign of reproduction toxicity. In consequence, the number of fetuses in percentage of implantation sites was reduced. Determination of the fetal weight and the fetal sex ratio as well as the external and visceral inspection of the fetuses yielded no evidence of embryotoxic or teratogenic effects.	X
5.3	**Conclusion**	The NOEL of 20 mg/kg bw/d for parental toxicity was based on decreased food consumption and body weight gain during the treatment period. The NOEL of 20 mg/kg bw/d for fetotoxicity was based on increased post-implantative resorptions at 60 mg/kg bw/d and above.	
5.3.3	LO(A)EL maternal toxic effects	Maternal: 60 mg/kg/day, based on decreased body weight gains and food consumption during the treatment period.	
5.3.4	NO(A)EL maternal toxic effects	Maternal: 20 mg/kg/day	
5.3.5	LO(A)EL embryotoxic / teratogenic effects	Fetal: 60 mg/kg/day, based on increased post-implantation resorptions	
5.3.6	NO(A)EL embryotoxic / teratogenic effects	Fetal: 20 mg/kg/day	
5.3.7	Reliability	1	
5.3.8	Deficiencies	No	

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Reproductive toxicity

Oral developmental toxicity study in rabbits

BPD Data set IIA
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Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-09-01
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicants version is adopted with the following changes: *4.5.3 and 5.2*: The reduced pregnancy rate in the low dose group is not considered to be a consequence of treatment. No similar effects were observed at higher doses. *4.5.4 Litter effects*: Although not statistically significant the increase in postimplantation loss at 60 mg/kg bw/d and higher resulted in a lower mean litter size in the affected groups. *5.1 Materials and methods*: The description of foetal examinations is incorrect at this point. Refer to 3.4.7 for correct procedure. *5.2 Results and discussion*: The study has been conducted with rabbits not rats.
Conclusion	LO(A)EL(maternal): 60 mg/kg bw/day NO(A)EL(maternal): 20 mg/kg bw/day LO(A)EL(developmental): 60 mg/kg bw/day NO(A)EL(developmental): 20 mg/kg bw/day Other conclusions: Embryolethality was observed at 60 mg/kg bw/day and higher (CA-Table 1). Maternal toxicity (decreased food consumption and body weight gain) was present in this dose range. Based on the findings of this study cyfluthrin is not considered to be a specific embryotoxicant in rabbits.
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*

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Reproductive toxicity

Oral developmental toxicity study in rabbits

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Annex Point VI.6.8.1

Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.8.1/03-1 General parental data

mg/kg bw/day	0	20	60	180
Food intake (%, days 6-11)	100	-15.1	-26.7*	-47.9**
Food intake (%, days 24-28)	100	+20.7	+33.1**	+47.1**
Weight gain (%, days 6-19)	-0.9	-0.8	-4.6**	-5.6**
Weight gain (%, days 6-28)	2.1	3.4	1.0	-0.1
Corrected weight gain (g)	-9.9	-7.3	-9.8	-10.9

* = p<0.05, ** = p<0.01

Table A6.8.1/03-2 General reproduction data

Mean body weight gain (g)				
mg/kg bw/day	**0**	**20**	**60**	**180**
Number of pregnant dams	16	13	16	15
Corpora lutea	201	141	196	189
Implantation site	193	128*	183	186
Post-implantation loss	21	14	36*	53**
Embryonic resorptions	7	8	21**	28**
Total fetuses	172	114	147	133
% of implant. sites	89.1	89.1	80.3*	71.5**

* = p < 0.05; ** = p < 0.01

Evaluation by Rapporteur Member State, CA-Tables

CA-Table 1 Oral embryotoxicity study with cyfluthrin in rabbits – Litter data

Dose (mg/kg bw/day)	0	20	60	180
Pregnant dams	16	13	16	16
Dams with total litter loss	0	0	0	1
Litters evaluated	16	13	16	15
Dams with >2 resorptions	3	2	6	7
Corpora lutea (mean/dam)	12.6	10.8	12.1	12.6
Implantation sites (mean/dam)	12.1	9.8	11.4	12.4
Live foetuses (mean/dam)	10.8	8.8	9.2	8.9
Males (%)	50	62	54	54
Foetal weight (g)	29.2	32.4	30.3	30.9

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Reproductive toxicity

Multi-generation reproduction study in rats

BPD Data set IIA
Annex Point VI.6.8.2

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1 REFERENCE

		From addendum 2 of the monograph p48
1.1	**Reference**	[redacted] (1996) A two-generation reproduction study in rats using technical grade cyfluthrin administered via the diet. [redacted] Bayer AG Report No.: 107769 BES Ref.: M-032017-01-1 Report date: 8 March 1996 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes US-EPA-FIFRA, Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation, Human and Domestic Animals, Guideline 83-4, November 1984 US-EPA-TSCA, Health Effects Testing Guidelines, 40 CFR Section 798.4400 OECD Guidelines for Testing of Chemicals, Section 4, Guideline 416, May 1983 Japan, Ministry of Agriculture, Forestry and Fisheries, Guidance on Toxicology Study Data for Application of Agricultural Chemical Registration, 59 NohSan No. 4200, January 1985
2.2	**GLP**	Yes
2.3	**Deviations**	None that compromised the validity of the study results.

3 MATERIALS AND METHODS

3.1	**Test Material**	As given in section 2
3.1.1	Lot/batch number	Test Material:
3.1.2	Specification	Technical grade cyfluthrin, Purity: 94.6-96.2%, Batch No. 2030025: The mean treatment concentrations were ca 93-101% of the nominal concentrations.
3.1.2.1	Description	
3.1.2.2	Purity	Based on analytical chemistry determinations, cyfluthrin
3.1.2.3	Stability	was considered to be stable and homogeneously

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Annex Point VI.6.8.2

Reproductive toxicity

Multi-generation reproduction study in rats

distributed in the feed.

3.2 Test Animals

3.2.1 Species

3.2.2 Strain

3.2.3 Source

3.2.4 Sex

3.2.5 Age/weight at study initiation

3.2.6 Number of animals/group

3.2.7 Control animals

3.3 Administration/Exposure

3.3.1 Duration of treatment

3.3.2 Frequency of exposure

3.3.3 Postexposure period

3.3.4 Oral

3.3.4.1 Type

3.3.4.2 Concentration

3.3.4.3 Vehicle

3.3.4.4 Concentration in vehicle

3.3.4.5 Total volume applied

3.3.4.6 Controls

3.4 Examinations

3.5 Sacrifice and pathology

3.6 Further remarks

Test animals:

Male and Female Sprague-Dawley rats, age at study initiation: 7 weeks

[redacted]

Technical grade cyfluthrin was administered via the diet to Sprague-Dawley rats (30 rats/sex/group) for two generations (one mating per generation) to test for potential reproductive and neonatal effects. The test compound was administered at nominal dose levels of 0, 50, 125 and 400 ppm. The F_0 and F_1 adults received cyfluthrin in the diet throughout the entire study, beginning at seven weeks of age for the F_0 adults and at weaning for the F_1 adults. Prior to breeding, the animals received treated feed at least for a ten-week period.

Study performed according the OECD Guideline No. 416, as stated in the addendum on the monograph from PPP dossier, no deviations to this guideline were noted.

During the study, adult animals were evaluated for the effects of the test compound on body weight, food consumption, clinical signs, oestrus cycling, mating, fertility, gestation length, and litter size. The offspring were evaluated for compound-related effects on sex ratio, pup viability, body weight gain, and clinical signs. Gross necropsy evaluation was performed on all adults and pups. Histopathologic evaluation of reproductive organs, the pituitary, and gross lesions was performed on all F_0 and F_1 adults. Additionally due to clinical signs of neurotoxicity, the brain, spinal chord, and one sciatic nerve were collected from all F_1 adults and placed in buffered 10% formalin in the event that further microscopic examination was deemed necessary.

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BPD Data set IIA
Annex Point VI.6.8.2

Reproductive toxicity

Multi-generation reproduction study in rats

		4 RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical observations	There were no compound-related clinical signs for adult males. However, for F_0 and F females there was a compound-related splaying of the hind limbs at 400 ppm which occurred during the lactation phase (See Table A6.8.2/01-1 for details)	
4.1.2	Mortality	There were no compound-related mortalities.	
4.2	**Body weight gain**	There was no compound-related effect on body weight for F_0 and F_1 females or F_0 males during the premating period. In the mid and high dose group F_1 males, however, terminal body weights were statistically decreased by 6% and 8%, respectively, while females were affected only after exposure to the high dose of at 400 ppm (see Table A6.8.2/01-2 for details). F_0 females were affected during the gestation phase (-13% bw gain) and both F_0 and F_1 females during the lactation phase (bw gains decreased by 30% and 46% for F_0 and F_1 females, respectively (See Table A6.8.2/01-3 for details).	X
4.3	**Food consumption and compound intake**	There was no compound-related effect on food consumption for males or females (premating and gestation phases). During the lactation period, however, compound-related decreases in food consumption were observed at 125 ppm in F_1 females and at 400 ppm in both the F_0 and F_1 females. Compound intake values for nominal and actual mg//kg/daon are shown in Table A6.8.2/01-4. For risk assessment purposes, a time-weighted conversion factor of 15 was used for calculation of the test substance intake based on the test substance feed concentration as proposed by the WHO (2000)[1]	
4.4	**Reproductive parameters**	There were no compound-related effects on adult reproductive parameters (oestrus cycle staging; insemination length, mating, fertility and gestation indices, gestation length, number of implantation sites and birth index).	X
4.5	**Sacrifice and pathology**	No compound-related effects were observed.	
4.5.1	Organ weights	There were no compound-related absolute or relative organ weight changes in the F_0 and F_1 adults.	
4.6	**Offspring**		
4.6.1	Clinical observations	Compound-related coarse tremors were observed in the F_1 and F_2 pups at and above 125 ppm (Table A6.8.2/01-5). The tremors were observed as early as lactation day 5 and had ceased by lactation day 18.	
4.6.2	Pup gender	There were no compound-related effects on pup gender.	

[1] IPCS/00.5: "Pesticide residues – Guidelines for the preparation of toxicological working papers for the WHO Core Assessment Group of the Joint Meeting on Pesticide Residues" (Geneva, December 2000)

Document IIIA/ Section 6.8.2/01

Reproductive toxicity

Multi-generation reproduction study in rats

BPD Data set IIA
Annex Point VI.6.8.2

4.6.3	Litter size, live birth, viability and lactation indices	No compound-related effects on litter size, live birth, viability and lactation indices.	
4.6.4	Birth weight and pup body weight development during lactation	Cyfluthrin administration to F_0 and F_1 parents had no effect on birth weight of their offspring. Statistically decreased pup weights observed in F_2 pups at 50 and 400 ppm were not considered treatment-related in the absence of a relation to dose, because a corresponding decrease was not observed in F_1 pups and because the values were within the historical control range (Table A6.8.2/01-6). At 400 ppm, pup weights were statistically significantly lower than in the control group on days 4, 7, 14 and 21, for both generations, with the body weights ranging from 8 % - 26 % below the control group. At 125 ppm statistically significant lower pup weights were observed on days 7 and 14 for the F_1 pups and on days 7-21 for the F_2 pups. At 50 ppm statistically significant lower pup body weights were observed in the F_2 group on days 4 and 7; pup body weights remained slightly below control values also on days 14 and 21.	X
4.6.5	Gross pathology	There were no compound-related gross lesions in the F1or F2 pups. Micropathology data were not collected for pups.	

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Technical grade cyfluthrin was administered via the diet to Sprague-Dawley rats (30 rats/sex/group) for two generations (one mating per generation) to test for potential reproductive and neonatal effects. The test compound was administered at nominal dose levels of 0, 50, 125 and 400 ppm. The F_0 and F_1 adults received cyfluthrin in the diet throughout the entire study, beginning at seven weeks of age for the F_0 adults and at weaning for the F_1 adults. Prior to breeding, the animals received treated feed at least for a ten-week period. During the study, adult animals were evaluated for the effects of the test compound on body weight, food consumption, clinical signs, oestrus cycling, mating, fertility, gestation length, and litter size. The offspring were evaluated for compound-related effects on sex ratio, pup viability, body weight gain, and clinical signs. Gross necropsy evaluation was performed on all adults and pups. Histopathologic evaluation of reproductive organs, the pituitary, and gross lesions was performed on all F0 and F1 adults. Additionally due to clinical signs of neurotoxicity, the brain, spinal chord, and one sciatic nerve were collected from all F1 adults and placed in buffered 10% formalin in the event that further microscopic examination was deemed necessary.

5.2 Results and discussion

The increased incidence of splayed hind limbs in high dose dams was probably due to increased food consumption which caused the dose during the lactation phase to be approximately double the dose received during the premating and gestation phases.

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Reproductive toxicity

Multi-generation reproduction study in rats

		The significant decreased terminal body weights of the 125 ppm group F1 male rats was primarily due to the body weight differences that were already present at weaning (bw on premating week 1 reduced by 8% compared to controls); differences in body weight changes were minimal (3%) between F1 125 ppm males and controls during the 13-week premating period. From the results of this study, it could not be excluded that the statistically significantly decreased body weights of low-dose group F2 pups on days 4 and 7 of lactation were treatment-related although this was considered unlikely for the following reasons: 1. No significant effects were observed on days 14 and 21 2. F2 pup weights at 50 ppm and 125 ppm during the first week of lactation were virtually the same, thus there was no obvious dose-response relationship. 3. The pup body weights on days 4 and 7 were very close to historical control values. For clarification of the significance of the findings at 50 ppm, the supplemental 2-generation study was conducted in which no reduction in FI or F2 pup weights was seen . The increased incidence of coarse tremors and the decreased pup body weight observed during the lactation phase in F1 and F2 pups at 125 pm occurred in the absence of maternal toxicity. Therefore, it cannot be excluded that the presence of adverse effects in the offspring at 125 ppm was due to transfer of cyfluthrin or of its metabolite(s) in the milk during the lactation period. This conclusion is supported by the absence of adverse treatment effects on prenatal or peri-natal litter parameters. On the other hand, results of the 13-week oral feeding neurotoxicity study in rats do indicate that adverse treatment-related effects (paresthesia-induced skin lesions, decreased bw gain and food consumption) occur at doses of 125 ppm and above.	
5.3	**Conclusion**	Under the conditions of this 2-generation reproduction study, cyfluthrin had no effect on fertility when administered via the diet to rats up to 400 ppm, the highest dose tested. The NOEL for parental toxicity was established at 50 ppm, based on reduced body weights of F_1 males at and above 125 ppm; at 400 ppm clinical signs of neurotoxicity (splayed hind limts) were observed in F_0 and F_1 females during lactation and body weights and food consumption were reduced in both sexes. The NOEL for offspring toxicity was established at 50 ppm, based on increased incidences of coarse tremors and decreased pup body weights at and above 125 ppm during the lactation period.	X
5.3.1	LO(A)EL	Parental: 125 ppm- based on reduced body weights of F_1 males at and above 125 ppm Offspring: 125 ppm- based on increased incidences of coarse tremors and decreased pup body weights at and above 125 ppm during the	

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Reproductive toxicity

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		lactation period.
5.3.2	NO(A)EL	Parental: 50 ppm Offspring: 50 ppm (confirmed by the results of the second supplementary 2-generation reproduction study) Reproductive: 400 ppm
5.3.3	Other	None
5.3.4	Reliability	1
5.3.5	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	2006-09-12
Materials and Methods	Applicant's version is acceptable.
Results and discussion	*4.2 Body weight gain:* The body weight gain of F_0 males during the premating period was reduced by about 10 % in the 400 ppm group when compared to controls; this is considered a compound-related effect. *4.4 Reproductive parameters:* A slight reduction in the mean number of implantation sites was found in the F_0 and F_1 females at the dose of 400 ppm. It is unclear whether this reflects an increase in preimplantation loss or a possible lower production of corpora lutea due to a reduced maternal fitness in these animals. The effect is slight but reproducible and therefore is considered to be compound-related (see CA-Table 1). *4.6.4 Pup birth weight and body weight development:* When mean litter size is considered as a confounding factor, cyfluthrin administration to F_0 and F_1 parents affected the birth weight of their offspring at the dose of 400 ppm. In addition, reduced pup growth was noted in the mid and high dose groups. At 400 ppm, pup weights were statistically significantly lower than in the control group on days 4, 7, 14 and 21, for both generations, with the body weights ranging from 8 % - 26 % below the control group. At 125 ppm, statistically significant lower pup weights were observed, on days 7 and 14 for the F_1, and on days 7-21 for the F_2. The lower body weights at 50 ppm in F_2 pups on days 4 and 7 are considered to be due to the larger litter size at birth and thus unrelated to cyfluthrin.

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Reproductive toxicity

Multi-generation reproduction study in rats

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Conclusion	$LO(A)EL_{parental}$: 29 / 33 mg/kg bw/day (400 ppm) males / females $NO(A)EL_{parental}$: 9 / 10 mg/kg bw/day (125 ppm) males / females $LO(A)EL_{reproduction}$: 33 mg/kg bw/day (400 ppm) $NO(A)EL_{reproduction}$: 10 mg/kg bw/day (125 ppm) $LO(A)EL_{offspring}$: 20 mg/kg bw/day (125 ppm) $NO(A)EL_{offspring}$: 10 mg/kg bw/day (50 ppm) Other conclusions: The parental NOAELs are based on reduced body weight gains at the dose of 400 ppm in males during the premating period and in females during the premating period and pregnancy. Neurotoxic signs occurred in females of the 400 ppm group during the last two weeks of lactation when they consumed 60 mg/kg bw/day and more of the test substance. For a detailed listing of intake data see CA-Table 2. The reproductive NOAEL is based on a reduced number of implantation sites at the dose of 400 ppm. This may either represent increased preimplantation loss or a decrease in ovulated oocytes as a (unspecific) consequence of toxicity in females. Exposure of the females during the premating period is considered relevant for this endpoint. The offspring NOAEL is based on two endpoints: 1. Reduced birth weights of the F_2 pups at 400 ppm where the mothers consumed approximately 33 mg/kg bw/day during the relevant period of pregnancy. At the NOAEL, the intake of the dams amounted to approximately 10 mg/kg bw/day. 2. Tremors in offspring and reduced pup growth at 125 ppm and higher, observed when dams consumed about 20 mg/kg bw/day or more during lactation. At the NOAEL, the maximum intake of the dams amounted to 9-10 mg/kg bw/day. As the tremors were first observed when the dams increased their food intake to meet the increased lactational demand and subsided after the pups started eating the diet of their mothers, cyfluthrin exposure through the milk is considered to be the main determinant of offspring neurotoxicity in this study.
Reliability	1
Acceptability	Acceptable
Remarks	-

	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*

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Reproductive toxicity

Multi-generation reproduction study in rats

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Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.8.2/01-1. Incidence of splayed hind limbs in females during lactation

Clinical Observations	0 ppm	50 ppm	125 ppm	400 ppm
F0 females	0/30	0/27	0/26	15/29**
F1 females	0/25	0/27	0/27	9/25**

* = p < 0,05, ** = p ≤0.01 Fisher's Exact Test)

Table A6.8.2/01-2. Terminal body weights

Generation	0 ppm	50 ppm	125 ppm	400 ppm
F0 males	411.1 ± 49.5 (100%)	405.1 ± 42.7 (99%)	391.5 ± 52.2 (95%)	392.6 ± 37.4 (95%)
F0 females	288.9 ± 19.1 (100%)	286.1 ± 22.6 (99%)	285.0 ± 22.0 (99%)	276.9 ± 21.9 (96%)
F1 males	422.6 ± 29.0 (100%)	431.4 ± 43.5 (102%)	396.2± 46.1* (94%)	389.7 ± 46.3* (92%)
F1 females	289.0 ± 27.4 (100%)	289.6 ± 26.6 (100%)	278.5 ± 30.2 (96%)	266.0 ±26.7* (92%)

*Statistically significant (Anova + Dunnett's Test): p ≤ 0.05

Table A6.8.2/01-3: Body weight gains of F0 and F1 adults

	Body weight gains (g)							
	F0 generation adults				F1 generation adults			
	Males	Females			Males	Females		
PPM	Premating	Premating	Gestation	Lactation	Premating	Premating	Gestation	Lactation
0	188 (100%)	75.6 (100%)	121.8 (100%)	25.8 (100%)	196 (100%)	78.3 (100%)	112.9 (100%)	40.9 (100%)
50	184 (98%)	78.4 (104%)	122.0 (100%)	23.7 (92%)	203 (104%)	82.9 (106%)	120.8 (107%)	31.6 (77%)
125	173 (92%)	72.5 (96%)	108.1 (89%)	25.8 (100%)	191 (97%)	84.4 (108%)	107.7 (95%)	29.2 (71%)
400	169 (90%)	64.5 (85%)	106.3** (87%)	18.1[a] (70%)	181 (92%)	74.5 (95%)	100.2 (89%)	21.1[a] (54%)

** = p≤ 0.01 (Dunnett's test)

a = body weight of F0 and F1 high dose females significantly reduced compared to control levels on lactation days 4, 7, 14 and 21

Table A6.8.2/01-4. Test substance intake

Level	Mean doses in mg/kg bw/d				
	Males Premating	Females Premating	Females Gestation	Females Lactation	Default Calculation* Males & Females
50	3	4	4	7	3.3
125	9	10	10	19	8.3
400	29	33	33	59	26.7

* based on default conversion factor of 15 proposed by JMPR to be used for rat multigeneration studies

Table A6.8.2/01.5 Litter incidence of coarse tremors

Clinical Observations	0 ppm	50 ppm	125 ppm	400 ppm
F1 pups	0/30	0/27	4/25	15/28*
F2 pups	0/25	0/26	19/26*	9/25*

* $p \leq 0.05$ (Chi-square test & Fisher's Exact test (Bonferroni adjustment of the p value)

Table A6.8.2/01-6 Pup body weight development

Lactation day	Mean body weight of viable pups (g)								
	F1 pups (males + females combined				F2 pups (males + females combined)				H.C.[c] (range)
ppm	0	50	125	400	0	50	125	400	
1	6.6 (100%)	6.6 (100%)	6.4 (97%)	6.6 (100%)	6.7 (100%)	6.4 (97%)	6.4 (97%)	6.3** (95%)	6.8 (6.1-7.2)
4[a]	10.1 (100%)	10.2 (102%)	9.7 (97%)	9.2* (92%)	10.3 (100%)	9.3* (91%)	9.5 (92%)	8.2** (80%)	10.2 (9.2-11.3)
4[b]	10.0 (100%)	10.3 (103%)	9.7 (97%)	9.2* (92%)	10.3 (100%)	9.3* (91%)	9.5 (92%)	8.2** (80%)	
7	16.2 (100%)	16.4 (101%)	15.0* (93%)	13.7** (85%)	16.1 (100%)	14.7* (91%)	14.4** (89%)	12.0** (75%)	16.3 (14.8-18.7)
14	31.4 (100%)	31.5 (100%)	29.5* (94%)	25.2** (80%)	30.3 (100%)	28.8 (95%)	25.8** (85%)	23.0** (76%)	32.0 (29.6-35.8)
21	49.0 (100%)	50.1 (102%)	46.1 (94%)	39.4** (80%)	45.4 (100%)	42.8 (94%)	39.0** (86%)	33.6** (74%)	50.4 (46.6-56.9)

[a] = before culling

[b] = post culling

[c] = historical control data for F2 pup body weight compiled from 14 studies with Sprague-Dawley rats unequivocally originating from SASCO Inc.; studies conducted between 1988-1995 by Bayer Corp., Stillwell.

Statistics: Dunnett's test; * - $p \leq 0.05$; ** - $p \leq 0.01$

CA-Table 1 2-Generation study with cyfluthrin in rats – Fertility and litter data

Generation	F_0				F_1			
Dose (ppm)	**0**	**50**	**125**	**400**	**0**	**50**	**125**	**400**
Mating pairs	30	30	29	30	30	30	30	30
Pregnant females	30	28	26	29	25	27	27	26
Total prenatal litter loss	0	1	0	0	0	0	0	1
Live litters	30	27	26	29	25	27	27	25
Total postnatal litter loss	0	0	1	1	0	1	1	0
Implantation sites (mean/dam)	13.2	13.2	13.0	12.3	12.8	13.8	13.1	11.5
Pups born (mean/dam)	12.8	12.3	123.5	11.1	11.8	12.6	12.2	11.0
Males (%)	50	48	48	48	51	49	49	52

CA-Table 2 2-Generation study in rats – Substance intake in females (mg/kg bw/d)

Generation	F_0				F_1			
Dose (ppm)	**0**	**50**	**125**	**400**	**0**	**50**	**125**	**400**
Premating period	0	3.8	9.9	33.2	0	3.8	10.6	33.7
Pregnancy	0	3.5	9.3	31.9	0	3.9	10.2	33.7
Lactation Day 0-4	0	5.5	14.6	40.1	0	5.5	15.0	40.9
Lactation Day 4-7	0	7.3	19.7	61.4	0	7.2	19.6	62.1
Lactation Day 7-14	0	9.0	23.6	74.2	0	9.5	24.2	75.9
Lactation Day 14-21*	0	10.2	26.6	95.3	0	11.3	27.7	96.9

* pups are eating maternal diet by this time; no reliable intake value for dams

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Reproductive toxicity

Multi-generation reproduction study in rats

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1 REFERENCE

1.1	**Reference**	*From addendum 2 of the monograph p53* [redacted] (1997). A supplementary two-generation dietary reproduction study in rats using technical grade cyfluthrin. Supplemental Submission to Bayer Report No. 93-672-UZ. [redacted] Bayer AG Report No.: 107474 Ref. M-032020-01-1 Report date: 30 January 1997 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes US-EPA-FIFRA Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation, Human and Domestic Animals, Guideline 83-4, November, 1984 US-EPA-TSCA, Health Effects Testing Guidelines, 40 CFR Section 798.7400 OECD Guidelines for Testing of Chemicals, Section 4, Guideline 416, May 1983 Japan, Ministry of Agriculture, Forestry and Fisheries, Guidance on Toxicology Study Data for Application of Agricultural Chemical Registration, 59 NohSan No. 4200, January 1985
2.2	**GLP**	Yes
2.3	**Deviations**	Two instead of required three dose levels were tested. The study is considered to be acceptable as supplemental information only, since only a limited dose range (using two dose levels) was tested.

3 MATERIALS AND METHODS

3.1	**Test Material**	As given in section 2
3.1.1	Lot/batch number	Test Material:
3.1.2	Specification	Technical grade cyfluthrin, Purity: 94.6-96.2%, Batch No. 2030025: The mean treatment concentrations were ca 93-101%

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Reproductive toxicity

Multi-generation reproduction study in rats

3.1.3 Description

3.1.4 Purity

3.1.5 Stability

of the nominal concentrations.

Based on analytical chemistry determinations, cyfluthrin was considered to be stable and homogeneously distributed in the feed.

3.2 Test Animals

Test animals:

Male and Female Sprague-Dawley rats, age at study initiation: 7 weeks

[redacted]

3.2.1 Species

3.2.2 Strain

3.2.3 Source

3.2.4 Sex

3.2.5 Age/weight at study initiation

3.2.6 Number of animals/group

3.2.7 Control animals

3.3 Administration/Exposure

Technical grade cyfluthrin was administered at nominal dose levels of 0, 25 and 50 ppm via the diet to Sprague-Dawley rats (30 rats/sex/group) for two generations (one mating per generation) to test for potential reproductive and neonatal effects.

With three exceptions, material and methods applied in this supplemental 2-generation study fully corresponded to the 2-generation study by Eigenberg & Elcock (1996):

(1) Other dose levels were used.

(2) Rats were supplied by SASCO Inc. from Omaha, Nebraska not by SASCO Inc., St. Louis, Missouri.

(3) In the absence of clinical signs of neurotoxicity, the brain, spinal chord, and one sciatic nerve were not collected from all Fl adults in the supplemental two generation study.

3.3.1 Duration of treatment

3.3.2 Frequency of exposure

3.3.3 Postexposure period

3.3.4 Oral

3.3.4.1 Type

3.3.4.2 Concentration

3.3.4.3 Vehicle

3.3.4.4 Concentration in vehicle

3.3.4.5 Total volume applied

3.3.4.6 Controls

3.4 Examinations

3.5 Sacrifice and

	pathology	
3.6	**Further remarks**	
	4 RESULTS AND DISCUSSION	
4.1	**Observations**	
4.1.1	Clinical observations	No compound-related clinical signs were observed in adults.
4.1.2	Survival	There were no compound related mortalities.
4.2	**Body weight gain**	There were no compound-related effects on body weights during the premating, gestation or lactational phases of the study.
4.3	**Food consumption and compound intake**	There were no compound-related effects on food consumption during the premating, gestation, or lactational periods. Compound intake values for nominal and actual mg//kg/day are shown in table 6.8.2/02-1.
4.4	**Reproductive parameters**	There were no compound-related effects on adult reproductive parameters.
4.5	**Sacrifice and pathology**	No compound-related effects were observed.
4.5.1	Organ weights	No treatment-related changes in absolute or relative organ weights were noted in F_0 and F_1 adults.
4.6	**Offspring**	
4.6.1	Clinical observations	No clinical observations were noted.
4.6.2	Pup gender	No compound-related effects on pup gender were noted in the study.
4.6.3	Litter size, live birth, viability and lactation indices	No compound-related effects on litter size, live birth, viability and lactation indices were noted in either the main or supplementary study.
4.6.4	Birth weight and pup body weight development during lactation	No compound-related pup effects on birth weights, or pup body weight development during lactation were noted (Table A6.8.2/02-2)
4.6.5	Gross pathology	No compound-related effects on gross pathology were noted in either the main or supplementary study.
	5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Technical grade cyfluthrin was administered at nominal dose levels of 0, 25 and 50 ppm via the diet to Sprague-Dawley rats (30 rats/sex/group) for two generations (one mating per generation) to test for potential reproductive and neonatal effects.

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Multi-generation reproduction study in rats

With three exceptions, material and methods applied in this supplemental 2-generation study fully corresponded to the 2-generation study by [redacted] (1996):

(1) Other dose levels were used.

(2) Rats were supplie [redacted]

(3) In the absence of clinical signs of neurotoxicity, the brain, spinal chord, and one sciatic nerve were not collected from all F1 adults in the supplemental two generation study.

5.2 Results and discussion

No compound-related clinical signs were observed in the adults. There were no compound related mortalities. There was no compound-related effect on body weight or food consumption during the premating, gestation, or lactation periods. There were no compound- related effects on adult reproductive parameters. There were no compound-related effects on pup parameters. There were no compound-related gross or micropathological findings. No reproductive, neonatal, or parental toxicity was observed in this study.

5.3 Conclusion

No reproductive, neonatal or parental toxicity was observed in this supplemental study, which demonstrates that the statistically significant lower body weights of F2 pups observed at 50 ppm at birth, an on lactation days 4 and 7 in the prior two-generation reproduction study were not due to cyfluthrin administration. The NOEL for this study was 50 ppm, equivalent to 3.3 mg/kg bw/d.

5.3.1 LO(A)EL

Parental: >50 ppm-

Offspring: >50 ppm

5.3.2 NO(A)EL

Parental: 50 ppm

Offspring: 50 ppm

Reproductive: 50 ppm

5.3.3 Other

None

5.3.4 Reliability

1

5.3.5 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	2006-09-13
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	LO(A)EL: > 50 ppm NO(A)EL: 50 ppm Other conclusions: Applicant's version is adopted.
Reliability	1
Acceptability	Acceptable
Remarks	The RMS considers this study to be unnecessary. The main study by [redacted] (1996) resulted in a clear NOAEL for offspring at 50 ppm.
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.8.2/02-1 Test substance intake

Level	Mean doses in mg/kg bw/d				
	Males Premating	Females Premating	Females Gestation	Females Lactation	Default Calculation* Males & Females
25	1.9	2.1	2.0	4.1	1.7
50	3.8	4.2	3.9	8.0	3.3

* based on default conversion factor of 15 proposed by JMPR to be used for rat multi-generation studies

A6.8.2/02-2 Pup body weight development

Lactation day	Mean body weight of viable pups (g)					
	F1 pups (males + females combined)			F2 pups (males + females combined)		
	0 ppm	25 ppm	50 ppm	0 ppm	25 ppm	50 ppm
1	6.8	6.7	6.6	6.6	6.9	6.9
4[a]	10.2	10.2	10.0	9.9	10.6	10.3
4[b]	10.2	10.1	10.0	9.8	10.6	10.3
7	15.5	15.8	15.7	15.3	16.4	16.0
14	29.2	30.9	30.8	29.4	30.6	30.6
21	47.9	48.1	49.7	48.4	49.2	50.3

[a] = before culling

[b] = post culling

Document IIIA/ Section 6.9/01 Acute neurotoxicity

BPD Data set IIIA/ Annex Point VI.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	*From addendum 2 of the monograph p58* [redacted] (1999) Cyfluthrin: Special study for acute oral toxicity in rats (slip angle test). [redacted] Bayer AG Report No.: PH 29371 BES ref.: M-035139-01-1 Report date: 13 December 1999 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No guideline exists for this special type of study	
2.2	**GLP**	Yes	
2.3	**Deviations**		
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in section 2	
3.1.1	Lot/Batch number	Test material	
3.1.2	Specification	Cyfluthrin, purity 96.1%, Batch 380760276	
3.1.2.1	Description		X
3.1.2.2	Purity		
3.1.2.3	Stability	Test animals:	
3.2	**Test Animals**	Wistar rats ([redacted]	
3.2.1	Species	Source:	
3.2.2	Strain	[redacted]	
3.2.3	Source		
3.2.4	Sex		X
3.2.5	Age/weight at study initiation		X
3.2.6	Number of animals per group		X
3.2.7	Control animals		X
3.3	**Administration/ Exposure**		
3.3.1	Duration of treatment		X
3.3.2	Frequency of exposure		X
3.3.3	Postexposure		X

Document IIIA/ Section 6.9/01 — Acute neurotoxicity

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period			
3.3.3.1	Type	An inclined plane test in Wistar rats was conducted with to establish a pharmacological no-observed-effect level for acute neurotoxic effects. The vehicle for cyfluthrin was an aqueous Cremophor ® EL suspension which is known to provide a high bioavailability. The ability of female Wistar rats to maintain a stable position on the inclined plane was tested in groups of 5 or 10 animals orally treated with cyfluthrin doses ranging from 0.015 to 9 mg/kg bw. Triplicate measurements of the slip angle were made prior to oral administration, and at predetermined times 0.5 - 24 hours later.	X
3.3.3.2	Concentration		X
3.3.3.3	Vehicle		X
3.4	**Examinations**		X
3.5	**Sacrifice and pathology**		X
3.6	**Further remarks**		

4 RESULTS AND DISCUSSION

4.1	**Observations**		
4.1.1	Clinical signs	Clinical signs in all 5 animals tested were almost exclusively observed at 9 mg/kg bw starting from approx. 1 h after administration. There were reduced motility, laboured breathing, increased salivation, uncoordinated gait, sternal recumbency, rolling over, narrowed palpebral fissures, digging and preening movements, diarrhea, vocalization and temporary shaking. The main surge of clinical signs had subsided after approx. 6 h. At 7-5 mg/kg bw, digging and preening movements of very short duration were observed in all 5 animals. Very slight reactions were observed in only 2 animals at 2.5 mg/kg bw (Table A6.9/01-1).	X X
4.1.2	Significant findings	Changes in slip angle were not yet observable 1 hour after administration of 9 mg/kg bw when many clinical signs had already been observed. Only 2 hours after administration, the slip angle was significantly reduced at 9 mg /kg bw. This time point, 2 hours after administration, has to be regarded as the time of peak effect, which is also in agreement with the pharmacokinetic studies that indicated a t_{max} of 1.5 - 2 h, and with the occurrence of acute clinical signs. Changes in slip angle were no longer observed 6 hours after treatment when almost all clinical signs had subsided. A dose of 7.5 mg/kg bw resulted in a marginal effect which, however, was not statistically significant. There were no changes in slip angle in animals treated with 0.015 -3 mg/kg bw.	
4.2	**Other**		

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	The test material was cyfluthrin, purity 96.1%, Batch 380760276. The test animals were Wistar rats [redacted] An inclined plane test in Wistar rats was conducted with to establish a pharmacological no-observed-effect level for acute neurotoxic effects. The vehicle for cyfluthrin was an aqueous Cremophor ® EL suspension which is known to provide a high bioavailability. The ability of female Wistar rats to maintain a stable position on the inclined plane was tested in groups of 5 or 10 animals orally treated with cyfluthrin doses ranging from 0.015 to 9 mg/kg bw. Triplicate measurements of the slip angle	

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		were made prior to oral administration, and at predetermined times 0.5 - 24 hours later.
5.2	**Results and discussion**	Clinical signs in all 5 animals tested were almost exclusively observed at 9 mg/kg bw starting from approx. 1 h after. The main surge of clinical signs had subsided after approx. 6 h. At 7.5 mg/kg bw, digging and preening movements of very short duration were observed in all 5 animals. Very slight reactions were observed in only 2 animals at 2.5 mg/kg bw. Changes in slip angle were not yet observable 1 hour after administration of 9 mg/kg bw when many clinical signs had already been observed. Only 2 hours after administration, the slip angle was significantly reduced at 9 mg /kg bw. This time point, 2 hours after administration, has to be regarded as the time of peak effect, which is also in agreement with the pharmacokinetic studies that indicated a t_{max} of 1.5 - 2 h, and with the occurrence of acute clinical signs. Changes in slip angle were no longer observed 6 hours after treatment when almost all clinical signs had subsided.
5.3	**Conclusion**	A dose of 7.5 mg/kg bw resulted in a marginal effect which, however, was not statistically significant. There were no changes in slip angle in animals treated with 0.015 -3 mg/kg bw.
5.3.1	LO(A)EL	7.5 mg/kg bw based on slight changes in slip angle, and clinical signs.
5.3.2	NO(A)EL	An oral single dose of 3.0 mg/kg bw is considered to be the NOAEL in the slip-Angle test.
5.3.3	Other	No
5.3.4	Reliability	1
5.3.5	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 2006-09-04

Materials and Methods

3.1.2.1 Description: Yellowish-brown mass of oily consistency
3.2.5 Age/weight at study initiation: > 7 weeks (162-212 g)
3.2.6 Number of animals per group: 5 or 10 (dose groups 0/1/2.5/7.5 mg/kg bw)
3.2.7 Control animals: Yes
3.3.2 Frequency of exposure: Single treatment
3.3.3 Postexposure period: 7 d, 14 d (dose groups 0/1/2.5/7.5 mg/kg bw)
3.3.3.1 Type: Oral, by gavage
3.3.3.2 Concentrations: 0.015-9 mg/kg bw
3.3.3.3 Vehicle: Cremophor EL or milk
3.4 Examinations: Inclined plane test, body weight, appearance, behavior, nervous system, respiration, cardiovascular system, posture, gastrointestinal function
3.5 Sacrifice and pathology: Gross pathology

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Results and discussion	At 7.5 mg/kg bw, digging and preening movements of very short duration were observed in 6/10 animals. At 3 mg/kg bw temporary shaking was observed in 2/5 animals. Digging and preening movements of very short duration were observed at 3 mg/kg bw in 1 animal and at 2.5 mg/kg bw in one animal.
Conclusion	LO(A)EL: 7.5 mg/kg bw based on slip angle test 3 mg/kg bw based on clinical signs NO(A)EL: 3 mg/kg bw based on slip angle test 2.5 mg/kg bw based on clinical signs
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.9/01-1 Temporal pattern of occurrence of clinical signs (number of animals affected after treatment)

Clinical signs	Minutes after treatment						
	50-58	59-67	79-87	95-106	120-129	148-156	307-313
9 mg cyfluthrin/kg body weight							
Reduced motility	5	5	5	5	5	5	5
Digging and preening movements	5	5	5	5	5		
Laboured breathing	5	5	5	5	5	5	
Increased salivation	5	5	5	5	5	5	
Uncoordinated gait	5	5	5	5	5		
Narrowed palpebral fissures	5	5	5	5			
Temporary shaking	5	5	5	5	5		
Rolling over		5	5	5	5		
Diarrhea				5	5	5	
Sternal recumbency					5	5	
Vocalisation			2				
Lateral recumbency*		1		1			
Hind leg paralysis*							1
7.5 mg cyfluthrin/kg body weight							
Digging and preening movements				3	1		
3 mg cyfluthrin/kg body weight							
Temporary shaking			2				
Digging and preening movements							
2.5 mg cyfluthrin/kg body weight							
Temporary shaking				1			

* Animal (no. 107) sacrifice in extremis 24 hours after treatment.

CA: 9 mg/kg bw: 5 animals
7.5 mg/kg bw: 10 animals
3 mg/kg bw: 5 animals
2.5 mg/kg bw: 10 animals

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			Official use only
		1 REFERENCE	
		From addendum 2 of the monograph p59	
1.1	**Reference**	[redacted] (1997) An acute oral neurotoxicity screening study with technical grade FCR 4545 in Fischer 344 rats. [redacted] Bayer AG Report No. 107752 BES Ref.: M-038521-01-1 Report date: 2 October 1997 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	US EPA-FIFRA Pesticide Assessment Guideline No. 540/09-91-123, PB 91-154617	
2.2	**GLP**	Yes	
2.3	**Deviations**	None that compromised the validity of the study results	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in section 2	
3.1.1	Lot/Batch number	Test material:	
3.1.2	Specification	Technical grade beta-cyfluthrin,	
3.1.2.1	Description	Purity: 96.9-97.3%, batch no. 3030125/0250074	
3.1.2.2	Purity	Identity was confirmed by NMR and MS.	
3.1.2.3	Stability		
3.2	**Test Animals**		
3.2.1	Species		
3.2.2	Strain	Test animals:	
3.2.3	Source	Fischer 344 [redacted] rats, Male and female	
3.2.4	Sex	Age: approximately 9 weeks old	
3.2.5	Age/weight at study initiation		
3.2.6	Number of animals per group	[redacted]	X
3.2.7	Control animals		
3.3	**Administration/ Exposure**	Technical grade beta-cyfluthrin was administered by gavage in a single dose to fasted male and female Fischer 344 rats (12/sex/dose) at doses of 0, 0.5, 2 and 10 mg/kg bw. The test substance was heated and suspended in 1% Cremophor ® EL in deionised water at a dosing volume of 10 ml/kg	
3.3.1	Duration of treatment		
3.3.2	Frequency of exposure		

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3.3.3	Postexposure period	
3.3.3.1	Type	
3.3.3.2	Concentration	
Vehicle		
3.4	**Examinations**	The following observations and measurements were included in the study: clinical observations, mortality checks, body weight, automated measurements of activity (figure-eight maze), a functional observational battery, brain weight, and a gross necropsy. Skeletal muscle, peripheral nerves, eyes (with optic nerves), and tissues from the central nervous system were examined microscopically for lesions.
3.5	**Sacrifice and pathology**	
3.6	**Further remarks**	
		4 RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical signs	Compound-related clinical signs (e.g. oral stain in both sexes; urine stain in males) were evident at 10 mg/kg bw. An increased incidence of peri-anal staining was observed at 2 and 10 mg/kg bw in both sexes, but with regard to the relative high incidences of this clinical sign in control and low dose animals, it was not considered as an adverse compound-related effect (Table A6.9/02-1). Clinical signs were resolved in all animals by day 5 following treatment.
4.1.2	Mortality	No deaths occurred at any dose level prior to scheduled terminal sacrifice, 15 days following administration.
4.1.3	Functional Observational Battery (FOB)	For the functional observational battery (FOB), compound-related and significant effects were evident on day 0 in males and females at 10 mg/kg bw. A small number of the behavioural functions registered were slightly, but not significantly increased in only a few animals that received 2 and 10 mg/kg bw. Chewing movements in few animals, which were ascribed to a local effect of the test substance on the oral mucosa, were observed at all dose levels. This open field finding was confirmed in the home cage only at the highest dose level. All signs of toxicity resolved in all dose groups by the next observation period on day 7. X
		Relative to the decreasing motor and locomotor activities in controls, compound-related decreases in motor and locomotor activity occurred on day 0 in males and females of the 10 mg/kg bw groups (Table A6.9/02-2). These effects were statistically significant for first two 10 minutes intervals in males and the first three 10 minutes intervals in females, but not for the entire 90-minute test session. Additionally, a significant higher decrease was observed in female rats of the 2 mg/kg bw group only in the 3rd interval, which is not considered to be a toxicologically adverse effect. Complete recovery occurred in males and females by the next test occasion, seven days following treatment. Habituation was not affected by treatment with beta-cyfluthrin. X
4.2	**Body weight gain**	Body weight was not affected by treatment in males or females at any dose level.
4.3	**Sacrifice and**	

	pathology	
4.3.1	Gross and histopathology	There were no compound-related gross or microscopic lesions in males or females at terminal sacrifice. Brain weight was not affected by treatment in males or females at any dose level.
4.4	**Other**	Compound-related microscopic lesions were not evident in the high dose males and females.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Technical grade beta-cyfluthrin (batch no. 3030125/025004, purity 96.9-97.3%) was administered by gavage in a single dose to fasted male and female Fischer 344 rats (12/sex/dose) at doses of 0-0.5-2 and 10 mg/kg bw. The test substance was heated and suspended in 1% Cremophor ® EL in deionised water at a dosing volume of 10 ml/kg The following observations and measurements were included in the study: clinical observations, mortality checks, body weight, automated measurements of activity (figure-eight maze), a functional observational battery, brain weight, and a gross necropsy. Skeletal muscle, peripheral nerves, eyes (with optic nerves), and tissues from the central nervous system were examined microscopically for lesions.
5.2	**Results and discussion**	No deaths occurred at any dose level prior to scheduled terminal sacrifice, 15 days following administration. Compound-related clinical signs (e.g. oral stain in both sexes; urine stain in males) were evident at 10 mg/kg bw. An increased incidence of peri-anal staining was observed at 2 and 10 mg/kg bw in both sexes, but with regard to the relative high incidences of this clinical sign in control and low dose animals, it was not considered as an adverse compound-related effect. The compound-related signs were apparent in both sexes on the day of treatment and resolved by day 5 following treatment. Body weight was not affected by treatment in males or females at any dose level. For the functional observational battery (FOB), compound-related and significant effects were evident on day 0 in males and females at 10 mg/kg bw. A small number of the behavioural functions registered were slightly, but not significantly increased in only a few animals that received 2 and 10 mg/kg bw. Chewing movements in few animals, which were ascribed to a local effect of the test substance on the oral mucosa, were observed at all dose levels. This open field finding was confirmed in the home cage only at the highest dose level. All signs of toxicity resolved in all dose groups by the next observation period on day 7. Relative to the decreasing motor and locomotor activities in controls, compound-related decreases in motor and locomotor activity occurred on day 0 in males and females of the 10 mg/kg bw groups. These effects were statistically significant for first two 10 minutes intervals in males and the first three 10 minutes intervals in females, but not for the entire 90-minute test session. Additionally, a significant higher decrease was observed in female rats of the 2 mg/kg bw group only in the 3rd

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		interval, which is not considered to be a toxicologically adverse effect. Complete recovery occurred in males and females by the next test occasion, seven days following treatment. Habituation was not affected by treatment with beta-cyfluthrin. There were no compound-related gross lesions in males or females at terminal sacrifice. Brain weight was not affected by treatment in males or females at any dose level. Compound related microscopic lesions were not evident in the high dose males or females.	
5.3	**Conclusion**	Based on the above mentioned findings (clinical signs, functional observational battery, motor and locomotor activity) at 10 mg/kg bw, the overall NOAEL of this acute neurotoxicity study is 2 mg/kg bw for males and females. Evidence of toxicity resolved within 7 days following treatment. It should be taken into account that the formulation with an aqueous vehicle resulted in a distinct higher acute toxicity (oral LDso in rats with Cremophor EL/water: 16.2 mg/kg bw), which is to be attributed to faster and more complete enteric absorption.	
5.3.1	LO(A)EL	10 mg/kg based on clinical signs, FOB, motor and locomotor activity.	X
5.3.2	NO(A)EL	2 mg/kg bw	X
5.3.3	Other	No	
5.3.4	Reliability	1	
5.3.5	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	2006-08-31
Materials and Methods	*3.2.6 Number of animals per group:* 12/sex/group
Results and discussion	*4.1.3 Functional Observational Battery:* Compound-related effects observed at 10 mg/kg bw included urine staining, gait incoordination, decreased activity, repetitive pawing movements, diminished approach and touch response, impaired aerial righting, salivation, and perianal and oral staining in males and females, as well as diminished tail pinch response, writhing behaviour, prolapsed penis and a decreased body temperature in males (see CA-Table 2). Decreases in motor and locomotor activity occurred on day 0 in females of the 2 mg/kg bw group and in males and females of the 10 mg/kg bw groups (Table A6.9/02-2 and CA-Table 1, not statistically significant). Otherwise applicant's version is adopted.
Conclusion	LOAEL: 10 mg/kg bw based on FOB findings NOAEL: 2 mg/kg bw NOEL: 0.5 mg/kg bw (F) based on decreased motor and locomotor activity
Reliability	1
Acceptability	Acceptable

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Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.9/02-1: Clinical observations in rats on day of treatment

Sex	Males				Females			
Dose (mg/kg bw)	**0**	**0.5**	**2**	**10**	**0**	**0.5**	**2**	**10**
Animals examined	12	12	12	12	12	12	12	12
Oral stain	-	-	-	10	-	-	-	9
Urine stain	-	-	-	4	5	3	2	5
Peri-anal stain	8	8	12	12	5	6	11	11

Table A6.9/02-2: Summary of motor activity results (Percent difference from controls)[a]

Males				
Nominal dose	**Pre-treatment**	**Day 0**	**Day 7**	**Day 14**
0.5	8	-15	-13	-6
2	-10	-11	-3	-1
10	-2	**-66**	-15	+1
Females				
0.5	+7	-14	+7	+2
2	+18	**-32**	-2	+7
10	+5	**-72**	-1	-1

[a] Percent greater (+) or less (-) than concurrent control for n = 12

Summary session motor activity was not significantly different from control ($p \leq 0.05$; ANOVA) at any time for any dose groups. Differences from control that are considered biologically significant are shown in bold type.

CA-Table 1: Summary of locomotor activity results (Percent difference from controls)[a]

Males				
Nominal dose	**Pre-treatment**	**Day 0**	**Day 7**	**Day 14**
0.5	3	-20	-11	-7
2	-11	-12	-2	-1
10	2	**-77**	-19	-7
Females				
0.5	10	-13	2	0
2	21	**-36**	0	20

10	1	**-76**	-5	2

[a] Percent greater (+) or less (-) than concurrent control for n = 12

Summary session motor activity was not significantly different from control ($p \leq 0.05$; ANOVA) at any time for any dose groups. Differences from control that are considered biologically significant are shown in bold type.

CA-Table 2: Compound-Related FOB Findings on day 0

		Male, 12/group				**Female, 12/group**			
		dose (mg/kg bw)				**dose (mg/kg bw)**			
		0	**0.5**	**2**	**10**	**0**	**0.5**	**2**	**10**
Home cage	Gait incoordination, slight	0	0	0	0	0	0	0	**7***
	Gait incoordination, mod. - severe	0	0	0	**6***	0	0	0	**2***
	Decreased activity	0	0	0	**7***	0	0	0	**2**
	Lying flattened	0	0	0	**1**	0	0	0	**0**
	Writhing	0	0	0	**2**	0	0	0	**1**
Handling	Clear salivation, slight	0	0	0	0	0	0	0	**2***
	Clear salivation, mod. - severe	0	0	0	**1**	0	0	0	**1***
	Clear oral stains, slight	0	0	**1**	**7***	0	0	0	**6***
	Clear oral stains, mod. – severe	0	0	0	**3***	0	0	0	**3***
	Brown perianal stains	0	0	0	**1**	0	0	0	**1**
	Urine stains	0	0	0	**5***	0	0	0	**2**
Open field	Gait incoordination, slight	0	0	0	**4***	0	0	0	**8***
	Gait incoordination, mod. – severe	0	0	0	**4***	0	0	0	**2***
	Lying flattened	0	0	0	**2***	0	0	0	0
	Repetitive chewing, slight	0	0	0	**2**	0	**2**	0	**2**
	Repetitive chewing, mod. – severe	0	0	0	**1**	0	0	0	0
	Repetitive pawing movement	0	0	0	**2**	0	0	0	**2**
	Writhing	0	0	0	**2**	0	0	0	0
	Muscle fasciculations, slight	0	0	0	0	0	0	0	**1**
	Sluggish arousal	0	0	0	0	**5**	**6**	**8**	**9**
Reflex	No approach response	**1**	**2**	**3**	**4**	0	0	**1**	**1**
	No touch response	0	0	0	**4**	0	0	0	**1**
	No tail pinch response	0	0	0	**3**	0	0	0	0
	Righting response, incoordinated	0	0	0	**1**	**1**	**2**	0	**7***
	Righting response, landing on back/side	0	0	0	**4**	0	0	0	**1***
Other	Prolapsed penis	0	0	0	**3***	-	-	-	-

* $p \leq 0.05$

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			Official use only
		1 REFERENCE	
1.1	**Reference**	*From addendum 2 of the monograph p62* [redacted] (1997) A subchronic neurotoxicity study with technical grade FCR-4545 (β-cyfluthrin) in Fischer 344 rats. [redacted] Bayer AG Report No.: 107491 BES Ref.: M-038537-01-1 Report date: 9 May 1997 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	US EPA-FIFRA Pesticide Assessment Guideline No. 540/09-91-123, PB 91-154617	
2.2	**GLP**	Yes	
2.3	**Deviations**	None that compromised the validity of the study results	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in section 2	
3.1.1	Lot/Batch number	Test material:	
3.1.2	Specification	Technical grade beta-cyfluthrin,	
3.1.2.1	Description	Purity 96.5-97.3%, batch no.: 3030125/0250074	
3.1.2.2	Purity	Identity was confirmed by NMR and MS.	
3.1.2.3	Stability		
3.2	**Test Animals**	Test animals:	
3.2.1	Species	Fischer 344 [redacted] rats, Male and female	
3.2.2	Strain	Age: approximately 8 weeks old	
3.2.3	Source	[redacted]	
3.2.4	Sex		
3.2.5	Age/weight at study initiation		
3.2.6	Number of animals per group	Beta-cyfluthrin was administered in the diet for 13 weeks to young-adult male and female Fischer 344 rats (12/sex/dose) at nominal concentrations of 0-30-125-400 ppm (equal to 0-2.02-7.99-26.81 mg/kg bw/d for males and 0-2.34-9.40-30.83 mg/kg bw/d for females). All 12 rats/sex/dietary level were used for neurobehavioral evaluation, with half used for neuropathology.	X
3.2.7	Control animals		
3.3	**Administration/ Exposure**		
3.3.1	Duration of treatment		
3.3.2	Frequency of exposure		

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3.3.3	Postexposure period	
3.3.3.1	Type	
3.3.3.2	Concentration	
Vehicle		
3.4	**Examinations**	The following observations and measurements were included in the study: clinical observations, mortality, body weight, food consumption, automated measurements of activity (figure-eight maze), functional observational battery, ophthalmic exams, brain weight, and a gross necropsy. Skeletal muscle, peripheral nerves, eyes (with optic nerves) and tissues from the central nervous system were also examined microscopically for lesions.
3.5	**Sacrifice and pathology**	
3.6	**Further remarks**	

4 RESULTS AND DISCUSSION

4.1	**Observations**	
4.1.1	Clinical signs	Compound-related clinical signs were evident in males of the 125 ppm group and in males and females of the 400 ppm group. Effects in males of the 125 ppm group were limited to self-induced lesions from scratching due to paraesthesias following absorption to the skin and stimulation sensory nerve endings in the dermis. Compound-related clinical signs generally persisted with continued exposure but there was no evidence of cumulative toxicity after approximately 2-4 weeks of exposure.
4.1.2	Mortality	There were no deaths prior to terminal sacrifice.
4.1.3	Functional Observational Battery (FOB)	For the functional observation battery (FOB), compound-related findings were apparent in both sexes at 400 ppm. These findings were transient with no evidence of cumulative toxicity after 4 weeks of exposure. The only treatment-related effects at 125 ppm are attributed to local (dermal) effects due to paresthesia, and decreased body weight. Automated measures for motor and locomotor activity were not affected by treatment at any dietary level (Table A6.9/03-1). There were no compound-related ophthalmic findings.
4.2	**Body weight and food consumption**	Body weight and food consumption were reduced by treatment in males of the 400 ppm group and in females of the 125 ppm and 400 ppm groups.
4.3	**Sacrifice and pathology**	
4.3.1	Gross and histopathology	Compound-related gross lesions were not evident in males or females at terminal sacrifice. Brain weight was not affected by treatment in either sex. There were no compound-related microscopic lesions in 400 ppm for males and females.
4.4	**Other**	

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	The test material was technical grade beta-cyfluthrin, purity 96.5-97.3%, batch no.: 3030125/0250074. The test animals were Fischer 344 [redacted] rats, Male and female with an age of approximately 8 weeks

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		old [redacted]
		Beta-cyfluthrin was administered in the diet for 13 weeks to young-adult male and female Fischer 344 rats (12/sex/dose) at nominal concentrations of 0-30-125-400 ppm (equal to 0-2.02-7.99-26.81 mg/kg bw/d for males and 0-2.34-9.40-30.83 mg/kg bw/d for females). All 12 rats/sex/dietary level were used for neurobehavioral evaluation, with half used for neuropathology.
		The following observations and measurements were included in the study: clinical observations, mortality, body weight, food consumption, automated measurements of activity (figure-eight maze), functional observational battery, ophthalmic exams, brain weight and a gross necropsy. Skeletal muscle, peripheral nerves, eyes (with optic nerves) and tissues from the central nervous system were also examined microscopically for lesions.
5.2	**Results and discussion**	There were no deaths prior to terminal sacrifice. Compound-related clinical signs were evident in males of the 125 ppm group and in males and females of the 400 ppm group. Effects in males of the 125 ppm group were limited to self-induced lesions from scratching due to paraesthesias following absorption to the skin and stimulation sensory nerve endings in the dermis. Compound-related clinical signs generally persisted with continued exposure but there was no evidence of cumulative toxicity after approximately 2-4 weeks of exposure.
		Body weight and food consumption were reduced by treatment in males of the 400 ppm group and in females of the 125 ppm and 400 ppm groups. For the functional observation battery (FOB), compound-related findings were apparent in both sexes at 400 ppm. These findings were transient with no evidence of cumulative toxicity after 4 weeks of exposure. The only treatment-related effects at 125 ppm are attributed to local (dermal) effects due to paresthesia, and decreased body weight. Automated measures for motor and locomotor activity were not affected by treatment at any dietary level. There were no compound-related ophthalmic findings.
		Compound-related gross lesions were not evident in males or females at terminal sacrifice. Brain weight was not affected by treatment in either sex. There were no compound-related microscopic lesions in 400 ppm for males and females.
5.3	**Conclusion**	The present feeding study with beta-cyfluthrin produced characteristic evidence of toxicity at the two highest dietary concentrations of 125 and 400 ppm. The lowest dose of 30 ppm (equal to 2.02 mg/kg bw/day) is considered to be a NOAEL in both sexes. All effects of treatment are considered reversible, with complete recovery expected with discontinuation of exposure.
5.3.1	LO(A)EL	125 ppm (7.99 mg/kg bw/day in males, 9.40 mg/kg/day in females) based on decreased body weights, and clinical signs
5.3.2	NO(A)EL	30 ppm (2.02 mg/kg bw/day in males, 2.34 mg/kg/day in females)
5.3.3	Other	No
5.3.4	Reliability	1

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5.3.5 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	2006-09-01
Materials and Methods	*3.2.6 Number of animals per group:* 12/sex/group *3.3.3.3 Vehicle:* Corn oil was used as vehicle in this study.
Results and discussion	Applicant's version is adopted.
Conclusion	LO(A)EL: 125 ppm (7.99 mg/kg bw/day in males, 9.40 mg/kg/day in females) based on decreased body weights, and clinical signs NO(A)EL: 30 ppm (2.02 mg/kg bw/day in males, 2.34 mg/kg/day in females)
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.9/03-1: Motor (MA) and locomotor (LA) activity (percent difference from control)[1]

Males								
	Pretreatment		Week 4		Week 8		Week 13	
Dose(ppm)	MA	LA	MA	LA	MA	LA	MA	LA
30	+26	+17	+32	+26	+10	+13	+5	+11
125	+18	+12	+63*	+56	+10	+8	+22	+25
400	+4	+8	+47*	+26	+18	+8	+44	+36
Females								
30	-7	-11	+6	+7	-11	-21	-16	-16
125	-6	-6	+9	+11	+11	-1	-9	-14
400	-13	-13	+1	-9	+10	-1	-2	-6

[1] Percent greater (+) or less (-) than control

* $p < 0.05$

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1 REFERENCE

1.1	**Reference**	[redacted] (2003) A developmental Neurotoxicity sceening study with technical beta-cyfluthrin in wistar rat, [redacted] Report-No. 200620, BES Ref : M-103213-01-1 29 July 2003 unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	U.S. EPA Office of Prevention, Pesticides and Toxic Substances (OPPTS) Guideline 870.6300, Developmental Neurotoxicity Study (August, 1998).
2.2	**GLP**	Yes
2.3	**Deviations**	Yes, the period of exposure was extended to include the entire period of gestation and lactation (i.e., from GD 0 through LD 21), rather than from GD 6 through LD 10

3 MATERIALS AND METHODS

3.1	**Test material**	Technical Grade beta-Cyfluthrin (FCR 4545)
3.1.1	Lot/Batch number	8030130
3.1.2	Specification	As described in Section 2
3.1.2.1	Description	Off-White Powder
3.1.2.2	Purity	97.6 (April 2002)
3.1.2.3	Stability	
3.2	**Test Animals**	
3.2.1	Species	Wistar Hannover rat
3.2.2	Strain	[redacted]
3.2.3	Source	[redacted]
3.2.4	Sex	Female (adults males served only as “breeders”)
3.2.5	Age/weight at study initiation	12 weeks
3.2.6	Number of animals per group	30/female per dietary level
3.2.7	Control animals	Yes

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3.2.8	Mating period	
3.3	**Administration/ Exposure**	via the diet
3.3.1	Duration of treatment	from gestation day (GD) 0 through lactation day (LD) 21 to mated female Wistar rats
3.3.2	Postexposure period	none
3.3.3		Oral
3.3.3.1	Type	via the diet
3.3.3.2	Concentration	Nominal concentrations of 0, 30, 125 and 200 ppm. Measured concentration 0.0, 29.0, 133 and 215 ppm
3.3.3.3	Vehicle	none
3.4	**Examinations**	
3.4.1	Body temperature	Body temperatures of dams and pups were measured early in the morning, before the litter was disturbed by telemetry on days 10, 15, 18 and 21 postpartum.
3.4.2	Parental generation	
3.4.2.1	Clinical sign	Mortality, moribundity, behavioral changes, and overt were observed (cage-side) for clinical signs at least once daily
3.4.2.2	Observational battery	Animals were observed on GD 6 and GD 20 and also on LD 11 and LD 21. This observational battery included, but was not limited to, assessments (with severity scoring) of lacrimation, salivation, piloerection, exophthalmia, urination, defecation, pupillary function, palpebral closure, convulsions, tremor, abnormal movements, unusual behaviors, posture and gait abnormalities.
3.4.2.3	Bodyweight and food consumption	Body weight and food consumption were measured once per week during gestation and lactation, as follows: Gestation days 0, 6, 13 and 20 and lactation days 0, 7, 14 and 21.In addition, dams were also weighed on LD 4.
3.4.2.4	Delivery and culling	Each dam was evaluated daily for evidence of delivery from GD 20 to the completion of delivery, designated lactation day 0 (LD 0) for the dam and postnatal day 0 (PND 0) for the pups
3.4.3	F1 generation	
3.4.3.1	Clinical sign	All pups were observed (cage-side) for mortality, moribundity, overt toxicity and neurobehavioral changes.
3.4.3.2	Detailed Observational Battery.	On PND 4, 11, 21, 35 (±1 day), 45 (±1 day) and 60 (±2 days). This evaluation was performed according to the procedures described for the dams (see above) except for the neonates (i.e., PND 4 and 11) which were not evaluated in the open field unless the observer considered this necessary for evaluation.
3.4.3.3	Bodyweight and food consumption	Surviving pups were weighed on PND 0, 4, 11, 17, and 21, and once weekly thereafter. The individual pups were also weighed when vaginal patency or preputial separation were first evident. Food consumption for individual pups was measured weekly from the week of PND 28, when they were placed into single housing, until termination.
3.4.3.4	Sexual maturation and pupil constriction	All pups were examined daily for evidence of sexual maturation by inspecting females for vaginal patency beginning on PND 29 and males for preputial separation beginning on PND 38. On PND 21, all pups were tested for a pupil constriction in response to light.

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3.4.3.5	Neurobehavioral test	Motor Activity: An automated test to measure activity was performed on postnatal days 13, 17, 21 and 60 (+2 days) on one male and/or one female from each litter. Acoustic Startle Habituation: acoustic startle habituation was evaluated on postnatal days 22, 38 (+2 days) and 60 (+2days) on one male and/or one female from each litter. Passive Avoidance Conditioning: on postnatal days 22 and 29, learning, short-term retention, and long-term retention were examined in a passive avoidance test on one male and/or one female from each litter. Water Maze: One male and/or one female from each litter were assigned for testing on postnatal day 60 (+2 days), and again seven days later. Only animals that demonstrated acquisition were tested for retention.	
3.4.3.6	Sacrifice and pathology	Were also performed brain concentrations of beta-Cyfluthrin, micropathology and morphometry and the necropsy involving an examination of all organs (including the brain), body cavities, cut surfaces, external orifices and surfaces. All gross abnormalities were recorded. Gross lesions in neural tissues or skeletal muscle were appropriately sampled for microscopic examination.	
3.5	**Further remarks**	At approximately 50-60 days of age, ophthalmic exams were conducted using the males and females (a minimum of 10/sex/dietary level; representing at least 20 litters per level) that were selected for perfusion at study termination.	
		4 RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	No compound-related clinical signs were observed during gestation or lactation at any dietary level on dams or pups.	
4.1.2	Mortality	There were no deaths at any dietary level that are ascribed to treatment	
4.1.3	Functional Observational Battery (FOB)	There were no treatment-related findings during gestation or lactation at any dietary level on dams or pups	X
4.2	**Body weight and food consumption**	Maternal: Body weight was reduced during gestation and lactation for high-dose animals but not at lower dietary levels. Body weight gain was not affected during gestation or lactation at any dietary level. Food consumption was not affected during gestation at any dietary level but was reduced during lactation at the 200 ppm dietary level. See table A6.9/04-1 and A6.9/04-2	X
		Offsprings: At birth and on PND 4, there were no effects on body weight at any dietary level. However, decreased weight gain occurred thereafter in high dose males and females (e.g., 12% less than control from PND 4-11), such that high dose animals weighed an average 9-10% less than control from PND 11 to PND 21. Body weight and weight gain were not affected at lower dietary levels. Food consumption was not affected by treatment at any dietary level. Terminal body weight was not affected by treatment on PND 21 or at study termination. See table A6.9/04-3	X
4.3	**Food intake**	Based on analytical results, the average concentrations of p-cyfluthrin in the diet were 0.0, 29.0, 133 and 215 ppm and the average daily intake of active ingredient was as follows : Gestation: 0, 2.4, 11.0 and 17.8 mg/kg/day, respectively; and Lactation: 0, 5.9, 25.4 and 40.9 mg/kg/day, respectively.	X

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4.4	**Body temperature**	Body temperature of dams and pups was not affected at any dietary level .	
4.5	**Sacrifice and pathology of offsprings**		
4.5.1	Gross and histopathology	Gross lesions. There were no compound-related lesions evident at necropsy in animals that were either found dead or sacrificed (on PND 21 or at study termination). Brain weight. There was no compound-related effect at any dietary level, on PND 21 or at study termination. Brain morphometry. There were no differences in gross or microscopic brain measurements on PND 21 or at study termination at any dietary level. Micropathology. There were no compound-related microscopic lesions in the brain on PND 21, nor in the brain, other neural tissues, or skeletal muscle at study termination. Ophthalmology. No compound-related lesions were evident at any dietary level.	
4.6	**Neurobehavioral test on offsprings**	Motor and locomotor activity. Compound-related effects were not evident in either sex, atany dietary level. Acoustic startle habituation. Response amplitude was reduced by treatment in high-dose males at the end of exposure (PND 22). This effect was associated with reduced body weight. There were no effects in high-dose males on subsequent test occasions, in males at lower dietary levels, or in females at any dietary level on any test occasion. Habituation and latency were not affected by treatment at any dietary level, on any test occasion. Passive avoidance. No compound-related effects were evident at any dietary level. Water maze. No compound-related effects were evident at any dietary level.	X
4.7	**Brain concentrations of beta-cyfluthrin**	Brain concentrations of beta-cyfluthrin were measured in the dams on LD 21. The test substance was detected at each dietary level, with the concentration increasing in proportion to the dietary concentration. Beta-Cyfluthrin was detected in brain tissue from pups on both days measured (PND 4 and PND 21) at all dietary levels, with the concentration increasing in proportion to the dietary concentration. These findings provide clear evidence of exposure during lactation.	X

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Technical-grade beta-cyfluthrin was administered via the diet from gestation day (GD) 0 through lactation day (LD) 21 to mated female Wistar rats, at nominal concentrations of 0, 30, 125 and 200 ppm.

Brain tissues were assayed for beta-cyfluthrin in the dams on LD 21 and in the offspring on postnatal day (PND) 4 and PND 21. The offspring were evaluated using detailed clinical observations, body weight, body temperature, food consumption, developmental landmarks for sexual maturation, automated measures of activity (the figure-eight maze), acoustic startle habituation, learning and memory (passive avoidance and a water maze task), and an ophthalmic examination. Tissues were collected for morphometry and microscopic examination on PND 21

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		(brain) and at study termination (brain, an assortment of additional neural tissues and skeletal muscle).
5.2	**Results and discussion**	Based on analytical results, the average concentrations of beta-cyfluthrin in the diet were 0.0, 29.0, 133 and 215 ppm and the average daily intake of active ingredient was as follows : Gestation: 0, 2.4, 11.0 and 17.8 mg/kg/day, respectively; and Lactation: 0, 5.9, 25.4 and 40.9 mg/kg/day, respectively. There were no effects on reproduction parameters at any dietary level. Beta-Cyfluthrin was detected in brain tissue from the dams (LD 21) and the offspring (PND 4 and 21) at all dietary levels, providing clear evidence of exposure during postnatal development. Effects on dams were limited to decreased body weight during gestation and lactation and decreased food consumption during lactation at 200 ppm Effects on offsprings were limited to decreased body weight during lactation and after weaning at 200 ppm, with complete recovery of females and incomplete recovery of males by study termination, and decreased startle amplitude in males at the end of exposure on PND 22.
5.3	**Conclusion**	The present study established an overall NOAEL of 125 ppm in maternal animals, based on decreased body weight and food consumption. For the offspring, 125 ppm was a NOEL, based on decreased body weight in both sexes during lactation and after weaning.
5.3.1	LO(A)EL	
5.3.2	NO(A)EL	NOAEL of 125 ppm in maternal animals NOEL of 125 ppm for offsprings
5.3.3	Other	
5.3.4	Reliability	1
5.3.5	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	2006-09-13
Materials and Methods	Applicants version is acceptable with the following addition: *3.3.2 Postexposure period:* None for the dams; offspring postexposure periods ranged between 0 and 52 days for the various tests and measurements.

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Results and discussion	Applicant's version is adopted with following revisions: *4.1.3 FOB:* An increased number of male and female offspring in the 200 ppm group reacted with vocalisation to removal from the cage or handling on PND 4. Incidences were 2/32, 4/32, 2/32 and 10/32 pups at 0, 30, 125 and 200 ppm, respectively. *4.2 Body weight:* During pregnancy, net maternal body weight gain in the 200 ppm group was 13 % lower than in the control group (calculated by comparing body weights on GD 0 and LD 0, after delivery of the litter). No effect on body weight gain was observed during the lactation period. Offspring: Male offspring in all treated groups maintained slightly lower body weights than controls until termination of the study. *4.3 Test substance intake:* For more detailed intake data during lactation see CA-Table 1. *4.6 Acoustic startle habituation:* When expressed as peak response amplitude per gram body weight, males from all treated groups had lower values than control males on PND 22. However, there was no dose relationship. *4.7 Brain concentrations:* Beta-cyfluthrin concentration ranges in the brains of dams and offspring are shown in CA-Table 2.
Conclusion	LO(A)EL (maternal): 17.8 mg/kg bw/day (200 ppm) NO(A)EL (maternal): 1.20 mg/kg bw/day (125 ppm) LO(A)EL (offspring and neurotoxicity): 30.6 mg/kg bw/day (200 ppm) NO(A)EL (offspring and neurotoxicity): 19.0 mg/kg bw/day (125 ppm) Other conclusions: The maternal NOAEL is based on a decrease in net weight gain during pregnancy at a dose of 200 ppm. The NOAEL for offspring and developmental neurotoxicity is based on a decrease in body weight gain after the neonatal period and increased vocalisation in pups at 200 ppm and maternal intake data in the first week of lactation.
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*

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Remarks

Table A6.9/04-1 : Body weight during gestation (grams)

DOSE GROUP					
Day		CONTROL 0 ppm untreated	LEVEL I 30 ppm diet	LEVEL II 125 ppm diet	LEVEL III 200 ppm diet
0	Mean	206.0	201.9	203.6	200.3
	S.E.	2.27	3.09	2.76	2.38
	N.	30	30	30	30
6	Mean	224.9	222.5	222.3	208.6**
	S.E.	2.27	3.06	2.72	4.35
	N.	30	30	30	30
13	Mean	247.8	246.0	249.0	238.6
	S.E.	2.72	3.40	2.94	3.37
	N.	30	30	30	30
20	Mean	299.2	302.5	306.0	294.7
	S.E.	6.24	5.21	4.51	5.60
	N.	30	30	30	30
GAIN	Mean	93.1	100.7	102.4	94.5
	S.E.	5.81	4.61	3.63	4.87
	N.	30	30	30	30

Mean includes only dams known to deliver pups (either alive or dead)

** : = p≤0.01

Table A6.9/04-2 : Food consumption during gestation (grams)

DOSE GROUP					
Day		CONTROL 0 ppm untreated	LEVEL I 30 ppm diet	LEVEL II 125 ppm diet	LEVEL III 200 ppm diet
0 - 6	Mean	15.6	15.8	16.3	15.5
	S.E.	0.29	0.48	0.35	1.05
	N.	29	30	29	30
6 - 13	Mean	20.2	19.3	18.7	18.0
	S.E.	1.18	0.89	0.43	0.41
	N.	29	30	29	30
13 - 20	Mean	20.1	20.7	20.7	19.9
	S.E.	0.67	0.57	0.45	0.51
	N.	30	29	30	28

Mean includes only dams known to deliver pups (either alive or dead)

Table A6.9/04-3 : Mean weight viable pups (grams)

DOSE GROUP				
	CONTROL 0 ppm untreated	**LEVEL I 30 ppm diet**	**LEVEL II 125 ppm diet**	**LEVEL III 200 ppm diet**
Birth	5.7	5.6	5.6	5.5
Day 4 (precull)	9.5	9.1	9.4	8.8
Day 4 (postcull)	9.5	9.1	9.4	8.8
Day 11	24.1	23.1	23.6	21.8**
Day 17	38.0	36.6	36.8	34.6**
Day 21	48.2	45.8	46.4	43.6**
Gain	42.5	40.3	40.8	38.00**

** : = p≤0.01

Evaluation by Rapporteur Member State, CA-Tables

CA-Table 1 Developmental neurotoxicity study with beta-cyfluthrin in rats – Substance intake in females during lactation (mg/kg bw/d)

Dose (ppm)	**0**	**30**	**125**	**200**
Lactation Day 0-7	0	5.0	19.0	30.6
Lactation Day 7-14	0	5.8	26.0	42.3
Lactation Day 14-21*	0	7.0	31.2	49.8

* pups are eating maternal diet by this time; no reliable intake value for dams

CA-Table 2 Developmental neurotoxicity study with beta-cyfluthrin in rats – Brain concentrations of test substance in dams and offspring (ng/g tissue)

Dose (ppm)	**0**	**30**	**125**	**200**
Pup (PND 4)	0.1-1.3	1.6-7.4	4.2-35.9	15.4-38.0
Pup (PND 21)+	0.1-1.1*	2.7-10.7	13.9-33.9	11.9-65.2
Dam (lactation day 21)+	0-0.6	4.0-9.1	11.8-47.4	7.7-72.3

+ table headers in the individual data report section of the study are erroneously labelled “Day 4 Pup Brains Summary” for treated groups
* one outlier with 19.4 ng/g not included

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1 REFERENCE

1.1	**Reference**	[redacted] (1982). Safety pharmacology study with FCR 1272 on oral administration. [redacted]. Unpublished Report No. R 2405 , Study No. 92088 - 92096, Report date: December 01, 1982 [BES Ref :M-039504-01-1]
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
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
2.2	**GLP**	All tests were carried out in accordance with a test plan conforming to GLP specification.
2.3	**Deviations**	Not applicable.

3 MATERIALS AND METHODS

3.1	**Test material**	FCR 1272 (cyfluthrin)
3.1.1	Lot/Batch number	Batch No. 816 170 019
3.1.2	Specification	As given in section 2
3.1.2.1	Description	
3.1.2.2	Purity	94.9% analytically checked.
3.1.2.3	Stability	Stability in vehicle (Cremophor EL 2%) checked at room temperature over 24 hours
3.2	**Reference substance (positive control)**	None
3.3	**Test Animals**	*Non-entry field*
3.3.1	Species	Mice and rats
3.3.2	Strain	Mice, strain [redacted] Rats, strain [redacted]
3.3.3	Source	[redacted]

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3.3.4	Sex	Male
3.3.5	Age/weight at study initiation	Mice: approx. 6 weeks old, weight 17 to 26 g; Rats: approx. 7 weeks old, weight 150 to 185 g and 7 months, weight 370 to 415 g.
3.3.6	Number of animals per group	10/group for all tests except the linguomandibular reflex test: 3/group
3.3.7	Control animals	No, control: vehicle only.
3.4	**Administration/ Exposure**	Oral by gavage
3.4.1	Exposure	Single oral dose
3.4.2	Frequency of exposure	Single dose for all tests except linguomandibular reflex test: administration over 6 hours. Linguomandibular reflex test: escalading dose regimen at 2 h intervals.
3.4.3	Postexposure period	Up to 6 hours.
3.4.4	Vehicle	Cremophor EL 2%
3.4.5	Concentration in Vehicle	0, 0.1, 0.3, 1 mg/kg bw in cremophoe EL 2%.
3.4.6	Controls	yes
3.5	**Examinations**	
3.5.1	Body weight	Not performed
3.5.2	Observations	Test for anaesthesia potentiation in the mouse (Sleep period): 60 min after administration of the test substance, animals received 100 mg/kg bw hexobarbital sodium by sub-cutaneous injection. The course of anesthesia was then observed for up to a maximum of 6 hours. Incidence of anaesthesia stages was noted for each animal at each test time and the mean times at which anesthesia stage I was reached was calculated to evaluate the effectiveness of the test substance. Test for effect on central co-ordination capability and analgetic and anti-convulsive effect in the mouse (HBE test: hot-plate – balance rod – electric shock): 30 min after administration of the test substance the animals were placed on a plate heated at 51.5°C and observed for 2 min. Positive reaction was considered if the animal did not lick its rear paws within this time or did not try to jump up. 40 min after treatment with the test substance the animal's capability to stay on a balancing rod was evaluated over a 3 min period. Animals falling off the rod 3 consecutive times within this period were considered positive for inhibition of coordination. 50 min after treatment animals were subjected to an electric shock by ear electrodes. Electrical stimulus parameters were current strength 30 mA, pulse length 5 ms, pulse interval 20 ms and stimulus length 0.4 s. Animals showing no tonic seizures were considered protected and therefore positive. Traction test on the mouse: 40 min after substance administration traction ability was tested on an horizontal metal rod. Animals which did not reach the rod with at least one rear paw within 5 s were assessed as positive for inhibition of traction capability.

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Catalepsy test on the rat: Following treatment, catalepsy was tested hourly by evaluating animals remaining with one front paw on a 6 cm high wood block for at least 10 s. The effect of a substance was rated as positive when the state of catalepsy was observed in at least at least 3 times out of five sessions.

Catalepsy test on the mouse: Catalepsy test on the mouse: Testswere conducted 30, 60, 90, 120 and 180 min after substance administration of the test substance. Animals were considered in a cataleptic state when remaining motionless on a vertical rod for 30 s. The effect of a substance was rated as positive when the state of catalepsy was observed at least 3 times out of five sessions.

Test for anticonvulsive effect on the mouse: 30 min after treatment with the test substance, animals received 5mg/ml of a pentetrazol solution by i.v. until a clonic seizure of all 4 extremities was observed. The dose inducing seizures expressed in mg/kg bw was calculated. The effect of the test substance was considered positive when the animal tolerated over 90 mg pentetrazol/kg until the onset of the seizures.

Test for inhibition of orientation on the mouse: The test was conducted using animals with an altered day-night rhythm. Animals received the test substance towards the end of the dark period. 5 min after treatment the light was switched on and locomotor activity was measured every 5 min for a 40 min period.

Test for stimulation of spontaneous motility on the mouse: The test was conducted using animals with an altered day-night rhythm. Animals received treatment 3 hours after the onset of the light period. 40 min after treatment locomotor activity was measured every 5 min for a 40 min period.

Inhibition of the linguomandibular reflex and neuromuscular transmission in the rat: The trachea was canulated for artificial respiration, and a tibial nerve as well as the tendon of the respective anterior tibial muscle were set free. The tibial nerve was placed on a double electrode, the muscle contractions were registered with a multichannel recorder using a DMS transducer on a thermosensitive paper. The linguomandibular reflex was obtained after stimulation of the tongue using a pair of needle electrodes pierced laterally. The contractions of the mandibula were recorded as described above. The stimulation of 10 ms duration was performed using an electric stimulator; the voltage was set between 1 and 20 V according to the individual sensitivity of the animal. When the response became constant the rat was treated first with the placebo solution/suspension, then with the test compound at the doses stated in the experimental protocol, with intervals of 1 hour between the individual doses. The pharmacological response was tested 10, 20, 30, 40 and 60 min after each administration.

3.5.3	Clinical chemistry	No
3.5.4	Sacrifice and pathology	No
3.5.5	Histopathology	No

3.6	**Further remarks**	None

4 RESULTS AND DISCUSSION

4.1	**Observations**	
4.1.1	Clinical signs	Not applicable.
4.1.2	Mortality	None.
4.1.3	Tests	Test for potentiation of anaesthesia in the mouse: At 1 mg/kg the duration and depth of anaesthesia was slightly potentiated ($p<0.05$). Lower doses had no effect (Table A6.9/05-1). Test for effect on central co-ordination ability and for analgetic and anticonvulsive effect on the mouse: No analgetic or anti-convulsive effects were observed. The balancing ability was not affected. Traction test in the mouse: Inhibition of traction was observed in 2 mice at 0.3 mg/kg and one mouse at 1 mg/kg. These effects were not statistically significant with the chi-square test. Catalepsy test: In both species no cataleptic effect was observed at any dose level. Test for anticonvulsive effect in the mouse: The test substance exhibited no protective effect against pentetrazol seizures. Inhibition of the orientation motility in the mouse: A very weak non significant inhibitory effect on orientation was observed at 0.3 and 1 mg/kg. This effect was not dose related. Stimulation of the spontaneous motility in the mouse: A weak stimulating effect on spontaneous motility was observed at all doses but there was no dose correlation. Statistical significance was only observed at 0.1 mg/kg Test for inhibition of linguomandibular reflex and neuromuscular transmission in the rat: Partial inhibition of the linguomandibular reflex and neurotransmission was observed in 1 rat out of 10. Lower doses had no effect on the same animal and none of the doses had any effect on the other animals. In order to check whether this animal was a random case the test was repeated with 3 rats. No effects were observed in any of the 3 rats.
4.2	**Body weight and food consumption**	Not applicable.
4.3	**Sacrifice and pathology**	
4.3.1	Gross and histopathology	Not applicable.
4.4	**Other**	-

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BPD Data set IIA/ Annex Point VI.1

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The test material was technical grade cyfluthrin, purity 94.9%, batch no.: 816 170 019. The test animals were male mice, strain [redacted] approx. 6 weeks old, weight 17 to 26 g and male rats, strain [redacted] approx. 7 weeks old, weight 150 to 185 g and 7 months, weight 370 to 415 g.

Cyfluthrin was administered by gavage in 2% cremophor EL to male rats and male mice (10/dose level except the linguomandibular reflex test: 3/dose level) at dose levels of 0, 0.1, 0.3, 1 mg/kg bw. A single dose was administered for all tests except the linguomandibular reflex test for which escalading dose regimen was used at 2 h intervals over a 6 hour-period. Post-exposure period was up to 6 hours.

The following tests were included in the study: Test for the potentiation of anaesthesia in the mouse, test for effect on central co-ordination ability and for analgetic and anticonvulsive effect on the mouse, traction test in the mouse, catalepsy test, test for anticonvulsive effect in the mouse, test for inhibition of the orientation motility in the mouse, test for stimulation of the spontaneous motility in the mouse and test for inhibition of linguomandibular reflex and neuromuscular transmission in the rat.

5.2 Results and discussion

A dose of 1 mg/kg bw slightly potentiated duration and depth of hexobarbital anaesthesia in the mouse. Lower doses had no effect.

At 0.1 mg/kg slight stimulation of spontaneous motility was observed in the mouse and isolated cases of spontaneous movements of the animals were seen throughout the dose groups. This finding was therefore not considered as relevant.

Linguomandibular reflex and neurotransmission was found to be partly inhibited in one rat out of 10 at 1 mg/kg bw but this effect was not reproducible and was therefore considered as a random finding.

All other effects were neither statistically significant nor of pharmacological importance.

5.3 Conclusion

At doses of 0.1, 0.3 and 1 mg/kg bw cyfluthrin exhibited no analgetic, anticonvulsive, muscle relaxant and cataleptic properties and did not affect the central coordination and the orientation motility.

5.3.1 LO(A)EL

Mouse: 1 mg/kg bw based on slight potentiation of hexobarbital anaesthesia

Rat: > 1 mg/kg bw

5.3.2 NO(A)EL

Mouse: 0.3 mg/kg bw based on potentiation of hexobarbital anaesthesia

Rat: >1 mg/kg bw

5.3.3 Reliability

3

5.3.4 Deficiencies

No guidelines; No standardised methods.

This study is superseded by the neurotoxicity guideline studies which are summarised under point A6.9/02 and A6.9/03

Document IIIA/ Section 6.9/05 **Neurotoxicity**

BPD Data set IIA/ Annex Point VI.1

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2013/07/23
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is acceptable.
Conclusion	LOAEL/NOAEL: 0.3/1 mg/kg bw on the basis of extension of barbiturate sleeping time
Reliability	2 (due to lack of standardization, specification, reporting deficiencies e.g. no raw data presented, study report represents ☐ summary of results on
Acceptability	Acceptable
Remarks	The effect observed – extension of barbiturate sleeping time – is regarded not appropriate to derive ADI for assessment of cyfluthrin under BPD.
	COMMENTS FROM ... (specify)
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.9/05-1: Test for potentiation of anaesthesia in the mouse – Influence on hexobarbital anesthesia

		Depth of anesthesia, stage frequency (%)							
		After 30 min				After 60 min			
Dose(mg/kg)	**Mean duration of anaesthesia (minute)**	**III**	**IV**	**V**	**VI**	**0[#]**	**III**	**IV**	**V**
0	73 ± 13	20	30	50	0	20	80	0	0
0.1	79 ± 15	0	20	80	0	10	80	10	0
0.3	83 ± 23	0	0	80	20	20	60	10	10
1.0	96 ± 21[*]	0	0	40	60*	10	80	10	0

* $p < 0.05$; [#]: animals awake

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1 REFERENCE

1.1	**Reference**	[redacted] (1985). CNS safety pharmacology study with BAY VL 1704 on oral administration. [redacted] Unpublished report No. R 3459, Experiments No. B-00585 to 013811 Report date: July 19, 1985 [BES Ref :M-039515-01-1]
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
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.
2.2	**GLP**	Yes.
2.3	**Deviations**	Not applicable.

3 MATERIALS AND METHODS

3.1	**Test material**	BAY VL 1704 (BAY L 1704, FCR 1272, Cyfluthrin)
3.1.1	Lot/Batch number	Batch No. 233 490 583
3.1.2	Specification	
3.1.2.1	Description	-
3.1.2.2	Purity	Purity not specified, material identity analytically checked
3.1.2.3	Stability	Stability of the material in vehicle (polyethylene glycol 400) checked
3.2	**Reference substance (positive control)**	None
3.3	**Test Animals**	*Non-entry field*
3.3.1	Species	Mice and rats
3.3.2	Strain	Mice, strain [redacted] Rats, strain [redacted]
3.3.3	Source	[redacted]
3.3.4	Sex	Male

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3.3.5	Age/weight at study initiation	Mice: approx. 6 weeks old; Rats: approx. 7 weeks and 7 months old.
3.3.6	Number of animals per group	Reflexes test: 5 x 1; Orientation and motility tests: 6/group; 10/group for all other tests.
3.3.7	Control animals	No, control: vehicle only.
3.4	**Administration/ Exposure**	Oral by gavage
3.4.1	Exposure	Single oral (gavage) dose for all tests except linguomandibular reflex test: 6 hours.
3.4.2	Frequency of exposure	Single oral (gavage) dose for all tests except linguomandibular reflex test: escalading dose regimen at 2 h intervals.
3.4.3	Postexposure period	Up to 6 hours.
3.4.4	Vehicle	PEG 400
3.4.5	Concentration in Vehicle	0, 3, 10, 30 mg/kg bw
3.4.6	Controls	yes
3.5	**Examinations**	
3.5.1	Body weight	Not performed
3.5.2	Observations	Test for anaesthesia potentiation in the mouse (Sleep period): 60 min after administration of the test substance, animals received 100 mg/kg bw hexobarbital sodium by sub-cutaneous injection. The effects of the test substance was assessed for each dose according to the mean time elapsed until the stage I of Magnus and Girndt (i.e. ataxy when running) was reached as well as according to the incidence of the anesthesia stages at each check time of 30 min and up to a maximum period of 6 hours. The results were evaluated with the two-tailed U-test of Wilcoxon, Mann and Whitney and with chi-square test, respectively (significance level p = 0.05 for both tests). Test for effect on central co-ordination capability and analgetic and anti-convulsive effect in the mouse (HBE-test: hot-plate – balance rod – electroshock): 30 min after administration of the test substance the animals were placed on a plate heated at 51.5°C and observed for 2 min. A mouse reacted positively when it neither licked its paws nor tried to escape by jumping up within the observation period. 40 min after treatment with the test substance, the animal's capability to keep their balance on a horizontal rod over a 3 min period was evaluated. Animals falling off the rod 3 times during this period were considered as showing a decrease in central coordination capability and were regarded as positive. 50 min after treatment animals were subjected to an electroshock by ear electrodes. Electrical stimulus parameters were current strength 30 mA, pulse length 5 ms, frequency 40 Hz and stimulation lasting 0.4 s. Animals showing no

tonic seizures were considered protected and test result positive.

Traction test on the mouse: 40 min after substance administration the animals were hanged with their forepaws on a horizontal metal rod. Mice that were unable to reach the rod with at least one hindpaw within 5 seconds were regarded positive for impaired traction ability.

Catalepsy test on the rat: Following treatment, catalepsy was tested hourly by evaluating animals remaining motionless with one front paw on a 6 cm high wood block for at least 10 s. The effect of a substance was rated as positive when the state of catalepsy was observed at least 3 times out of five sessions.

Catalepsy test on the mouse: Tests were conducted 30, 60, 90, 120 and 180 min after substance administration of the test substance. Animals were considered in a cataleptic state when remaining motionless on a vertical rod for 30 s. The effect of a substance was rated as positive when the state of catalepsy was observed at least 3 times out of five sessions.

Test for anticonvulsive effect on the mouse: 15 min after treatment with the test substance, animals received 5 mg/ml of a pentetrazol solution by i.v. until a clonic seizure of all 4 extremities was observed. The dose inducing seizures expressed in mg/kg bw was calculated. The effect of the test substance was considered positive when the animal tolerated over 90 mg pentetrazol/kg until the onset of the seizures.

Test for inhibition of orientation on the mouse: The test was conducted using animals with an altered day-night rhythm. Animals received the test substance at the end of the dark period. Animals were transferred in an illuminated room and observed for locomotor activity was measured every 5 min over a 40 min period.

Test for stimulation of spontaneous motility on the mouse: The test was conducted using animals with an altered day-night rhythm. Animals received treatment 3 hours after the onset of the light period. 40 min later, locomotor activity was measured every 5 min for a 40 min period.

Inhibition of the linguomandibular reflex and neuromuscular transmission in the rat: 7 months old rats were anesthetised with sodium pentobarbital. The trachea was canulated for artificial respiration, and a tibial nerve as well as the tendon of the respective anterior tibial muscle were set free. The tibial nerve was placed on a double electrode, the muscle contractions were registered with a multichannel recorder using a DMS transducer on a thermosensitive paper. The linguomandibular reflex was obtained after stimulation of the tongue using a pair of needle electrodes pierced laterally. The contractions of the mandibula were recorded as described above. The stimulation of 10 ms duration was performed using an electric stimulator; the voltage was set between 1 and 20 V according to the individual sensitivity of the animal. When the response became constant the rat was treated first with the placebo solution/suspension, then with the test compound at the doses stated in the experimental protocol, with intervals of 1 hour between the individual doses. The pharmacological response was tested 10, 20, 30, 40 and 60 min after each administration.

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3.5.3	Clinical chemistry	No
3.5.4	Sacrifice and pathology	No
3.5.5	Histopathology	No
3.6	**Further remarks**	None

4 RESULTS AND DISCUSSION

4.1	**Observations**	
4.1.1	Clinical signs	At 30 mg/kg bw, severe seizures were observed 60 min after treatment in all mice.
4.1.2	Mortality	60% death in mice treated at 30 mg/kg bw in the test for potentiation of anesthesia.
4.1.3	Tests	Test for potentiation of anaesthesia in the mouse: At 3 and 10 mg/kg no effects were observed on either the duration or the depth of anesthesia. Due to the early death of the 30 mg/kg bw group, no evaluation was made. Test for effect on central co-ordination ability and for analgetic and anticonvulsive effect on the mouse: No effects were observed. Traction test in the mouse: No effects were observed. Catalepsy test: No effects were observed. In both species. At 30 mg/kg bw, 3 mice at 90 min and 2 mice at 120 and 180 min could not be evaluated due to side-effects consisting in disappearance of the righting reflex and of the ability to hold oneself on the rod, and prostration. Test for anticonvulsive effect in the mouse: The test substance exhibited no protective effects against pentetrazol seizures. Inhibition of the orientation motility in the mouse: No effects were observed. Stimulation of the spontaneous motility in the mouse: No effects were observed. Test for inhibition of linguomandibular reflex and neuromuscular transmission in the rat: No effects were observed.
4.2	**Body weight and food consumption**	Not applicable.
4.3	**Sacrifice and pathology**	
4.3.1	Gross and histopathology	Not applicable.
4.4	**Other**	-

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BPD Data set IIA/ Annex Point VI.1

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The test material was BAY VL 1704, FCR 1272, cyfluthrin, purity unspecified, batch no.: 233 490 583. The test animals were male mice, strain [redacted] approx. 6 weeks old and male rats, strain [redacted], approx. 7 weeks old.

Cyfluthrin was administered by gavage in polyethylene glycol 400 to rats and mice (Reflexes test: 5 x 1; orientation and motility tests: 6/group; 10/group for all other tests) at dose levels of 0, 3, 10 and 30 mg/kg bw. A single dose was administered for all tests except the linguomandibular reflex test for which escalading dose regimen was used at 2 h intervals over a 6 hour-period. Post-exposure period was up to 6 hours.

The following tests were included in the study: test for the potentiation of anaesthesia in the mouse, test for effect on central co-ordination ability and for analgetic and anticonvulsive effect on the mouse, traction test in the mouse, catalepsy test, test for anticonvulsive effect in the mouse, test for inhibition of the orientation motility in the mouse, test for stimulation of the spontaneous motility in the mouse and test for inhibition of linguomandibular reflex and neuromuscular transmission in the rat.

5.2 Results and discussion

One hour after treatment the oral dose of 30 mg/kg bw induced a high mortality (60%) in mice and seizures in all animals which lasted up to 150 min in some animals. These effects which are typical signs of acute toxicity following exposure to type II pyrethroid did not allow the evaluation of the effects of cyfluthrin on hexobarbital anesthesia after 30 min, at the top dose level. However, at the mid- and low-dose, no effects of cyfluthrin on hexobarbital anesthesia were observed. The signs of acute toxicity seen in mice at 30 mg/kg bw did not allow to test 3 animals of this group in the catalepsy test. However, all other animals from this group as well as the other groups did not show any sign of catalepsy. All other tests including analgetic and anticonvulsive effects, central coordination, traction test and spontaneous motility and orientation did not show any effect of the tested substance up to and including a dose of 30 mg/kg bw.

5.3 Conclusion

Cyfluthrin had no effects on hexobarbital anesthesia, central coordination and spontaneous activity. Cyfluthrin has no analgetic or anticonvulsive properties and does not induce catalepsy.

5.3.1 LO(A)EL

30 mg/kg bw for acute toxicity;

> 30 mg/kg bw based on all parameters measured in this study.

5.3.2 NO(A)EL

10 mg/kg bw based on acute signs of toxicity;

30 mg/kg bw based on all parameters measured in this study.

5.3.3 Reliability

3

5.3.4 Deficiencies

No guidelines; No standardised methods; No material batch specified.

This study is superseded by the neurotoxicity guideline studies which are summarised under point A6.9/02 and A6.9/03

Document IIIA/ Section 6.9/06 Neurotoxicity

BPD Data set IIA/ Annex Point VI.1

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2012/12/12
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is acceptable with an exemption as follows: *4 Results and Discussions; 4.1.3 Tests:* Test for effect on central co-ordination ability and for analgetic and anticonvulsive effect on the mouse: At doses of 10 mg/kg bw inhibition of central coordination was observed in all animals (10/10).
Conclusion	Other conclusions: Derivation of LOAEL/NOAEL not possible due to major deficiencies (no standardization, no specification given).
Reliability	3 (not reliable due to lack of standardization, specification, reporting deficiencies e.g. no raw data presented, study report represents ☐ summary c
Acceptability	Not acceptable
Remarks	There are discrepancies between text and table in the study report concerning inhibition of central coordination (see above).
	COMMENTS FROM ... (SPECIFY)
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Influence on Hexobarbital Anesthesia
Beeinflussung der Hexobarbitalnarkose
n = 10

Dose Dosis mg/kg	Duration of anesthesia Narkosedauer (min, x±S.D.)	Depth of anesthesia, stage frequency (%) after Narkosetiefe, Häufigkeit der Stadien (%) nach							
		30 min			60 min		90 min		
		V	VI	S	III	IV	I	II	III
0.0	91 ± 8	40	60		70	30	70	0	30
3.0	90 ± 11	50	50		40	60	40	10	50
10.0	92 ± 17	20	80		40	60	50	0	50
30.0	*	100	0	a	*		*		

S = significance to the controls / Signifikanz zu Kontrolle: a) $p < 0.01$
*) impossible to evaluate (see text) / nicht auswertbar (s. Text)
Stage 0: animals awake / Stadium 0: Tiere wach

Document IIIA/ Section 6.10 Mechanistic study

BPD Data set IIIA/ Annex Point VI.7

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1 REFERENCE

1.1	**Reference**	[redacted] (1992) FCR 1272 (c.n.: Cyfluthrin) - Pilot study for acid-base status following inhalation exposure to the rat [redacted], Report No.: 21865, BES Ref: M-038738-01-1 Date: 24 November 1992 unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2		
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No, The test was conducted only in analogy to OECD Guidelines for testing of chemicals OECD no. 403 and to Directive 92/69 EEC method B2.
2.2	**GLP**	No, The study was designated as a methodological validation study and was therefore not performed as a GLP study
2.3	**Deviations**	Not relevant

3 MATERIALS AND METHODS

3.1	**Test material**	FCR 1272 (cyfluthrin)
3.1.1	Lot/Batch number	Batch No. 238005176
3.1.2	Specification	As given in sections 2
3.1.2.1	Description	yellow-brown, solidified mass, clear yellow brown oil above 50 °C.
3.1.2.2	Purity	96.2%
3.1.2.3	Stability	granted during the study
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Experiment 1 (CO_2 exposure) :Wistar rats [redacted] Experiment 2 (cyfluthrin exposure) : Sprague Dawley rats
3.2.3	Source	Experiment 1 (CO_2 exposure) : [redacted] Experiment 2 (cyfluthrin exposure): not stated
3.2.4	Sex	Experiment 1 (CO_2 exposure) :4 males Experiment 2 (cyfluthrin exposure) : 21 rats
3.2.5	Age/weight at study initiation	Approx 250g

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3.2.6	Number of animals per group	10/sex/group
3.2.7	Control animals	Yes, in experiment 1
3.3	**Administration/ Exposure**	Inhalation
3.3.1	Duration of treatment	4 h
3.3.2	Frequency of exposure	single administration
3.3.3	Postexposure period	240 min
3.3.4	**Inhalation**	
3.3.4.1	Concentrations	Experiment 1 (CO2 exposure) Control group: 10 1 air/min, CO2-group 1: 10 1 air/min and over intervals of 30 min followed by 0.1-0.2-0.4-1.0 1 CO2/min (nominal concentrations), CO2-group 2: 4 h with 10 1 air/min + 0.4 1 CO2/min (nominal concentration). Experiment 2 (cyfluthrin exposure) 13.2 mg cyfluthrin /m3 air/ for 4 hours
3.3.4.2	Particle size	The aerosol had respirable particle characteristics for the rat (MMAD = 1.16 juro, GSD = 1.3), particle mass < 3 /im: 100
3.3.4.3	Type of exposure	Nose/head only
3.3.4.4	Vehicle	Experiment 1 (CO2 exposure) none Experiment 2 (cyfluthrin exposure): The vehicle used was ethanol and Lutrol (polyethylene glycol 400) mixed 1:1.
3.3.4.5	Controls	Experiment 1 (CO2 exposure) Control group: 10 1 air/min,
3.4	**Examinations**	
3.4.1	Experiment 1 (CO2 exposure)	general observation: before and after the administration; body weight: before and after the administration (only group 2); rectal temperature: before and after the administration; lung function test: during the administration; blood sampling, blood gas analysis, pH and haemoglobin concentration: before and after administration (group 1 at once, group 2 30 minutes after the exposure).
3.4.2	Experiment 2 (cyfluthrin exposure	rectal temperature: before and after the administration; blood sampling, blood gas analysis, pH and haemoglobin concentration: before and during the exposure (approx. 30, 60, 120, 180 and 240 minutes after the beginning).
3.4.3	Other examinations	No
		4 RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Experiment 1 (CO2 exposure)	No clinical signs were seen. The rectal temperature was slightly lowered after the treatment. The lung function test revealed a concentration-dependent increase in minute volume.

Document IIIA/ Section 6.10 | **Mechanistic study**

BPD Data set IIIA/ Annex Point VI.7

Only in the CO2 group 1-animals the blood gas analysis revealed a slight respiratory acidosis, hypercapnia (increased blood-CO2) and a reduction in the venous oxygen partial pressure. In the group 2-animals blood gas analysis did not reveal any effect. The haemoglobin values were slightly lowered.

4.1.2 Experiment 2 (cyfluthrin exposure

During the exposure with cyfluthrin, the following time dependent changes were recognised: lowering of rectal temperature, decrease in haemoglobin concentration (presumably due to repeated blood sampling),
reduction in CO2 partial pressure and increase in pH value

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Inhalation toxicity studies with the rat have shown that cyfluthrin induces transient respiratory changes in this species. These changes result from sensory irritation and are manifested by reflex bradypnoea, which coincides with a reflexively induced hypothermia and respiratory alkalosis. In inhalative teratogenicity studies, the fetal development was influenced above the sensory irritant threshold concentration. No effects on the embryonic development were seen following oral administration of considerably higher doses. This pilot study was done in order to corroborate the hypothesis that a mechanistic relationship between changes in the physiological acid-base status and the influenced embryonic development exist.
Experiment 1: A blood gas analysis was done after CO2 exposure and retro orbital blood sampling. Groups of 4 male Wistar rats were acclimatised for two days and then dosed at the following dosing schedule:
Control group: 10 l air/min,
CO2-group 1: 10 l air/min and over intervals of 30 min followed by 0.1-0.2-0.4-1.0 l CO2/min (nominal concentrations),
CO2-group 2: 4 h with 10 l air/min + 0.4 l CO2/min (nominal concentration).
Experiment 2: An inhalative cyfluthrin-exposure study was done with intra-arterial blood sampling during the exposure. According to technical difficulties blood gas analysis was only performed on 3 (2 male and one female) of the 21 rats. The animals were acclimatised 1 day and then received cyfluthrin at a dose of 13.2 mg/m3 air for 4 hours.

5.2 Results and discussion

In experiment 1, no clinical signs were seen. The rectal temperature was slightly lowered after the treatment. The lung function test revealed a concentration-dependent increase in minute volume.

Only in the group 1-animals the blood gas analysis revealed a slight respiratory acidosis, hypercapnia (increased blood-CO2) and a reduction in the venous oxygen partial pressure. In the group 2-animals blood gas analysis did not reveal any effect. The haemoglobin values were slightly lowered.

During the exposure with cyfluthrin (experiment 2) , the following time dependent changes were recognised: lowering of rectal temperature, decrease in haemoglobin concentration (presumably due to repeated blood sampling),reduction in CO2 partial pressure and increase in pH value.

5.3 Conclusion

In experiment 1 (group 2), the induced reflectory blood gas changes normalised directly after the end of exposure. Around 30 minutes after

Document IIIA/ Section 6.10 | **Mechanistic study**

BPD Data set IIIA/ Annex Point VI.7

	the end of exposure no toxicologically significant changes were seen. Therefore, the only practicable way to measure the blood gas changes seems to be the measurement through intra-arterial blood sampling parallel to exposure. The results of these examinations support the hypothesis that reflex bradypnoea induce secondary hypothermia. In the literature it is pointed out, that hypothermia in gravid rodents influences the development of the embryo. In connection with this the results of this pilot study corroborate the hypothesis, that exposing of rats to a greater than the sensory irritant threshold concentration (approx. 0.5 mg cyfluthrin/m air in an embryotoxicity study) can induce compensatory mechanisms in thermoregulation which are tolerated by the dams, but not by the foetuses, without specific lesions occurring. A distinct hypothermia developed during the 4 h exposure period (experiment 2). The determinations of the blood gases resulted in a decrease in arterial partial pressure of carbon dioxide and a rise in arterial blood pH.
5.3.1 Other	
5.3.2 Reliability	1
5.3.3 Deficiencies	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2013-02-19
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted with additional remarks as follows: Actual and Standard Base Excess were unchanged or slightly higher in cyfluthrin exposed animals (data derived from 3 animals only).
Conclusion	Applicant's version is adopted with a remark as follows. Reduced body temperature may be caused by reflex bradypnoe but causality have not been shown. An influence of the procedure/exposure itself may also have caused observed hypothermia. An influence of reflex bradypnoa on fetal development can only be assumed as possible mechanism but is not sufficient to explain observed teratogenic effects on a stand alone basis.
Reliability	2 (technical problems: only three animals of the cyfluthrin group evaluated)
Acceptability	Acceptable
Remarks	Lung function parameters were not evaluated in experiment 2 (cyfluthrin exposure). Hence, the experiment gives no indication for reflex bradypnoea due to sensory irritation.
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*

Document IIIA/ Section 6.10 Mechanistic study

BPD Data set IIIA/ Annex Point VI.7

Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.11/01

Studies on Other Routes of Administration

Acute intraperitoneal toxicity in the rat

BPD Data set IIIA/ Annex Point III-0§

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1980). FCR 1272 Acute toxicity studies. [redacted] Bayer AG Report No.:8800 BES Ref.: M-038979-01-1 Report date: 7 January 1980 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	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, GLP was not compulsory at the time the study was performed (as study started before June 30 1988)	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	FCR 1272 (cyfluthrin) Cyclopropane carboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl, cyano (4-fluoro-3-phenoxyphenyl) methyl ester	
3.1.1	Lot/Batch number	Batch No. 16001/79, Lo-Nr. 2151	
3.1.2	Specification	Not given	
3.1.2.1	Description	Not given	
3.1.2.2	Purity	83.6%	
3.1.2.3	Stability	Not specified	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Wistar rats [redacted]	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male and female	
3.2.5	Age/weight at study initiation	Young adult approximately 160 to 240 g	
3.2.6	Number of animals per group	15/sex/group (controls had 5/sex/group)	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	**Intraperitoneal**	
3.3.1	Post-exposure period	14 days	

Document IIIA/ Section A6.11/01

BPD Data set IIIA/ Annex Point III-0§

Studies on Other Routes of Administration

Acute intraperitoneal toxicity in the rat

3.3.2	Concentration	0, 0.5*, 1, 10, 25*, 30*, 50, 100, 150, 250, 500** (* = male only, ** = female only)	
3.3.3	Vehicle	Lutrol	
3.3.4	Total volume applied	5 ml/kg body weight injected in to the abdominal cavity.	
3.3.5	Controls	Vehicle	
3.4	**Examinations**	Clinical observations, gross pathology	
3.5	**Method of determination of LD_{50}**	Probit-analysis. (Fink and Hund , Arzneimittelforschung 15, 624, 1965)	
3.6	**Further remarks**	None	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	At dose levels of 10 mg/kg and above, rats showed similar symptoms to oral exposure, i.e., starting about 10-60 minutes post-exposure rats displayed restlessness, salivation and hypermotility. Breathing rate was reduced. After 24-48 hours salivation and hyperkinesis resolved, and animals became apathetic and developed ataxia of the hind limbs and reduced sensitive. These symptoms disappeared 2 to 3 days earlier. Additionally, all animals including controls made sounds of pain and arched their backs immediately after application. See table 6.11/01-1	X
4.2	**Pathology**	Findings also corresponding to those of orally dosed rats, i.e spotted lungs, pale livers, spleens and kidneys, were seen in treated and control animals. All intraperitoneally treated animals, including controls, showed signs of peritonitis. These local alterations (irritant effect of polyethylene glycol E 400) did not mask the systemic effect of cyfluthrin. See table 6.11/01-1	
4.3	**Other**	None	
4.4	**LD_{50}**	Males: 66 mg/kg bw Females: 104 mg/kg bw	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Groups of 15 Wistar rats/sex/group weighing 160 to 240 grams received a single intraperitoneal dose of cyfluthrin (batch no: 16001/79, purity: 83.6%,) at doses of 0, 0.5, 1.0, 10, 25, 30, 50, 100, 150, 250, 500 mg/kg bw in Lutrol. Animals were observed for 14 days for clinical signs and autopsied as soon as possible after death or sacrifice. Statistical analysis method: Probit-analysis.	

Document IIIA/ Section A6.11/01	**Studies on Other Routes of Administration** Acute intraperitoneal toxicity in the rat
BPD Data set IIIA/ Annex Point III-0§	

5.2	**Results and discussion**	Deaths occurred at doses above 30 mg/kg bw, generally within the period 3 – 24 hours after dosing. At dose levels of 10 mg/kg and above, rats showed similar symptoms to oral exposure. Additionally, all animals including controls made sounds of pain and arched their backs immediately after application. Gross pathology did not reveal any treatment related effects. Effects of Lutrol were noted (pain, back arching on exposure, peritonitis). However, effects related to cyfluthrin could be distinguished and appeared to start at 10 mg/kg bw.
5.3	**Conclusion**	The LD_{50} for male and female rats is calculated to be 66 and 104 mg cyfluthrin/kg bw respectively. After intraperitoneal application to rats cyfluthrin is moderately toxic.
5.3.1	Reliability	2
5.3.2	Deficiencies	Vehicle makes it difficult to interpret effects.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-09-15
Materials and Methods	Applicant's version is acceptable.
Results and discussion	*4.1 Clinical signs:* These symptoms disappeared 2 to 3 days earlier than in orally dosed animals.
Conclusion	Applicant's version is adopted.
Reliability	2
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_11/01-1: Effects data

Dose (mg/kg bw)	Number: dead/symptoms/in group	Time of death (range), h	Observations
0	0/10/10		All animals including controls made sounds of pain and arched their backs immediately after application.
0.5	0/15/15		
1	0/30/30		
10	0/30/30		Starting about 10-60 minutes post-exposure rats displayed restlessness, salivation and hypermotility. Breathing rate was reduced. After 24 -48 hours salivation and hyperkinesis resolved, and animals became apathetic and developed ataxia of the hind limbs and reduced sensitive. Reduced breathing rate and uncoordinated ataxic movements resolved in 3-4 days and apathy cleared in 4-7 days
25	0/15/15		
30	2/15/15	6-24	
50	8/30/30	3-24	
100	19/30/30	3-24	
150	24/30/30	3-48	
250	27/30/30	3-24	
500	15/15/15	6-72	

Document IIIA/ Section A6.11/02 — Studies on Other Routes of Administration

Acute subcutaneous toxicity in the mouse

BPD Data set IIIA/ Annex Point III-0§

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1980). FCR 1272 Acute toxicity studies. [redacted] Bayer AG Report No.: 8800 BES study No.: M-038979-01-1 Report date: 7 January 1980 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience	
1.2.2	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, GLP was not compulsory at the time the study was performed (as study started before June 30 1988)	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
1.1	**Test material**	FCR 1272 (cyfluthrin) Cyclopropane carboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl, cyano (4-fluoro-3-phenoxyphenyl) methyl ester	
3.1.1	Lot/Batch number	Batch No. 16001/79, Lo-Nr. 2151	
3.1.2	Specification	Not given	
3.1.2.1	Description	Not given	
3.1.2.2	Purity	83.6%	
3.1.2.3	Stability	Not specified	
3.2	**Test Animals**		
3.2.1	Species	Mouse	
3.2.2	Strain	[redacted]	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male and female	
3.2.5	Age/weight at study initiation	Approximately 18 to 25 g	
3.2.6	Number of animals per group	15/sex/group	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	**Subcutaneous**	
3.3.1	Post-exposure period	14 days	

Document IIIA/ Section A6.11/02 — **Studies on Other Routes of Administration**

Acute subcutaneous toxicity in the mouse

BPD Data set IIIA/ Annex Point III-0§

3.3.2	Concentration	10, 50, 100, 500, 1000, 2500 mg/kg bw
3.3.3	Vehicle	Lutrol
3.3.4	Total volume applied	5 or 10 ml/kg body weight in the dorsocaudal region of the scapulae
3.3.5	Controls	None
3.4	**Examinations**	Clinical observations, gross pathology
3.5	**Method of determination of LD_{50}**	Probit-analysis. (Fink and Hund, Arzneimittelforschung 15, 624, 1965)
3.6	**Further remarks**	None

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	No mortality occurred at any dose level. At dose levels of 50 mg/kg and above, mice showed similar symptoms to oral exposure, i.e., mice displayed restlessness, hypermotility, dyspnoea, uncoordinated and sometimes ataxic movements, and apathy. Dyspnoea and uncoordinated movements cleared after 1-3 days and apathy after 4-6 days. See table 6.11/02-1
4.2	**Pathology**	No pathology reported.
4.3	**Other**	None
4.4	**LD_{50}**	Males and females: > 2500 mg/kg bw

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Groups of 15 [redacted] mice/sex/group weighing 18 to 25 grams received a single subcutaneous dose of cyfluthrin (batch no: 16001/79, purity: 83.6%,) at doses of 10, 50, 100, 500, 1000, 2500 mg/kg bw in Lutrol. Animals were observed for 14 days for clinical signs and autopsied at sacrifice. Statistical analysis method: Probit-analysis.
5.2	**Results and discussion**	Clinical signs corresponding to those after oral administration; on the whole a better tolerability, no mortalities. The NOEL was estimated to be 10 mg/kg bw. The LD_{50} for male and female mice was in excess of 2500 mg/kg bw.
5.3	**Conclusion**	Cyfluthrin has a low toxicity via subcutaneous administration. The better tolerability can be explained by a poor or delayed resorption of the substance from the subcutaneous connective tissue.
5.3.1	Reliability	2
5.3.2	Deficiencies	Not guideline

Document IIIA/ Section A6.11/02

Studies on Other Routes of Administration

Acute subcutaneous toxicity in the mouse

BPD Data set IIIA/ Annex Point III-0§

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-09-15
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted
Reliability	2
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_11/02-1: Effects data

Dose, (mg/kg bw)	Number: dead/symptoms/in group	Time of death (range), h	Observations
10	0/0/30	n/a	-
30	0/30/30	n/a	Mice displayed restlessness, hypermotility. dyspnoea, uncoordinated and sometimes ataxic movements, and apathy. Dyspnoea and uncoordinated movements cleared after 1-3 days and apathy after 4-6 days.
100	0/30/30	n/a	
500	0/30/30	n/a	
1000	0/30/30	n/a	
2500	0/30/30	n/a	

Document IIIA/ Section A6.12.1/01 Human Case Report - Occupational medical experiences

BPD Data Set IIA/ Annex Point VI.6.9.1

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2003). Occupational medical experiences with cyfluthrin. BES Ref: M-106507-01-1 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2	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 (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Substance**	Cyfluthrin
3.2	**Persons exposed**	
3.2.1	Sex	Not stated
3.2.2	Age/weight	Not stated
3.2.3	Known Diseases	No data presented
3.2.4	Number of persons	100 employees handling product
3.2.5	Other information	Personal safety measures are full mask with filter ABEK-P3, protective gloves for chemicals, chemical-resistant suit.
3.3	**Exposure**	Inhalation and Dermal
3.3.1	Reason of exposure	Occupational
3.3.2	Frequency of exposure	Occupational exposure
3.3.3	Overall time period of exposure	Production period 2000 – 2002
3.3.4	Duration of single exposure	Not relevant
3.3.5	Exposure concentration/dose	Not available
3.3.6	Other information	62.000 kg a.i. used

Document IIIA/ Section A6.12.1/01 — Human Case Report - Occupational medical experiences

BPD Data Set IIA/ Annex Point VI.6.9.1

3.4	**Examinations**	Occupational medical surveillance of workers exposed to cyfluthrin, performed annually on a routine basis, including: Full physical examination with orientating neurological status, skin status, BSR, differential blood count, AST, ALT y-GT, glucose, creatinine, cholesterol, urine status, audiometry, vision testing, lung function, ergometry, chest X-ray, sonography.
3.5	**Treatment**	Not applicable
3.6	**Remarks**	None
		4 RESULTS
4.1	**Clinical Signs**	In accidental exposures, 5 workers suffered from parethesia of the exposed skin without any other symptoms or sequela.
4.2	**Results of examinations**	Routine medical examination did not reveal any unwanted effects in non-accidentally exposed workers.
4.3	**Effectivity of medical treatment**	Not applicable
4.4	**Outcome**	Not applicable
4.5	**Other**	Refer to 5.2 for a summary of the results.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Workers exposed to cyfluthrin have routine annual medical exams, which include the following testing: neurological status, skin status, bSR, differential blood count, AST, ALT y-GT, glucose, creatinine, cholesterol, urine status, audiometry, vision testing, lung function, ergometry, chest X-ray, sonography.
5.2	**Results and discussion**	Routine medical examination did not reveal any unwanted effects in non-accidentally exposed workers. Accidentally exposed workers suffered from paresthesia of exposed skin.
5.3	**Conclusion**	Routine medical examination did not reveal any unwanted effects in non-accidentally exposed workers. Accidentally exposed workers suffered from paresthesia of exposed skin.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-09-15
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.

Document IIIA/ Section A6.12.1/01 Human Case Report - Occupational medical experiences

BPD Data Set IIA/ Annex Point VI.6.9.1

Conclusion	Applicant's version is adopted.
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.12.1/02 — Human Case Report - Occupational medical experiences

BPD Data Set IIA/ Annex Point VI.6.9.1

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2005). Occupational medical experiences with cyfluthrin., Bayer Industry Services. BES Ref: M-257642-01-1 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2	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 (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Substance**	Cyfluthrin
3.2	**Persons exposed**	
3.2.1	Sex	Not stated
3.2.2	Age/weight	Not stated
3.2.3	Known Diseases	No data presented
3.2.4	Number of persons	10 employees handling product
3.2.5	Other information	Personal safety measures are full mask with filter ABEK-P3, protective gloves for chemicals, chemical-resistant suit
3.3	**Exposure**	Inhalation and Dermal
3.3.1	Reason of exposure	Occupational
3.3.2	Frequency of exposure	Multiple
3.3.3	Overall time period of exposure	Production period : 9.3.-10.3.2004, 29.4-30.4.2004, 14.7-20.7.2004,
3.3.4	Duration of single exposure	Not relevant
3.3.5	Exposure concentration/dose	Not available
3.3.6	Other information	4227 kg of a.i. used

Document IIIA/ Section A6.12.1/02 — Human Case Report - Occupational medical experiences

BPD Data Set IIA/ Annex Point VI.6.9.1

3.4	**Examinations**	Occupational medical surveillance of workers exposed to cyfluthrin, performed annually on a routine basis, including: full physical examination with orientating neurological status, skin status, BSR, differential blood count, AST, ALT y-GT, glucose, creatinine, cholesterol, urine status, audiometry, vision testing, lung function, ecg/ergometry, chest X-ray, sonography.
3.5	**Treatment**	Not applicable
3.6	**Remarks**	None
		4 RESULTS
4.1	**Clinical Signs**	None
4.2	**Results of examinations**	Routine medical examination did not reveal any unwanted effects in non-accidentally exposed workers.
4.3	**Effectivity of medical treatment**	Not applicable
4.4	**Outcome**	Not applicable
4.5	**Other**	Refer to 5.2 for a summary of the results.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Workers exposed to cyfluthrin have routine annual medical exams, which include the following testing: neurological status, skin status, BSR, differential blood count, AST, ALT y-GT, glucose, creatinine, cholesterol, urine status, audiometry, vision testing, lung function, ecg/ergometry, chest X-ray, sonography.
5.2	**Results and discussion**	Routine medical examination did not reveal any unwanted effects in non-accidentally exposed workers
5.3	**Conclusion**	Routine medical examination did not reveal any unwanted effects in non-accidentally exposed workers.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-09-15
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Remarks	-

Document IIIA/ Section A6.12.1/02 — Human Case Report - Occupational medical experiences

BPD Data Set IIA/ Annex Point VI.6.9.1

	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.12.1/03 — Human Case Report - Occupational medical experiences

BPD Data Set IIA/ Annex Point VI.6.9.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2005). Occupational medical experiences with cyfluthrin. BES Ref: M-267221-01-1 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	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 (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	Cyfluthrin	
3.2	**Persons exposed**		
3.2.1	Sex	Not stated	
3.2.2	Age/weight	Not stated	
3.2.3	Known Diseases	No data presented	
3.2.4	Number of persons	4 employees handling product	
3.2.5	Other information	Personal safety measures are hand gloves, safety goggles safety shoes, Facemask with breathing Air/ face shied.	
3.3	**Exposure**	Inhalation and Dermal	
3.3.1	Reason of exposure	Occupational	
3.3.2	Frequency of exposure	Occupational exposure	
3.3.3	Overall time period of exposure	Production period February-2005 to November –2005 [redacted]	
3.3.4	Duration of single exposure	Not relevant	
3.3.5	Exposure concentration/dose	Not available	
3.3.6	Other information	215915 Kg a.i produced	
3.4	**Examinations**	Occupational medical surveillance of workers exposed to cyfluthrin, performed every three months the first year: Laboratory examinations : Blood picture, y-GT, urine Technical examinations : Lung Function Test	
3.5	**Treatment**	Not applicable	

Document IIIA/ Section A6.12.1/03 — Human Case Report - Occupational medical experiences

BPD Data Set IIA/ Annex Point VI.6.9.1

3.6	**Remarks**	None	
		4 RESULTS	
4.1	**Clinical Signs**	No accidental exposure.	
4.2	**Results of examinations**	During the production period February 2005 to November 2005 no accidents with Cyfluthrin occurred with workers, and no consultations of the Medical Department due to work or contact with Cyfluthrin were required.	
4.3	**Effectivity of medical treatment**	Not applicable	
4.4	**Outcome**	Not applicable	
4.5	**Other**	Refer to 5.2 for a summary of the results.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	X
5.1	**Materials and methods**	Occupational medical surveillance of workers exposed to Cyfluthrin, is performed quarterly. The examinations included the above laboratory parameters and clinical and technical examinations: Laboratory examinations : Blood picture, y-GT, urine Technical examinations : Lung Function Test	X
5.2	**Results and discussion**	Occupational medical surveillance of workers exposed to Cyfluthrin, did not reveal any unwanted effects in the workers.	X
5.3	**Conclusion**	During the cyfluthrin production period February 2005 to November 2005 [redacted] no accidents with Cyfluthrin occurred in the workers, and no consultations of the Medical Department due to work or contact with Cyfluthrin were required.	X

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007-02-26
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Remarks	Only blood picture, Gamma-GT, urine, and Lung Function Test were examined every three month. Other parameters are not reported (cp. A6.12.1/01, A6.12.1/02).
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*

Document IIIA/ Section A6.12.1/03 — Human Case Report - Occupational medical experiences

BPD Data Set IIA/ Annex Point VI.6.9.1

Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.12.1/04 — Human Case Report - Occupational medical experiences

BPD Data Set IIA/ Annex Point VI.6.9.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2006). Occupational medical experiences with Solfac® EW 050. BES Ref: M-267224-01-1 Report date: 23 January 2006 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	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 (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	Solfac® EW 050	
3.2	**Persons exposed**		
3.2.1	Sex	Not stated	
3.2.2	Age/weight	Not stated	
3.2.3	Known Diseases	No data presented	
3.2.4	Number of persons	6 different employees: 2 in formulation step 4 in packaging	
3.2.5	Other information	Personal safety measures for the formulation are solvent-resistant nitrile gloves, safety glasses with side-shields, half mask a1P2 filter, usual working clothes. For the packaging step, only working clothes are worn but in case of accident the same PPE as the one used in formulation are worm.	
3.3	**Exposure**	Inhalation and Dermal	
3.3.1	Reason of exposure	Occupational	
3.3.2	Frequency of exposure	Occupational exposure	
3.3.3	Overall time period of exposure	June and November 2005	
3.3.4	Duration of single exposure	Not given	
3.3.5	Exposure concentration/dose	Not available	
3.3.6	Other information	4400 L produced in 2005	

Document IIIA/ Section A6.12.1/04 — **Human Case Report - Occupational medical experiences**

BPD Data Set IIA/ Annex Point VI.6.9.1

3.4	**Examinations**	Occupational medical surveillance of workers exposed to cyfluthrin, performed yearly of the whole workers involved in the formulation production including clinical and neurological examination: Laboratory examinations : Blood count, liver enzymes, creatinine Technical examinations : Spirometry
3.5	**Treatment**	Not applicable
3.6	**Remarks**	None

4 RESULTS

4.1	**Clinical Signs**	No accidental exposure.
4.2	**Results of examinations**	Occupational medical surveillance of workers exposed to Solfac® EW 050, performed yearly on a routine basis, did not reveal any unwanted effects in workers. The examinations included the laboratory parameters and clinical and technical examinations. Such as Laboratory examinations : Blood count, liver enzymes, creatinine Technical examinations : Spirometry During the production period(s) no accidents with Solfac® EW 50 occurred in the worker population, and no consultations of the Medical Department due to work or contact with Solfac® EW 050 were required.
4.3	**Effectivity of medical treatment**	Not applicable
4.4	**Outcome**	Not applicable
4.5	**Other**	Refer to A12 for a summary of the results.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Occupational medical surveillance of workers exposed to cyfluthrin, performed yearly of the whole workers involved in the formulation production including clinical and neurological examination: Laboratory examinations : Blood count, liver enzymes, creatinine Technical examinations : Spirometry
5.2	**Results and discussion**	Occupational medical surveillance of workers exposed to Solfac® EW 050, performed yearly on a routine basis, did not reveal any unwanted effects in workers
5.3	**Conclusion**	During the production period(s) no accidents with Solfac® EW 050 occurred in the worker population, and no consultations of the Medical Department due to work or contact with Solfac® EW 050 were required

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-09-15
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.12.2.02 — Direct observation, e.g. clinical cases, poisoning incidents if available

BPD Data Set IIA/ Annex Point VI.6.9.1

Official use only

1 REFERENCE

1.1	**Reference**	Das, R. et al., 2006. Worker Illness Related to Ground Application of Pesticide – Kern County, California, 2005. MMWR, CDC, USA 55(17):486-488
1.2	**Data protection**	No
1.2.1	Data owner	Published data
1.2.2	Criteria for data protection	No data protection claimed

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Substance**	Cyfluthrin (+ spinosad + petroleum oil)
3.2	**Persons exposed**	
3.2.1	Sex	Males and females
3.2.2	Age/weight	21-61 years
3.2.3	Known Diseases	Not reported
3.2.4	Number of persons	27 (4 M + 23 F)
3.2.5	Other information	None
3.3	**Exposure**	
3.3.1	Reason of exposure	Farmworkers exposed to cyfluthrin drift from a neighbouring field
3.3.2	Frequency of exposure	Single
3.3.3	Duration of single exposure	Approx. 1 h
3.3.4	Exposure concentration/dose	Not measurable on clothes or foliage.
3.3.5	Other information	Not reported
3.4	**Examinations**	Not reported
3.5	**Treatment**	Decontamination
3.6	**Remarks**	None

Document IIIA/ Section A6.12.2.02 — Direct observation, e.g. clinical cases, poisoning incidents if available

BPD Data Set IIA/ Annex Point VI.6.9.1

		4 RESULTS
4.1	**Clinical Signs**	Headache (96 %), nausea (89 %), respiratory symptoms (89 %), eye irritation/tearing (85 %), muscle weakness (79 %), anxiety (67 %), abdominal pain (52 %), anorexia (59 %), vomiting (26 %), confusion (59 %), dizziness (19 %), skin irritation (22 %) and skin itching (19 %). After evaluation in the emergency department all 27 farmworkers were discharged home.
4.2	**Effectivity of medical treatment**	Not reported
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	This report from the CDC focuses on the symptoms of 27 farmworkers exposed to cyfluthrin drifted from pesticide spraying on a neighbouring field.
5.2	**Results and discussion**	Onset of the symptoms was minutes after pesticide spraying. Symptoms were reported from 24 out of 27 exposed workers. Most commonly reported were headache (96 %), nausea (89 %), eye irritation and tearing (85 %), respiratory symptoms (89 %) like respiratory irritation, cough and shortness of breath, muscle weakness (70 %) and anxiety (67 %).
5.3	**Conclusion**	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-10-18
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.12.2 — Direct observation, e.g. clinical cases, poisoning incidents if available

BPD Data Set IIA/ Annex Point VI.6.9.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	He, F.S. et al (1989) Clinical Manifestations and Diagnosis of Acute Pyrethroid Poisoning Institute of Occupational Medicine, People's Republic of China Arch. Toxicol. (1989) 63; 54-58. 1989 BES Ref : : M-048869-01-1 Published	
1.2	**Data protection**	No	
1.2.1	Data owner	Published data	
1.2.2	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	Pyrethroids (deltamethrin, Fenvalerate, cypermethrin, others)	
3.2	**Persons exposed**		
3.2.1	Sex	Males and females (exact numbers not specified)	
3.2.2	Age/weight	Occupational exposure: 20 – 55 years; Accidental exposure: 1.5 – 82 years	
3.2.3	Known Diseases	Not reported	
3.2.4	Number of persons	Occupational: 229; Accidental: 344	
3.2.5	Other information	None	
3.3	**Exposure**		
3.3.1	Reason of exposure	Mishandling during agricultural use, accidental poisoning (mostly by ingestion).	
3.3.2	Frequency of exposure	Not reported	
3.3.3	Overall time period of exposure	Not reported	
3.3.4	Duration of single exposure	Not reported	
3.3.5	Exposure concentration/dose	Not reported	
3.3.6	Other information	-	
3.4	**Examinations**	-	
3.5	**Treatment**	Treatment was of a symptomatic and supportive nature (gastric lavage, atropine for salivation and pulmonary oedema, diazepam, baclofen, phenobarbital, chlorpromazine, phenytoin).	

Document IIIA/ Section A6.12.2 — Direct observation, e.g. clinical cases, poisoning incidents if available

BPD Data Set IIA/ Annex Point VI.6.9.1

3.6	**Remarks**	None

4 RESULTS

4.1	**Clinical Signs**	On occupational exposure (229 cases) the first signs, which set in after 4 -6 h, were burning, pruritus or tingling. The principal signs after ingestion (a frequent route of exposure in the 344 cases of accidental intoxication) were of a gastrointestinal nature (abdominal pain, nausea, vomiting within 10 min to 1 h), no dermal manifestations being recorded. Systemic symptoms included dizziness, headache, nausea, inappetence and fatigue. Severe cases were characterised by coarse twitching of the extremities, which correlated with repetitive discharges in the electromyogramme. Clouding of consciousness and convulsions (lasting between 30 sec and 2 min and occurring 10-30 times per day) were recorded in a few cases.
4.2	**Effectivity of medical treatment**	Treatment was of a symptomatic and supportive nature (gastric lavage, atropine for salivation and pulmonary oedema, diazepam, baclofen, phenobarbital, chlorpromazine, phenytoin). In all cases complete recovery occurred within 2-3 weeks, though in the majority of cases it took just 1-6 days. No late damage was observed. In all, 7 cases (2 x occupational exposure to deltamethrin, 2 x ingestion of fenvalerate, 1 x pulmonary oedema, 1 x mistaken diagnosis, 1 x erroneous treatment) had a fatal outcome.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	A report from China describes a series of 573 cases of intoxication with α-cyano-pyrethroids (deltamethrin, fenvalerate and cypermethrin). On occupational exposure (229 cases) the first signs, which set in after 4-6 h, were burning, pruritus or tingling. The principal signs after ingestion (a frequent route of exposure in the 344 cases of accidental intoxication) were of a gastrointestinal nature (abdominal pain, nausea, vomiting within 10 min to 1 h), no dermal manifestations being recorded. Systemic symptoms included dizziness, headache, nausea, inappetence and fatigue. Severe cases were characterised by coarse twitching of the extremities, which correlated with repetitive discharges in the electromyogramme. Clouding of consciousness and convulsions (lasting between 30 sec and 2 min and occurring 10-30 times per day) were recorded in a few cases. Treatment was of a symptomatic and supportive nature (gastric lavage, atropine for salivation and pulmonary oedema, diazepam, baclofen, phenobarbital, chlorpromazine, phenytoin). In all cases complete recovery occurred within 2-3 weeks, though in the majority of cases it took just 1-6 days. No late damage was observed. In all, 7 cases (2 x occupational exposure to deltamethrin, 2 x ingestion of fenvalerate, 1 x pulmonary oedema, 1 x mistaken diagnosis, 1 x erroneous treatment) had a fatal outcome
5.2	**Results and discussion**	
5.3	**Conclusion**	

Document IIIA/ Section A6.12.2 — Direct observation, e.g. clinical cases, poisoning incidents if available

BPD Data Set IIA/ Annex Point VI.6.9.1

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-09-18
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

This document has been prepared by the competent authority and does not necessarily represent the participant's opinion.

Section A6.12.3 **Human Case Report**

Annex Point IIA6.9.3 *Health records, both from industry and other available sources*

Official use only

1 REFERENCE

1.1 Reference

B. Wieseler, K-H. Kuhn, G. Leng and H. Idel carried out a study about "Effects of Pyrethroid Insecticides on Pest Control Operators published in: Bull. Environ. Contam. Toxicol. (1998)60:837-844.

1.2 Data protection

No, published

2 GUIDELINES AND QUALITY ASSURANCE

Not applicable

3 MATERIALS AND METHODS

The objective of this study was to compare the frequency of complains reported by Pest Control Operators exposed to pyrethroids including 16 persons exposed to cyfluthrin with unexposed subjects. To estimate any ill effects medical examinations as well as complete clinical laboratory analysis were performed.

4 RESULTS

No correlation between reported symptoms and blood levels of cyfluthrin or total amount of metabolites was observed.

5 AUTHORITIE'S SUMMARY AND CONCLUSION

5.1 Materials and methods

See 2

5.2 Conclusion

No correlation between reported symptoms and blood levels of cyfluthrin or total amount of metabolites was observed.

Section A6.12.4/01 Epidemiological studies on the general population

BPD Data set IIA/annex point IIA6.9.4

			Official use only
		1 REFERENCE	
1.1	**Reference**	Leng, G. *et al* (2003); Pyrethroids used indoors – Biological monitoring of exposure to pyrethroids following an indoor pest control operation.; International Journal of Hygiene and Environmental Health 206, 1-8 (2003) BES Ref : M-258943-01-1 Study conducted at the Fraunhofer Institute of Toxicology and Aerosol Research, Hanover, Germany between 1996 and 1999. Published paper	X
1.2	**Data protection**	No	
1.2.1	Data owner	n.a.	
1.2.2	Companies with letter of access	n.a.	
1.2.3	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
		Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Cyfluthrin (Solfac EW50®), permethrin (KO-Konzentrat 0.4% ®), cypermethrin (Microcip ®) and deltamethrin (Detmol-delta ®).	
3.1.1	Lot/Batch number		
3.1.2	Specification		
3.1.2.1	Description		
3.1.2.2	Purity		
3.1.2.3	Stability		
3.2	**Type of study**	Prospective	
3.3	**Method of data collection**	Biological monitoring after cyfluthrin application	
3.4	**Test Persons / Study Population**		
3.4.1	Selection criteria	Persons with diabetes mellitus, renal deficiency, auto immune diseases, neurological or psychiatric disorders were excluded from the study as well as subjects where alcoholism or drug consumption was assumed. Another exclusion factor was a history of Pest control Operator during the last 6 months before the study. Subjects were also excluded when a second PCO with pyrethroids was performed during the study.	

Section A6.12.4/01 Epidemiological studies on the general population

BPD Data set IIA/annex point IIA6.9.4

3.4.2	Number of test persons per group/cohort size	61 volunteers
3.4.3	Sex	40 men, 21 women
3.4.4	Age	Average of 37.8 years
3.4.5	Diseases	See Point 3.4.1
3.4.6	Smoking status	Not known
3.5	**Controls**	No
3.6	**Administration/ Exposure**	
3.6.1	Exposure Route	Inhalation/Dermal
3.6.2	Exposure Situation	Private home and work place (bakery, restaurant) after a PCO treatment for cockroach control. The duration of action of the products is about 4 hours. During this time, the participants were not allowed to be present in the rooms. Thereafter, the rooms were ventilated for 4 hours. The participants therefore entered the rooms approx 8 hours after the PCO.
3.6.3	Exposure concentration(s)	House dust and airborne particulate matter was sampled before PCO and one day, 4 to 6 months as well as 10 to 12 months after the PCO to be analyzed at the Fraunhofer Institute of Toxicology and Aerosol Research in Hannover, Germany (Berger-Preiβ et al., 2002).
3.6.4	Method(s) to determine exposure	Blood and urine analysis
3.6.5	Postexposure period	10-12 months
3.7	**Examinations**	
3.7.1	Type of disease	Not applicable
3.7.2	Parameters	Each medical examination consisted of a general medical and a neurophysiological examination accompanied by a questionnaire-based interview. In addition, blood and urine were sampled for determination of general clinical and immunological parameters as well as for performing biological monitoring
3.8	**Further remarks**	

Section A6.12.4/01 Epidemiological studies on the general population

BPD Data set IIA/annex point IIA6.9.4

4 RESULTS AND DISCUSSION

4.1	**Exposure**	
4.1.1.1	Number of measurements	5 (T1: before the PCO; T2: 1 day after the PCO; T3: 3 days after te PCO; T4: 4-6 months after the PCO; T5: 10-12 months after the PCO)
4.1.1.2	Average concentrations	See Table A6.12.4/01-1 for concentrations of metabolites in urine. No metabolites were found in plasma (LOD 5 µg/l).
4.1.1.3	Standard deviation	-
4.1.1.4	Date(s) of measurement(s)	T1: before the PCO; T2: 1 day after the PCO; T3: 3 days after te PCO; T4: 4-6 months after the PCO; T5: 10-12 months after the PCO
4.1.2	Other	Cyfluthrin metabolite concentrations (µg/l) in urine from pest control operators, see Table A6.12.4/01-1
4.2	**Number of cases for each disease / parameter under consideration**	Not applicable
4.3	**SMR (Standard mortality ratio), RR (relative risk), OR (Odds ratio)**	Not applicable
4.4	**Other Observations**	None

5 APPLICANT'S SUMMARY AND CONCLUSION

Section A6.12.4/01 Epidemiological studies on the general population

BPD Data set IIA/annex point IIA6.9.4

5.1	**Materials and methods**	The study objective was to provide an objective evaluation of possible human health effects caused by pyrethroids using a prospective epidemiological approach using indoor and biological monitoring combined with an assessment of the individual health status. The study was conducted between 1996 and 1999 and included 5 medical examinations performed at the locality of the pest control operation (PCO). Examinations were conducted before the PCO (T1), one day (T2), 3 days (T3), 4 to 6 months (T4) and 10 to 12 months (T5) after the PCO. Each medical examination consisted of a general medical and a neurophysiological examination accompanied by a questionnaire-based interview. In addition, blood and urine were sampled for determination of general clinical and immunological parameters as well as for performing biological monitoring. House dust and airbourne particulates were also samples before the PCO and at T2, T4 and T5. 61 volunteers (40 men and 21 women with a mean age of 37.8 yrs) were selected for participation in the study. Participants were exposed at their private homes (n=33) and at their work place (e.g. bakery or restaurant) (n=28). Forty subjects were exposed to cyfluthrin (Solfac EW50®), 9 to permethrin (KO-Konzentrat 0.4% ®), 7 to cypermethrin (Microcip ®) and 5 to deltamethrin (Detmol-delta ®). The duration of action of the products is about 4 hours. During this time, the participants were not allowed to be present in the rooms. Thereafter, the rooms were ventilated for 4 hours. The participants therefore entered the rooms approx 8 hours after the PCO. The levels of cyfluthrin in blood plasma were determined by GC-ECD. The respective metabolites cis- and trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (DCVA), cis-3-(2,2dibromovinyl)-2,2-dimethylcyclopropane carboxylic acid (DBCA), 3-phenoxybenzoic acid (3-PBA) and fluorophenoxybenzoic acid (FPBA) were measured in urine using GC-MS. The metabolite FPBA is specific for cyfluthrin, DBCA for deltamethrin, 3-PBA for permethrin, cypermethrin and deltamethrin, and cis/trans-DCAA for permethrin, cypermethrin and cyfluthrin. The ratio trans-DCVA:cisDCVA was calculated to investigate whether the majority of uptake was dermal (ratio ≤ 1) or inhalative/oral (ratio ≥ 1).	X

Section A6.12.4/01 Epidemiological studies on the general population

BPD Data set IIA/annex point IIA6.9.4

5.2 Results and discussion	As this submission is to support the Annex I listing of cyfluthrin (representative product, Solfac), only data relating to cyfluthrin have been presented from the paper. In all case the concentrations of cyfluthrin in plasma were below the determination limit of 5µg/l. Results from the analysis of urine for pyrethroid metabolites from time points T1 – T5 are presented in Table A6.12.4(01)-1. Before PCO (T1), samples revealed metabolite concentrations below the DL of 0.2 µg/l. At T2, the number of cases with detectable concentrations increased from 4 to 12 for cis-DCVA, from 2 to 18 for trans-DCVA and from 0 to 2 for FPBA. For cis-DCVA and trans-DCVA the number of cases with concentrations above DL decreased during the time course from T3 to T5 (also for FPBA but with a much lower number of cases above DL).	X
	The isomeric cis/trans-DCVA ratio indicated for 5 subjects there was a predominantly dermal uptake and for 134 subjects there was a predominantly inhalative/oral uptake. The route of uptake remained unchanged for the same persons during the study.	X
5.3 Conclusion	Based on the results of the present study it can be concluded that an appropriately performed pest control operation leads to a significantly increased pyrethroid metabolite concentration in the early phase (1 and 3 days) after pyrethroid application as compared to the pre-exposure values. In general, evaluated metabolite concentrations did not exceed values of published background levels.	X

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007-02-26
Materials and Methods	The study was performed at the Institute of Hygiene at the Heinrich-Heine-University Düsseldorf, FRG. Part of the study, published in another paper (Berger-Preiß et al., 2002) was analysed at the Fraunhofer Institute at Hanover. *5.1* The first paragraph should be supplemented with following sentence:The present study is focussed on the biological monitoring data. DCAA: DCCA (abbr. for the metabolite trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylix acid) DCVA: abbreviation in original publication and Dossier DocIIA-3 **DCCA** for the metabolite trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylix acid

Section A6.12.4/01 Epidemiological studies on the general population

BPD Data set IIA/annex point IIA6.9.4

Results and discussion	*5.2* DCVA is DCCA in the original paper. Before PCO (T1), samples revealed metabolite concentrations below the DL of 0.2 µg/l **urine**. The isomeric cis/trans-DCVA ratio indicated for 5 subjects there was a predominantly dermal uptake and for **13 subjects** there was a predominantly inhalative/oral uptake. The route of uptake remained unchanged for the same persons during the study. Table A6.12.4/01: Column T2, last line has to be corrected from 0 to **2** and the line before from 0,1 to **0,2.**
Conclusion	Applicant's version is adopted.
Remarks	This publication only presents biological monitoring data. Unfortunately the results of conducted air-monitoring and clinical examination are here not reported.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.12.4/01-1: Cyfluthrin metabolite concentrations (µg/l) in urine from pest control operators (PCO)

	T1	T2	T3	T4	T5
	Cis-DCVA				
Median	0.1	0.1	0.1	0.1	0.1
75th percentile	0.1	0.1	0.1	0.1	0.1
95th percentile	0.5	0.2	0.2	0.6	0.1
Max	1.2	12.8	5.2	1.0	0.7
Samples ≥ DL	4	12	9	7	1
	Trans-DCVA				
Median	0.1	0.1	0.1	0.1	0.1
75th percentile	0.1	0.2	0.1	0.1	0.1
95th percentile	0.1	0.5	0.4	1.5	1.3
Max	1.2	13.4	5.0	3.2	2.1
Samples ≥ DL	2	18	13	6	4

	FPBA				
Median	0.1	0.1	0.1	0.1	0.1
75th percentile	0.1	0.1	0.1	0.1	0.1
95th percentile	0.1	0.1	0.2	0.1	0.1
Max	0.1	0.1	0.3	0.2	0.1
Samples ≥ DL	0	0	3	1	0

DL = determination limit (5 µg/l)

CA:
Cis-DCCA
Trans-DCCA
DL: Detection limit 0.2 µg/l urine (5 µ/l: detection limit in plasma)

Section A6.12.4/02 Epidemiological studies on the general population

BPD Data set IIA/annex point IIA6.9.4

			Official use only
		1 REFERENCE	
1.1	**Reference**	Leng, G. *et al* (1996); Biological monitoring of pyrethroid metabolites in urine of pest control operators; Toxicology Letters **88** (1996) 215-220 BES Ref : M-074664-01-1 Published paper	
1.2	**Data protection**	No	
1.2.1	Data owner	n.a.	
1.2.2	Companies with letter of access	n.a.	
1.2.3	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
		Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Cyfluthrin, permethrin and cypermethrin containing pesticide formulations (identity and composition of formulations not provided).	
3.1.1	Lot/Batch number		
3.1.2	Specification		
3.1.2.1	Description		
3.1.2.2	Purity		
3.1.2.3	Stability		
3.2	**Type of study**	Prospective	
3.3	**Method of data collection**	Biological monitoring after cyfluthrin application	
3.4	**Test Persons / Study Population**		
3.4.1	Selection criteria	Not reported	
3.4.2	Number of test persons per group/cohort size	20 professional pest control operatives (PCO). Of these, 7 were exposed exclusively to cyfluthrin based formulations. 8 were exposed to organophosphates only, so served as control for the pyrethroid exposures.	
3.4.3	Sex	Male	
3.4.4	Age	Age range 27 – 58 yrs.	
3.4.5	Diseases	No data presented	
3.4.6	Smoking status	Not reported	
3.5	**Controls**	No	

Section A6.12.4/02 Epidemiological studies on the general population

BPD Data set IIA/annex point IIA6.9.4

3.6	**Administration/ Exposure**	
3.6.1	Exposure Route	Inhalation and dermal
3.6.2	Exposure Situation	Occupational exposure, one week of representative PCO use
3.6.3	Exposure concentration(s)	Not available. As professional operators were used in the study it can be assumed that operators followed the label recommendation for use of the pest control products. Operators using cyfluthrin based products wore single useable overalls and breathing masks (the specification of the breathing apparatus not stated).
3.6.4	Method(s) to determine exposure	Following the exposure period, samples of urine were collected (during this sample collection period, no additional exposure to pyrethroids occurred)
3.6.5	Postexposure period	
3.7	**Examinations**	
3.7.1	Type of disease	No medical examinations were conducted on the subjects prior to participation in the study. Previous exposure was assessed by questionnaire and interview. Over the previous 5 years, the operators had used pyrethroid-based products (mainly cyfluthrin, permethrin and cypermethrin) and also organophosphates.
3.7.2	Parameters	From each study participant spontaneous urine samples were collected (Monday-Friday) as well as 24 hour urine samples starting on the Friday evening. For one operator, urine was collected for 4 consecutive days in eight collection intervals of 12 hours.
3.8	**Further remarks**	The study objective was to development of a suitable biological monitoring program to determine exposure to pyrethroids.
	4	**RESULTS AND DISCUSSION**
4.1	**Exposure**	
4.1.1.1	Number of measurements	From each study participant spontaneous urine samples were collected (Monday-Friday), as well as 24 hour urine samples starting on the Friday evening. For one operator, urine was collected for 4 consecutive days in eight collection intervals of 12 hours.
4.1.1.2	Average concentrations	See Table A6.12.4/02-1
4.1.1.3	Standard deviation	none
4.1.1.4	Date(s) of measurement(s)	See 4.1.1.1
4.1.2	Other	none

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BPD Data set IIA/annex point IIA6.9.4

4.2	**Number of cases for each disease / parameter under consideration**	Not applicable
4.3	**SMR (Standard mortality ratio), RR (relative risk), OR (Odds ratio)**	Not applicable
4.4	**Other Observations**	None

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The aim of the study was to develop a method for monitoring the exposure of operators to pyrethroids following use representative of normal working practice.

The study was conducted in the region of Northrhine-Westphalia, Germany using a group of 20 male pest control operators (27 – 58 years old with 2 – 21 years experience). 12 operators were exposed to pyrethroids (7 to cyfluthrin only) and 8 to organophosphates. Previous experience and exposure to pyrethroids was assessed by questionnaire and interview. In the previous 5 years, the operators had been exposed to pyrethroids (mainly cyfluthrin, permethrin and cypermethrin) and also organophosphates.

Cyfluthrin pest control operators used personal protective equipment during the nebulising of cyfluthrin, specifically single useable overalls and breathing masks (the type and specification of the breathing apparatus was not specified).

From each study participant spontaneous urine samples were collected (Monday-Friday), as well as 24 hour urine samples starting on the Friday evening. For one operator, urine was collected for 4 consecutive days in eight collection intervals of 12 hours.

For quantification of pyrethroid metabolites, a subsample of the urine was evaporated to dryness and reconstituted in acidified methanol. The free and conjugated metabolites were converted to their corresponding esters prior to liquid-liquid extraction. After clean up by column chromatography, the metabolites were quantified by GC-MS using external calibration. The following metabolites were quantified: *cis*- and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (DCVA), 3-phenoxybenzoic acid (3-PBA) and fluorophenoxybenzoic acid (FPBA). The metabolite FPBA is specific for cyfluthrin, 3-PBA for permethrin and cypermethrin, and *cis/trans*-DCVA for permethrin, cypermethrin and cyfluthrin. The limits of determination were 0.5µg/l for *cis- and trans*-DCVA and 1 µg/l for 3-PBA and FPBA.

Creatinine in the urine was also measured to ensure that urine collection was complete.

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BPD Data set IIA/annex point IIA6.9.4

5.2	**Results and discussion**	As this submission is to support the Annex I listing of cyfluthrin, only data relating to cyfluthrin have been presented from the paper. For the 8 PCOs that were not exposed to pyrethroids during the week of investigation, the concentration of pyrethroid metabolites in urine samples were below the limit of determination. For operators exposed to cyfluthrin, in the first 12hr urine sample after exposure concentrations of 340 µg FPBA/g creatinine, 184 µg trans-DCVA/g creatinine and 53 µg *cis*-DCVA/g creatinine were determined. During the first day after exposure the highest amount of all metabolites were eliminated. FPBA could be measured up to 3.5 days after exposure and *cis and trans*-DCVA up to 1.5 days. After 3.5 days the concentration of FPBA was below the limit of determination, and after 1.5 days for *cis and trans*-DCVA. It should be noted that the concentrations of urinary pyrethroid metabolites varied among the PCOs. This is due to variation in the quantity of pyrethroid applied and application method varying between the operators.
5.3	**Conclusion**	DCVA isomers were detected in urine for 1.5 days after exposure. FPBA was excreted in urine for a period of 3.5 days and compared to DCVA isomers in a much higher quantity. The cyfluthrin-specific metabolite FPBA is considered to be a suitable indicator of a known cyfluthrin exposure.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007-02-26
Materials and Methods	DCVA is DCCA in the original paper. Acceptable
Results and discussion	Second paragraph has to be supplemented with: For PCOs exposed to pyrethroids it was demonstrated that pyrethroid metabolites could be detected in nine out of twelve 24 h urine samples. The concentrations of metabolites given as a sum of detected cis-/trans-DCCA-Me, 3-PBA-Me and FPBA-Me ranged between 20 and 277 µg/l urine. Third paragraph: For **one** operator exposed to cyfluthrin, in the first 12hr urine sample after exposure concentrations of 340 µg FPBA/g creatinine, 184 µg trans-DCVA/g creatinine and 53 µg *cis*-DCVA/g creatinine were determined. During the first day after exposure the highest amount of all metabolites were eliminated. Considering above-mentioned hints Applicant´s version is adopted.
Conclusion	Considering above-mentioned hints Applicant´s version is adopted.

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BPD Data set IIA/annex point IIA6.9.4

Remarks	Since it was the aim of this study to develop an analytical method for the determination of pyrethroid metabolites. Any clinical effects are not reported. For this reason this study is not really suitable for inclusion in Section A.6.12.4. The type of study is not prospective as mentioned in 3.2.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.12.4/02-1: Biological monitoring of 12 pest control, operators (PCOs) following exposure to products containing cyfluthrin

PCO No.	Previous pyrethroid exposure history (years)	Pyrethroid	Personal Protective Equipment (PPE)	Pyrethroid metabolites (µg/l 24hr urine)
1	2	Cyfluthrin	Overall + breathing mask	20
2	4	Cyfluthrin	Overall + breathing mask	50
3	10	Cyfluthrin	Overall + breathing mask	60
4	5	Cyfluthrin	Overall + breathing mask	30
5	3	Cyfluthrin	Overall + breathing mask	< LOQ
6	10	Cyfluthrin	Overall + breathing mask	< LOQ
7	10	Cyfluthrin	Overall + breathing mask	< LOQ
8	5	Cyfluthrin + permethrin	Overall + breathing mask	130

LOQ – Limit of quantification (determination) [0.5µg/l for *cis- and trans*-DCVA and 1 µg/l for 3-PBA and FPBA].

Section A6.12.4/03 Epidemiological studies on the general population

BPD Data set IIA/annex point IIA6.9.4

			Official use only
		1 REFERENCE	
1.1	**Reference**	Leng, G. *et al* (1997); Biological monitoring of pyrethroids in blood and pyrethroid metabolites in urine: applications and limitations The Science of the Total Environment (1997) **199.** 173-181. BES Ref : M-074666-01-1 published paper	
1.2	**Data protection**	No	
1.2.1	Data owner	n.a.	
1.2.2	Companies with letter of access	n.a.	
1.2.3	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
		Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Cyfluthrin, permethrin and cypermethrin containing pesticide formulations (identity and composition of formulations not provided).	
3.1.1	Lot/Batch number	Not reported	
3.1.2	Specification	Not reported	
3.1.2.1	Description	Not reported	
3.1.2.2	Purity	Not reported	
3.1.2.3	Stability	Not reported	
3.2	**Type of study**	Prospective	
3.3	**Method of data collection**	Biological monitoring after cyfluthrin application	
3.4	**Test Persons / Study Population**		
3.4.1	Selection criteria	Not reported	
3.4.2	Number of test persons per group/cohort size	30 professional pest control operatives (PCO).	
3.4.3	Sex	Male	
3.4.4	Age	Age range 22 – 58 yrs (8 months to 22 years of employment).	
3.4.5	Diseases	No data presented	
3.4.6	Smoking status	Not reported	
3.5	**Controls**	yes	

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3.5.1	Type of control	The control group was not occupationally exposed to pyrethroids.
3.5.2	Number of test persons per group/cohort size	40 subjects
3.5.3	Sex	20 male and 20 female
3.5.4	Age	22 – 60 years old
3.5.5	Diseases	No data presented
3.5.6	Smoking status	Not reported
3.6	**Administration/ Exposure**	
3.6.1	Exposure Route	Inhalation and Dermal
3.6.2	Exposure Situation	Occupational, one week of representative PCO use (The weekly working time of the PCOs ranged between 40 and 85 h) One healthy volunteer took a single oral dose at 0.03 mg/kg bw cyfluthrin. Metabolite concentrations were measured at 12 hour intervals for 2 days.
3.6.3	Exposure concentration(s)	Not available. As professional operators were used in the study it can be assumed that operators followed the label recommendation for use of the pest control products.
3.6.4	Method(s) to determine exposure	After exposure, 24-h urine samples were collected and 20 ml of blood was drawn.
3.6.5	Postexposure period	24h
3.7	**Examinations**	
3.7.1	Type of disease	No medical examinations were conducted on the subjects prior to participation in the study. Previous exposure was assessed by questionnaire.
3.7.2	Parameters	From each study participant 24 hr urine samples were collected over an exposure free period (volume and creatinine levels measured). Blood was also sampled 4-12 hours after the final exposure.
3.8	**Further remarks**	The study objective was to perform biological monitoring of subjects who are occupationally exposed to pyrethroids. Storage stability of pyrethroids in plasma and urine was examined. Urinary excretion rate of cyfluthrin metabolites in one male volunteer was examined

Section A6.12.4/03 Epidemiological studies on the general population

BPD Data set IIA/annex point IIA6.9.4

4 RESULTS AND DISCUSSION

4.1 Exposure

4.1.1.1	Number of measurements	From each study participant 24 hr urine samples were collected over the week end (exposure free period). Blood was also sampled 4-12 hours after the final exposure. Urine of non-exposed subjects were determined over 1 year (7 times on the whole) Urine of the healthy volunteer who took a single oral dose was sampled at 12 hour intervals for 2 days.
4.1.1.2	Average concentrations	Total metabolite concentration varied between < 0.5 and 277 µg/l urine, the median being 30 µg/l . The isomeric ratio (trans-DCVA/cis- DCVA) ranged from 1.5 to 3.2. In urine samples of 40 non-exposed subjects, the concentrations of metabolites were below the limit of detection (<0.5 µg/l). See Table A6.12.4/03-1
4.1.1.3	Standard deviation	none
4.1.1.4	Date(s) of measurement(s)	See 4.1.1.1
4.1.2	Other	Storage stability : In urine, the mean decrease in the concentrations of the metabolites *cis-/trans*-DCVA and FPBA was 11 ± 3%, which was within the between-run coefficient of variation (12 ± 4%). In plasma, the half life at 4ºC was 7 hours for cyfluthrin. The addition of formic acid to plasma at 4ºC did not improve storage stability. At -21ºC, the addition of formic acid enabled twice as much cyfluthrin to be recovered from the plasma samples compared to the samples without cholinesterase inhibition. Urinary excretion pattern : Following a single oral dose of cyfluthrin (2.6 mg) equivalent to 0.03 mg/kg bw/day, approximately 40% of the ingested dose was recovered in the urine. The mean half life time of the metabolites in urine was 6.44 ± 0.64 hr (*cis*-DCVA: 6.66 hr; *trans*-DCVA: 6.54 hr; FPBA: 6.13 hr), indicating that 94% of the metabolites were eliminated over the 48 hour period following 1st order kinetics.

4.2 Number of cases for each disease / parameter under consideration

4.3 SMR (Standard mortality ratio), RR (relative risk), OR (Odds ratio)

4.4 Other Observations

5 APPLICANT'S SUMMARY AND CONCLUSION

Section A6.12.4/03 Epidemiological studies on the general population

BPD Data set IIA/annex point IIA6.9.4

5.1 Materials and methods

The study was conducted in the region of Northrhine-Westphalia, Germany using a group of 30 male pest control operators (22 – 58 years old with 8 months to 22 years experience). 19 PCOs were exposed daily (Monday to Friday) to cyfluthrin, permethrin and cypermethrin. Seven PCOs were exposed to only 1 – 3 days and 4 were not exposed to pyrethroids at all.

A control group of 40 subjects (20 male and 20 female), 22 – 60 years old was also monitored for pyrethroid concentrations in blood and plasma (7 samples over 1 year).

Previous experience and exposure to pyrethroids was assessed by questionnaire.

At the end of the exposure period, 24 hour urine samples were collected (volume and creatinine levels measured). Blood was also sampled 4-12 hours after the final exposure.

For quantification of pyrethroid metabolites, a subsample of the urine was subjected to an acid-induced hydrolytic cleavage of the conjugates prior to liquid-liquid extraction. The metabolites were quantified by GC-MS using external and internal calibration. The following metabolites were quantified: *cis*- and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (DCVA), 3-phenoxybenzoic acid (3-PBA) and fluorophenoxybenzoic acid (FPBA). The metabolite FPBA is specific for cyfluthrin, 3-PBA for permethrin and cypermethrin, and *cis*/*trans*-DCVA for permethrin, cypermethrin and cyfluthrin. The limits of determination were 0.5µg/l for all metabolites. For plasma samples, the sample was subjected to liquid-liquid partition with analysis by GC-ECD. The limits of determination was 0.5µg/l

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5.2	**Results and discussion**	In urine from the 19 PCOs exposed daily to the pyrethroids cyfluthrin, permethrin and cypermethrin, total metabolite concentration varied between <0.5 µg/l and 277 µg/l (median 30 µg/l). The isomeric ratio (*trans*-DCVA:*cis*-DCVA) ranged from 1.5 to 3.2. In the urine from the 4 PCOs not exposed to pyrethroids and in the PCOs exposed to only 1-3 days (i.e. 1 PCO Monday-Wednesday, 2 PCOs Wednesday and Thursday, 3 PCOs one day only), metabolite concentrations were all <0.5 µg/l. Pyrethroid concentrations in plasma were <0.5 µg/l in all 30 cases (i.e. 19 PCOs exposed daily, 7 exposed for 1 – 3 days and 4 not exposed to pyrethroids). Pyrethroid concentration in urine and blood samples from the control group were below the limit of detection in all cases (blood: <5 µg/l; urine: <0.5 µg/l). Following a single oral dose of cyfluthrin (4.6 mg) equivalent to 0.03 mg/kg bw/day, approximately 40% of the ingested dose was recovered in the urine. The mean half life time of the metabolites in urine was 6.44 ± 0.64 hr (*cis*-DCVA: 6.66 hr; *trans*-DCVA: 6.54 hr; FPBA: 6.13 hr), indicating that 94% of the metabolites were eliminated over the 48 hour period following 1st order kinetics. An isomeric ratio of 2.3 for trans-DCVA:cis-DCVA was obtained. The total amount of FPBA was twice the total amount of cis/trans-DCVA. As no cis to trans conversion can be observed during acid hydrolysis and chromatography, a large excretion of trans-DCVA is a clear sign of significant oral/inhalative uptake. Therefore, the most likely exposure in this study was oral/inhalation.
5.3	**Conclusion**	This study demonstrates that the determination of cyfluthrin metabolites cis/trans-DCVA and FPBA in urine is suitable for biological monitoring of subjects who are occupationally exposed to cyfluthrin. Data obtained from the biological monitoring of 30 PCOs regularly exposed to cyfluthrin showed that pyrethroid metabolites were only found in the urine of the PCOs exposed daily before urine collection started. For PCOs non-exposed the day before urine collection started, no metabolites could be found.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-09-19
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Remarks	DCVA: DCCA originally in publication

Section A6.12.4/03 Epidemiological studies on the general population

BPD Data set IIA/annex point IIA6.9.4

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.12.4/03-1: Metabolite concentrations (*cis/trans*-DCVA, 3-PBA and FPBA) in urine of 19 pest control operators exposed daily (Monday-Friday) to the pyrethroids cyfluthrin, permethrin and cypermethrin

Total metabolite conc (µg/l 24 hr urine)	Frequency (absolute number of PCOs)
<0.5	3
0.5 – 10	0
10 – 20	3
20 – 30	6
30 – 40	1
40 – 50	2
50 – 60	2
>60	2

Document IIIA/ Section A6.12.4/04

BPD Data Set IIA/ Annex Point VI.6.9.4

Human Case Report

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1 REFERENCE

1.1 Reference

[redacted] (1998). Safety and Tolerability Study of FCR 1272 0.04 AE in Healthy Volunteers. [redacted]

Report-Number: 11590 BES Ref.: M-031568-01-1
Report date: 7 October 1998
Unpublished

1.2 Data protection Yes

1.2.1 Data owner: Bayer CropScience AG

1.2.2 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 The study was conducted in accordance with the provisions of the Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983) and Hong Kong (1989) revisions. The study was approved by an independent ethics review committee of Inveresk Research.

2.2 GLP Yes

2.3 Deviations None

3 MATERIALS AND METHODS

3.1 Substance Insecticide spray-can aerosol "FCR 1272 0.04 AE" (contains active ingredients 0.044 % (w/w) cyfluthrin and 0.22 % (w/w) piperonyl butoxide)

3.2 Persons exposed 10 healthy male volunteers aged 21 – 37 years.

3.2.1 Sex
3.2.2 Age/weight
3.2.3 Known Diseases
3.2.4 Number of persons
3.2.5 Other information

Group 1: 5 subjects

Group 2: 5 subjects

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3.3	**Exposure**	The study was designed as an open study. At the outset of the study 5 subjects were exposed to different concentrations of cyfluthrin for up to 1 h dependant upon tolerability, 4 h apart on the same day. The defined concentrations were < 0.1 mg cyfluthrin/m^3 air and 0.5-0.8 mg cyfluthrin/m^3 air respectively. The initial exposure concentration was not tolerated and the higher exposure concentration was then cancelled.
3.3.1	Reason for exposure	
3.3.2	Frequency of exposure	
3.3.3	Overall timeperiod of exposure	Laboratory analysis revealed that the initial actual concentration of the test substance had exceeded the defined concentration. The protocol was then amended to allow a further 5 subjects, at a later date, to be exposed to a lower concentration of < 0.075 mg cyfluthrin/m^3 air for up to 1 h dependent upon tolerability.
3.3.4	Duration of single exposure	
3.3.5	Exposure concentration/dose	On this occasion, to alleviate anxiety, the subjects were exposed to an atmosphere of placebo spray-can aerosol before the test substance.
3.3.6	Other information	
3.4	**Examinations**	The safety and tolerability of cyfluthrin 0.044% (w/w) was assessed by the measurement of vital signs, measurements of heart rate and blood pressure, clinical laboratory tests (haematology, clinical chemistry and urinalysis), examination of mucous membranes and reporting of adverse events. Plasma and urine sampling were performed for detection of metabolite levels for Group 1. Urine sampling only was performed for Group 2.
3.5	**Treatment**	Not applicable
3.6	**Remarks**	None

4 RESULTS

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4.1 Clinical Signs
4.2 Results of examinations
4.3 Effectivity of medical treatment
4.4 Outcome
4.5 Other

There were no clinically significant or drug related abnormalities in vital signs, ECGs or clinical laboratory tests after either exposure session.

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For the first exposure session the corrected initial actual concentration for the subjects was ca. 0.2 mg cyfluthrin/m^3 air. The corrected initial actual concentration for one subject was ca. 0.09 mg cyfluthrin/m^3 air. For the second exposure session the corrected initial actual concentration for the subjects was ca. 0.1 mg cyfluthrin/m^3.

Only 2 of the subjects in Group 1 tolerated the first exposure session for the defined period of 1 h. Four of the subjects experienced subjective adverse events (symptoms) which were considered to be "definitely" related to the test substance. The adverse events reflected irritation of the mucous membranes of the nose (4 instances), upper respiratory tract (coughing, 2 instances), throat and eyes (single instances). These adverse events were all mild or moderate in severity and resolved within 1 h without treatment. Three subjects had no symptoms and one subject who was exposed to an initial concentration of ca. 0.09 cyfluthrin/m^3, had mild hyperaemia of the nasal mucosa on examination of mucous membranes following exposure. X

All subjects in Group 2 tolerated the 20 minutes exposure to the placebo spray-can aerosol on the evening before exposure to the test substance and no adverse events were reported. This exposure session was designed to alleviate anxiety which may have been a contributing factor in certain subjects leaving the atmosphere early during the first exposure session. The subjects all tolerated the second exposure session for the defined period of 1 h. Four of the subjects experienced subjective adverse events which were considered to be "definitely" related to the test substance. The adverse events reflected irritation of the mucous membranes of the nose (3 instances) and throat (2 instances). They were mild in severity and resolved within 1 h without treatment. A single subject had mild hyperaemia of the nasal mucosa on examination of the mucous membranes following exposure. X

The subjective adverse events were all expected side effects of the test substance with reference to pre-clinical studies and observations in agrochemical workers and reflected irritation of the mucous membranes of the nose, throat, upper respiratory tract and eyes in order of frequency. They were all self-limiting and resolved within minutes after cessation of exposure. The objective evidence of hyperaemia of the nasal mucosa was very marginal and transient resolving within 1 h. There was no evidence of changes in the mucous membranes of the eyes, mouth or throat.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

10 healthy male volunteers aged between 21 and 37 years were exposed to different concentrations of cyfluthrin for up to 1 hour depending on tolerability. The study objective was to provide an objective evaluation of possible human health effects caused by cyfluthrin.

The safety and tolerability of cyfluthrin 0.04 AE was assessed by the

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BPD Data Set IIA/ Annex Point VI.6.9.4

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		measurement of vital signs, ECGs, clinical laboratory tests, examination of mucous membranes and reporting of adverse events.
5.2	**Results and discussion**	Three subjects from group 1 (0.2 mg/m3 air) had objective evidence of mild hyperemia of the nasal mucosa. All subjects in Group 2 (0.1 mg/m3 air) tolerated a 20 min exposure to placebo spray-can aerosol to alleviate anxiety before the second exposure session and no adverse events were reported. All subjects tolerated the second exposure session for 1h and 5 adverse events that were considered to be "definitely" related to the test substance were reported. The adverse events were all expected side effects of the test substance with reference to preclinical studies and observations in agrochemical workers and reflected irritation of the mucous membranes of the nose, throat, upper respiratory tract and eyes in order of frequency. The adverse events were all self-limiting and resolved within minutes after cessation of exposure.
5.3	**Conclusion**	An initial actual concentration of ca. 0.1 mg cyfluthrin/m^3 air appears to be in the range of an irritant threshold concentration for humans since 4 (of 5) subjects showed transient signs of irritation of the mucous membranes and symptoms experienced were transient and self-limiting. Slightly higher concentrations caused similar effects of greater intensity in all subjects.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007-02-26
Materials and Methods	Applicant' version is acceptable.
Results and discussion	*4 Results:* For exposure details and adverse effects see CA-Table 1 (group 1) and CA-Table 2 (group 2). Otherwise applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Remarks	The study was conducted in accordance with the provisions of the Declaration of Helsinki (1964) and Tokyo (1975), Venice (1983) and Hong Kong (1989) revisions. In accordance with the principles of the Declaration, ethics committee approval and written informed consent of the study subjects are reported. This Study is suitable for human case report but not for the general population as indicated in the headline.
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*

Document IIIA/ Section A6.12.4/04

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Remarks

CA-Table 1: Exposure details and adverse effects in group 1

Group 1 - Adverse Events

Subject No.	Initial Exposure Concentration ($mg.FCR\ 1272.m^3$ air)	Start of Exposure	End of Exposure	Adverse Event	Severity	Time of Onset	Time of Resolution	Relationship to Test Substance
001	0.2	0853	0953	S: No symptoms O: Hyperaemia of nasal mucosa	Mild	0955	1055	Definitely related
002	0.2	0853	0933	1. S: Nasal irritation O: Hyperaemia of nasal mucosa	Moderate	0918	1018	Definitely related
				2. S: Nose running clear mucous O: Nose running clear mucous	Mild	0918	0955	Definitely related
				3. S: Irritation of the throat O: Normal	Mild	0858	0925	Definitely related
003	0.2	0853	0856	1. S: Coughing O: Chest clear	Moderate	0855	0905	Definitely related
				2. S: Headache	Mild	2130	0830	Unrelated
004	0.2	0853	0953	1. S: Nose running, sneezing O: Normal	Mild	0858	0958	Definitely related
				2. S: Eyes watering O: Normal	Mild	0917	0954	Definitely related
				3. S: Coughing - intermittent	Mild	0855	0901	Definitely related
005	0.09	0902	0927	S: Nose streaming O: Nasal mucosa more injected than previously	Mild	0907	0952	Definitely related

Key: S - Indicates subjective symptom experienced by the subject
O - Indicates an objective sign seen on examination by the investigator

Note: Subject 005 entered the exposure environment 9 min late and was exposed to a lower initial concentration of test substance

CA-Table 2: Exposure details and adverse effects in group 2

Group 2 - Adverse Events

Subject No.	Initial Exposure Concentration ($mg.FCR\ 1272.m^3$ air)	Start of Exposure	End of Exposure	Adverse Event	Severity	Time of Onset	Time of Resolution	Relationship to Test Substance
006	0.1	0835	0935	S: Slight nasal irritation O: Slight hyperaemia	Mild	0905	0941	Definitely related
007	0.1	0835	0935	S: Nasal irritation O: Normal	Mild	0930	0939	Definitely related
009	0.1	0835	0935	1. S: Irritation at back of throat O: Normal	Mild	0850	0940	Definitely related
				2. S: Nose running O: Normal	Mild	0905	0940	Definitely related
010	0.1	0835	0935	S: Slight irritation at back of throat O: Normal	Mild	0925	0936	Definitely related

Key: S - Indicates subjective symptom experienced by the subject
O - Indicates an objective sign seen on examination by the investigator

Note: Subject 008 had no adverse events

Document IIIA/ Section A6.12.4/05

Epidemiological Study

Prospective study on immune status

BPD Data Set IIA/ Annex Point VI.6.9.4

			Official use only
		1 REFERENCE	
1.1	**Reference**	Hadnagy, W. *et al* (2003). Pyrethroids used indoors – Immune status of humans exposed to pyrethroids following an indoor pest control operation—a one year follow-up study. International Journal of Hygiene and Environmental Health 206, 93-102 (2003) BES Ref.: M-259521-01-1 Published paper	
1.2	**Data protection**	No	
1.2.1	Data owner	n.a.	
1.2.2	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not applicable	
2.2	**GLP**	Not applicable	
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Cyfluthrin (Solfac EW50®), permethrin (KO-Konzentrat 0.4% ®), cypermethrin (Microcip ®) and deltamethrin (Detmol-delta ®).	
3.1.1	Lot/Batch number	Not reported	
3.1.2	Specification	Not reported	
3.1.2.1	Description	Not reported	
3.1.2.2	Purity	Not reported	
3.1.2.3	Stability	Not reported	
3.2	**Type of study**	Prospective study	
3.3	**Method of data collection**	Biological monitoring after cyfluthrin application	
3.4	**Test Persons / Study Population**		
3.4.1	Selection criteria	Follow up to previous study (Leng et al. 2003), see IIIA 6.12.4/01 for selection criteria, briefly: Persons with diabetes mellitus, renal deficiency, auto immune diseases, neurological or psychiatric disorders were excluded from the study as well as subjects where alcoholism or drug consumption was assumed. Another exclusion factor was a history of Pest Control Operator during the last 6 months before the study. Subjects were also excluded when a second PCO with pyrethroids was performed during the study.	
3.4.2	Number of test persons per	61 volunteers	

Document IIIA/ Section A6.12.4/05 — Epidemiological Study

Prospective study on immune status

BPD Data Set IIA/ Annex Point VI.6.9.4

	group/cohort size	
3.4.3	Sex	40 men, 21 women
3.4.4	Age	Average of 37.8 years
3.4.5	Diseases	See Point 3.4.1
3.4.6	Smoking status	Not known
3.5	**Controls**	No
3.5.1	Type of control	Not applicable
3.5.2	Number of test persons per group/cohort size	Not applicable
3.5.3	Sex	Not applicable
3.5.4	Age	Not applicable
3.5.5	Diseases	Not applicable
3.5.6	Smoking status	Not applicable
3.6	**Administration/ Exposure**	
3.6.1	Exposure Route	Oral/Inhalation/Dermal
3.6.2	Exposure Situation	Private home and work place (bakery, restaurant..) after a PCO treatment for cockroach control. Location was treated for 4 hours. During this time, the participants were not allowed to be present in the rooms. Thereafter, the rooms were ventilated for 4 hours. The participants therefore entered location approx 8 hours after the PCO.
3.6.3	Exposure concentration(s)	Not stated
3.6.4	Method(s) to determine exposure	Not stated
3.6.5	Postexposure period	1 day, 3 days, 4-6 months, and 10-12 months
3.7	**Examinations**	
3.7.1	Type of disease	Not applicable
3.7.2	Parameters	Immune parameters (blood sample), including: 1) immunological parameters of the humoral defence, i.e. immunoglobulins of the classes A, G, M, and E, complement components C3c and C4, acute phase proteins such as acid α1-glycoprotein, haptoglobin, C-reactive protein; 2) mediators and receptors of immunity, i.e. neopeterin, soluble interleukin-2 receptor (sIL-2R), soluble interleukin-6 receptor (sIL-6R), soluble tumour necrosis factor receptor (sTNF RII); 3) immunological markers of the cellular defence, i.e. white blood cell counts and lymphocyte (sub)populations such as total lymphocytes (CD2), mature lymphocytes (CD3), T-helper/inducer cells (CD4), T-suppressor/cytotoxic cells (CD8), B-cells (CD20), natural killer cells (CD56) as well as the ratio of CD4/CD8.
3.8	**Further remarks**	None

Document IIIA/ Section A6.12.4/05

BPD Data Set IIA/ Annex Point VI.6.9.4

Epidemiological Study

Prospective study on immune status

		4 RESULTS AND DISCUSSION	
4.1	**Exposure**	See Leng *et al.* 2003 for internal measurements of exposure (IIIA 6.12.4/01)	
4.1.1.1	Number of measurements	See Leng *et al.* 2003 for internal measurements of exposure (IIIA 6.12.4/01)	
4.1.1.2	Average concentrations	See Leng *et al.* 2003 for internal measurements of exposure (IIIA 6.12.4/01)	
4.1.1.3	Standard deviation	See Leng *et al.* 2003 for internal measurements of exposure (IIIA 6.12.4/01)	
4.1.1.4	Date(s) of measurement(s)	Prior to exposure, then 1 day, 3 days, 4-6 months and 10-12 months post-exposure	
4.1.2	Other		
4.2	**Number of cases for each disease / parameter under consideration**	See table A6.12.4/05-1. A number of parameters were statistically significantly changed as compared to parameters prior to exposure. However, median values were always, and 10^{th} and 90^{th} percentile values were largely within normal reference values.	
4.3	**SMR (Standard mortality ratio), RR (relative risk), OR (Odds ratio)**	Not applicable	
4.4	**Other Observations**	None	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	A multiparametric analysis of immune components was performed in blood and serum of 61 volunteers before and after (1 day, 3 days, 4-6 months and 10-12 months) a professional pest control operation (PCO) using pyrethroids. The following parameters were included in the study 1) immunological parameters of the humoral defence, i.e. immunoglobulins of the classes A, G, M, and E, complement components C3c and C4, acute phase proteins such as acid α1-glycoprotein, haptoglobin, C-reactive protein; 2) mediators and receptors of immunity, i.e. neopeterin, soluble interleukin-2 receptor (sIL-2R), soluble interleukin-6 receptor (sIL-6R), soluble tumour necrosis factor receptor (sTNF RII); 3) immunological markers of the cellular defence, i.e. white blood cell counts and lymphocyte (sub)populations such as total lymphocytes (CD2), mature lymphocytes (CD3), T-helper/inducer cells (CD4), T-suppressor/cytotoxic cells (CD8), B-cells (CD20), natural killer cells (CD56) as well as the ratio of CD4/CD8.	X
5.2	**Results and discussion**	The medians of all investigated immune parameters at all timepoints were within their respective reference ranges, with few exceptions the 10^{th} and 90^{th} percentile values were also within the reference ranges. A few parameters showed significant decreases at early time points. These had resolved by later timepoints and were within normal physiological range, thus are not considered to be toxicologically or physiologically relevant. Atopics did not differ in immune response	X

Document IIIA/ Section A6.12.4/05
BPD Data Set IIA/ Annex Point VI.6.9.4

Epidemiological Study
Prospective study on immune status

		from non-atopics.	
5.3	**Conclusion**	The data suggest a modulation of immune components after a correct performed PCO within the physiological range towards lower values during the first days. However, these immune changes are considered to be subtle and underlying compensatory mechanisms of immunoregulation.	X
5.4	**Other**	none	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007-02-26
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant´s version is adopted but Table A6.12.4/01-1, Parameter $CD3^+$ has to be corrected: fifth line: 1488 (988-2737)
Conclusion	Applicant's version is adopted.
Remarks	Unfortunately this publication only presents immune parameters. Results of air-monitoring data are not reported.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers given to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.12.4/05 — **Epidemiological Study**
Prospective study on immune status

BPD Data Set IIA/ Annex Point VI.6.9.4

Table A6.12.4/05-1: Results of prospective study on immune parameters

Parameter, units / Reference value (low-high)	Time, median (10^{th}-90^{th} percentile)	
	T1	
	T2	
	T3	
	T4	
	T5	
Lymphocytes, $10^3/\mu L$		
	2.35	(1.9-3.3)
	2.15	(1.5-3.1)
	2.10	(1.3-3.2)
	2.0*	(1.4-2.9)
	1.9	(1.4-3.4)
	1.0-4.4	
Neutrophils, $10^3/\mu L$		
	4.5	(2.7-6.2)
	3.75	(2.1-7.0)
	4.40	(1.7-5.2)
	3.6*	(2.8-5.9)
	4.05	(2.7-6.8)
	2.0-8.3	
IgG, g/L		
	11.02	(8.4-14.2)
	10.83*	(8.1-14.2)
	10.96	(8.4-14.0)
	10.63	(8.1-14.1)
	10.57	(8.1-14.5)
	7.0-16.0	
IgA, g/L		
	2.42	(1.4-3.8)
	2.36**##	(1.3-3.6)
	2.41**#	(1.2-3.8)
	2.36	(1.3-3.9)
	1.96	(1.4-4.3)
	0.7-5.0	
IgM, g/L		
	1.57	(0.7-3.0)
	1.47*##	(0.5-2.6)
	1.46**##	(0.5-2.7)

1.37 (0.5-2.9)
1.34* (0.7-2.4)
0.4-2.8

C3c, g/L

1.44 (1.0-2.2)
1.43* (1.0-2.0)
1.38* (0.9-2.2)
1.36 (1.0-2.4)
1.34 (1.1-1.7)
0.9-1.8

C4

0.34 (0.2-0.7)
0.33 (0.2-0.6)
0.33* (0.2-0.6)
0.30 (0.2-0.6)
0.29 (0.2-0.5)
0.1-0.4

AAG, g/L

0.94 (0.6-1.3)
0.9**# (0.6-1.3)
0.90*# (0.6-1.4)
0.94 (0.7-1.5)
0.85 (0.6-1.4)
0.5-1.2

CD3$^+$, counts/µL

1558 (1323-2228)
1602# (1204-2304)
1554*# (1294-2028)
1642# (1100-2483)
1448 (998-2737)
760-2920

CD4$^+$, counts/µL

1066 (733-1437)
950 (696-1666)
994* (845-1431)
1133 (753-1782)
824 (555-1903)
420-2210

CD20$^+$, counts/µL

309 (175-519)
311* (120-507)
243 (149-343)
265## (141-375)
297 (163-704)

60-510

CD56$^+$, counts/µL

136	(53-162)
133	(37-316)
138	(37-213)
157	(70-263)
132*	(54-445)

25-680

Only those parameters showing significance are shown; significantly different from T1 (Wilcoxon signed rank test) at * $p \leq 0.05$, ** $p \leq 0.01$ or significant for trend from T1 (Friedman test) at # $p \leq 0.05$, ## $p \leq 0.01$. Parameters not shown because no significant difference was seen include: monocytes, IgE, HPT, Neopterin, sIL-2R, sIL-6R, CD2+, CD8+, CD4/CD8. N not reported because it was different for every parameter and every time point.

Document IIIA/ Section A6.12.5

BPD Data Set IIA/ Annex Point VI.6.9.5

Diagnosis of poisoning including specific signs of poisoning and clinical tests.

Official use only

1 REFERENCE

1.1 Reference

[redacted] (2005); Cyfluthrin. Bayer Crop Sciences. Global QHSE. Intoxication treatment database.
BES N°M-258944-01-1

1.2 Data protection Yes

1.2.1 Data owner: Bayer CropScience AG

1.2.2 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 (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1 Test substance Cyfluthrin CAS No. 68359-37-5

4 INDICATIONS OF INTOXICATION

4.1 Clinical Signs

In cases of contact to pyrethroids the first sign of exposure is a specific paresthesia/irritation, often described as "cold burn". This may appear immediately or shortly after contact to the substance, may last up to 24 (rarely to 48) hours, and often is reported to be worsened by warmth (e.g. showering). This "cold burn" is due to a stimulation of free nerve endings, and is dependant on concentration, not on dose. It is strictly a local symptom only and not a symptom of a general poisoning. The irritation can occur both on the skin and on the mucous membranes of the airways. In the latter case in sensible individuals an asthma-like unspecific response can be triggered. No late sequelae of pyrethroid poisoning have been described in the scientific literature.

4.2 Organ systems

Organ (system)	Signs/symptoms	Remarks (if any)
Skin/	Paresthesia/irritation ("cold burn")	Local only
Mucous membranes	Irritation, cough, sneezing	Local only
Lung	Chest tightness, airway hyperreaction, pulmonary oedema	
Heart/circulation	Tachycardia, hypotension, palpitations	
Gastrointestinal tract	Nausea, vomiting, diarrhoea, abdominal pain, salivation	
Central Nervous System	Dizziness, blurred vision, headache, listlessness, anorexia, somnolence/coma, seizures/convulsions; tremor, ataxia, choreoathetosis (observed in animals only); muscle fasciculation	

Document IIIA/ Section A6.12.5

BPD Data Set IIA/ Annex Point VI.6.9.5

Diagnosis of poisoning including specific signs of poisoning and clinical tests.

5 FIRST AID AND TREATMENT

5.1 First Aid

Remove patient from exposure/terminate exposure. Thorough skin decontamination with water and copious amounts of detergents/soap - pyrethroids are only slightly soluble in water. Note: Warm water may increase the subjective severity of irritation/paresthesia. Flush eyes with lukewarm water for 15 minutes, apply soothing eyedrops; if needed anesthetizing eyedrops. Induction of vomiting should only be considered if a significant amount has been swallowed (more than a mouthful), if the ingestion was less than one hour ago, and if the patient is fully conscious. Induced vomiting can remove maximum 50% of the ingested substance.

5.2 Treatment

Gastric lavage can be considered in cases of significant ingestions within the first (2) hour(s); it should be considered in cases of ingestion of water/surfactant formulations. However, the application of activated charcoal and sodium sulphate is always advisable in significant ingestions. There is no specific antidote for pyrethroids; any treatment thus can only be symptomatic.

Skin irritation may be painful and require the application of analgesics; anaesthetic eyedrops may be required in case of eye contamination after flushing. In cases of severe ingestions cardiac and respiratory function should be monitored. In case of convulsions diazepam is the anticonvulsant of choice. Thus seizure management should follow standard practice using benzodiazepines (with oxygen and airway protection), if insufficiently effective followed by phenobarbital infusion as required for status epilepticus. Recovery is spontaneous and without sequelae.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-09-19
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	Applicant's version is adopted.
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*

Document IIIA/ Section A6.12.5	**Diagnosis of poisoning including specific signs of poisoning and clinical tests.**
BPD Data Set IIA/ Annex Point VI.6.9.5	
Remarks	

Document IIIA/ Section A6.12.6 **BPD Data set IIA/ Annex Point VI.6.9**	**Sensitisation/allergenicity observations, if available.**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [x]**	
Detailed justification:	In detailed examinations from industry found in A6.12.1, no sensitisation and allergenicity of workers were seen. No sensitisation and allergenicity observation was documented.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2006-09-19	
Evaluation of applicant's justification	-	
Conclusion	Applicant's justification is acceptable.	
Remarks	-	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Document IIIA/ Section 6.12.7/01 — Specific treatment in case of an accident or poisoning : first aid, antidotes and medical treatment, if known

BPD Data set IIA/

Annex Point VI.6.9

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] 1983) Tests to determine antidote effect against FCR 1272 toxicity in rats [redacted] Report No.: 11854, Edition Number: M-037789-01-1 Date: 01.06.1983 unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No	
2.2	**GLP**	No, When the study was performed, GLP was not compulsory.	
2.3	**Deviations**	Not relevant	
		3 MATERIALS AND METHODS	
3.1	**Test material**	FCR 1272 (cyfluthrin)	
3.1.1	Lot/Batch number	1.Batch no.: 816170019 2.Batch no.: 816270030	
3.1.2	Specification	As given in section 2 of Doc IIIA	
3.1.2.1	Description	Not stated	
3.1.2.2	Purity	1.Purity: 94.9% 2.Purity: 94.7%	
3.1.2.3	Stability	Not stated	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Wistar Rats [redacted]	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male	
3.2.5	Age/weight at study initiation	160-200 g	
3.2.6	Number of animals per group	5 – 20 per dose group	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	Oral	
3.3.1	Postexposure period	14 days	

Document IIIA/ Section 6.12.7/01 — Specific treatment in case of an accident or poisoning : first aid, antidotes and medical treatment, if known

BPD Data set IIA/

Annex Point VI.6.9

3.3.2 Cyfluthrin administration	**Oral**
3.3.2.1 Type	Gavage
3.3.2.2 Concentration	10, 16, 20, 22.4 and 25 mg cyfluthrin /kg
3.3.2.3 Vehicle	Cremophor EL and distilled water (5 drops per 10 ml)
3.3.2.4 Concentration in vehicle	Not stated
3.3.2.5 Total volume applied	10 ml/kg body weight
3.3.3 Andote administration	
3.3.3.1 Type	intraperitoneal, intravenous
3.3.3.2 Concentration	Acetylsalicylic acid: 5, 10 mg/kg b.w. Aspisol®: 5,10 mg/kg b.w. Calceno "D": 10 mg/kg b.w. Ergenyl®: 2.5, 25 mg/kg b.w. Methyldopa 250 Stada®: 11 mg/kg b.w. methylene blue: 10 mg/kg b.w. Musaril®: 50 - 400 mg/kg b.w. Myoscain®: 3.7 mg/kg b.w. Sodium thiosulfate-5-hydrate: 10 mg/kg b.w. Niconacid®: 11 mg/kg b.w. Pancuronium "Organon": 0.05 mg/kg b.w. Rhex Hobein®: 86 mg/kg b.w. Thionin: 5 mg/kg b.w. The dose levels of the antidotes were based on the mean rat body weight of 200 g (converted from the manufacturer's recommended daily dose for humans).
3.3.4 Total volume applied	10 ml/kg b.w. (intraperitoneal) 1 mg/kg b.w. (intravenous)
3.3.5 Others	antidotes administered at appearance of symptoms (approx. 30 minutes after oral administration of FCR 1272
3.4 Examinations	Clinical observations,mortality
3.5 Method of determination of LD_{50}	The mean lethal dose (LD50) was statistically determined by the method of Litchfield and Wilcoxon(1949).
3.6 Further remarks	None

Document IIIA/ Section 6.12.7/01 — **Specific treatment in case of an accident or poisoning : first aid, antidotes and medical treatment, if known**

BPD Data set IIA/

Annex Point VI.6.9

4 RESULTS AND DISCUSSION

4.1 Clinical signs

FCR 1272 treatment produced the following clinical signs: writhing, splayed gait, uncoordinated movements, increased activity, vocalization, salivation, difficult breathing, and lethargy. The symptoms appeared approx. 30 to 60 minutes after administration and persisted for up to 5 days. Death occurred between 2 to 3 hours post treatment. The LD_{50} was 19.6 (17.7 – 21.7) mg/kg.

4.2 Antidote effects

Results are summarised in table A6.12.17/01-1 to table A6.12.17/01-7
In these experiments substances with anti-inflammatory, analgesic, antiepileptic, sedative or neuromuscular-regulatory activity proved insufficient as antidotes to oral intoxication with cyfluthrin. Drugs with regulatory effects on the blood pressure or circulation as well as typical cyanide antidotes and calcium also failed to antagonise the acute effects of cyfluthrin. Intraperitoneal administration of Musaril (100 mg/kg bw) succeeded in moderate increasing the LD_{50}. Musaril also proved able to suppress the toxic signs (vocalisation, rolling = choreoathetosis) and delayed the onset of death.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Groups of 5 to 20 male rats received cyfluthrin via single oral administration (for LD_{50} determination: 10 - 25 mg/kg bw; for determination of antidote-effects: 10- 50 mg/kg bw). When symptoms appeared, the respective antidote was administered in the following doses and application modus:
- Aspisol®: 5 mg/kg bw (i.v.); Calceno "D": 10 mg/kg bw (i.v.); Methyldopa 250 Stada®: 11 mg/kg bw (i.v.); methylene blue: 10 mg/kg bw (i.v.); Myoscain®: 3.7 mg/kg bw (i.v.); sodium thiosulfate-5-hydrate: 10 mg/kg bw (i.v.); Niconacid®: 11 mg/kg bw (i.v.); Pancuronium "Organon": 0.05 mg/kg bw (i.v.); Rhex Hobein®: 86 mg/kg bw (i.v.); Thionin: 5 mg/kg bw (i.v.)
- acetylsalicylic acid: 5, 10 mg/kg bw (i.p.); Ergenyl®: 2.5, 25 mg/kg bw(i.p.)
- Musaril®: 50-300 mg/kg bw (oral), 50-400 mg/kg bw (i.p.).
The dose levels of the antidotes were based on the mean rat body weight of 200 g (converted from the manufacturer's recommended daily dose for humans). Recording period: 0-14 days.

5.2 Results and discussion

In these experiments substances with anti-inflammatory, analgesic, antiepileptic, sedative or neuromuscular-regulatory activity proved insufficient as antidotes to oral intoxication with cyfluthrin. Drugs with regulatory effects on the blood pressure or circulation as well as typical cyanide antidotes and calcium also failed to antagonise the acute effects of cyfluthrin. Intraperitoneal administration of Musaril (100 mg/kg bw) succeeded in moderate increasing the LD_{50} . Musaril also proved able to suppress the toxic signs (vocalisation, rolling = choreoathetosis) and delayed the onset of death.

5.3 Conclusion

The administration of Musaril, a centrally-acting muscle relaxant, led to the reduced acute toxicity of cyfluthrin.

5.3.1 Reliability — 2

5.3.2 Deficiencies — None

Document IIIA/ Section 6.12.7/01 — **Specific treatment in case of an accident or poisoning : first aid, antidotes and medical treatment, if known**

BPD Data set IIA/

Annex Point VI.6.9

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-09-19
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is adopted.
Conclusion	Other conclusions: Musaril increased the LD_{50} by a factor of 1.6 (LD50 = 30.5 mg/kg bw compared to 19.6 mg/kg bw – untreated).
Reliability	2
Acceptability	acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.12.7/01-1 : Antidote effects with acetylsalicylic acid, Aspisol® and Calceno "D"

FCR 1272 mg/kg	toxicological results*				
	without antidote	acetylsalicylic acid		Aspisol®	Calceno "D"
		5 mg/kg i.p.	10 mg/kg i.p.	5 mg/kg i.v.	10 mg/kg i.v.
15	2/5/5	3/5/5	1/5/5	2/5/5	0/5/5
20	5/5/5	-	-	-	3/5/5
25	5/5/5	5/5/5	5/5/5	5/5/5	5/5/5
30	5/5/5	-	-	-	-
LD50 (14 days) mg/kg b.w.	<20	<15	approx. 20	<20	<20

Table A6.12.7/01-2 : Antidote effects with Methylene blue, Sodium thiosulfate-5-hydrate and Thionin

FCR 1272 mg/kg	toxicological results*			
	without antidote	Methylene blue	Sodium thiosulfate-5-hydrate	Thionin
		10 mg/kg i.v.	10 mg/kg i.v.	5 mg/kg i.v.
15	2/5/5	0/5/5	0/5/5	2/5/5
20	5/5/5	1/5/5	4/5/5	-
25	5/5/5	4/5/5	5/5/5	5/5/5
30	5/5/5	-	-	-
LD50 (14 days) mg/kg b.w.	<20	<25	<20	approx. 20

Table A6.12.7/01-3 : Antidote effects with Ergenyl® and Methyldopa 250 Stada®

FCR 1272 mg/kg	toxicological results*			
	without antidote	Ergenyl®		Methyldopa 250 Stada®
		2.5 mg/kg i.p.	25 mg/kg i.p.	11 mg/kg i.v.
15	0/10/10	-	-	-
20	7/10/10	-	-	5/10/10
25	10/10/10	10/10/10	10/10/10	-
LD50 (14 days) mg/kg b.w.	<20	<25	<25	approx. 20

Table A6.12.7/01-4 : Antidote effects with Myoscain®, Niconacid®, Pancuronium "Organon" and Rhex Hobein®

FCR 1272 mg/kg	toxicological results*				
	without antidote	Myoscain®	Niconacid®	Pancuronium "Organon"	Rhex Hobein®
		3.7 mg/kg i.v.	11 mg/kg i.v.	0.05 mg/kg i.v.	86 mg/kg i.v.
15	0/10/10	-	-	-	-
20	7/10/10	8/10/10	6/10/10	7/10/10	8/10/10
25	10/10/10	-	-	-	-
LD50 (14 days) mg/kg b.w.	<20	<20	<20	<20	<20

Table A6.12.7/01-5 : Antidote effects with Musaril® by oral administration

FCR 1272 mg/kg	toxicological results*				
	without antidote	Musaril® - oral administration			
		50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
10	0/10/10	-		-	-
16	2/10/10	0/10/10		0/10/10	0/10/10
20	11/20/20	5/10/10	-	4/20/20	-
22.4	13/20/20	8/10/10	2/20/20	3/10/10	3/20/20
25	10/10/10	10/10/10	2/10/10	9/10/10	4/10/10
28	10/10/10	-	6/10/10	-	7/10/10
31.5	10/10/10		8/10/10	-	10/10/10
35.5	10/10/10	-	-	-	-
50	10/10/10	-	10/10/10	10/10/10	-
LD50 (14 days) mg/kg b.w.	19.6	19.8	27.6	22.4	26.0

Table A6.12.7/01-6 : Antidote effects with Musaril® by intraperitoneal administration

FCR 1272 mg/kg	toxicological results*					
	without antidote	Musaril® - intraperitoneal administration				
		50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg	400 mg/kg
10	0/10/10	-	-	-	-	-
16	2/10/10	-	-	-	0/10/10	-
20	11/20/20	2/10/10	-	1/10/10	1/10/10	-
22.4	13/20/20	4/10/10	0/10/10	1/10/10	5/10/10	-
25	10/10/10	8/10/10	1/10/10	7/10/10	5/10/10	-
28	10/10/10	-	5/20/20	9/10/10	-	-
31.5	10/10/10	-	5/10/10	-	9/10/10	7/10/10
35.5	10/10/10	-	9/10/10	-	-	-
50	10/10/10	10/10/10	10/10/10	10/10/10	-	-
LD50 (14 days) mg/kg b.w.	19.6	22.7	30.5	24.2	24.3	< 31.5

Table A6.12.7/01-7 : Antidote effects with Musaril®

FCR 1272 mg/kg	toxicological results*					
	without antidote	Musaril® (mg/kg b.w.)				
		200 i.p[x]	400 i.p[x]	5 x 200 i.p[xx]	3 i.v	12 i.v
20	8/10/10	-	-	-	9/10/10	6/10/10
25	9/10/10	0/10/10	1/10/10	10/10/10	-	-
31.5	10/10/10	9/10/10	6/10/10	-	-	-
35.5	10/10/10	-	9/10/10	-	-	
50	10/10/10	-	10/10/10	-	-	
LD50 (14 days) mg/kg b.w.	< 20	< 31.5	30	< 25	< 20	<20

* : The entries in the "toxicological result" column in the table mean :
1st figure = number of animals dying
2nd figure = number of animals with symptoms
3rd figure = number of animals used

x : antidote administered immediately after FCR 1272 administration
xx : antidote administered immediately after FCR 1272 administration, plus 2h, 4h, 6h and 8h afterward

Document IIIA/ Section 6.12.7/02
BPD Data set IIA/ Annex Point VI.6.9

Specific treatment in case of an accident or poisoning : first aid, antidotes and medical treatment, if known

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1984) FCR 1272 - Antidotal test, [redacted] Report No.: JAP271, Edition Number: M-044706-01-1 Date: 23.02.1984 unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No	
2.2	**GLP**	No, When the study was performed, GLP was not compulsory.	
2.3	**Deviations**	Not relevant	
		3 MATERIALS AND METHODS	
3.1	**Test material**	FCR 1272 5% SL	X
3.1.1	Lot/Batch number	8241/SL/NO4	
3.1.2	Specification	Not relevant	
3.1.2.1	Description	Not stated	
3.1.2.2	Purity	Not stated	
3.1.2.3	Stability	Not stated	
3.2	**Test Animals**		
3.2.1	Species	Mice and rat	
3.2.2	Strain	ICR mice, Sprague-Dawley rats	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male	
3.2.5	Age/weight at study initiation	ICR male mice (4 week age) and SD male rats (6 week age)	
3.2.6	Number of animals per group	10 per dose group	
3.2.7	Control animals	Yes, ; no treatment group (control group)	
3.3	**Administration/ Exposure**		
3.3.1	Post exposure period	7 days	
3.3.2	Cyfluthrin administration	Oral	

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BPD Data set IIA/ Annex Point VI.6.9

Specific treatment in case of an accident or poisoning : first aid, antidotes and medical treatment, if known

3.3.2.1	Type	Gavage
3.3.2.2	Concentration	350,500, 700, 1000, 1400 and 2000 mg cyfluthrin /kg
3.3.2.3	Vehicle	5 % solution of FCR 1272 (8241/SL/N04) was used, and added to distilled water to be prepared as 15 % w/v of emulsified solution for mice and 50 % w/v of emulsified solution for rats.
3.3.2.4	Concentration in vehicle	See 3.3.2.3
3.3.2.5	Total volume applied	Not stated
3.3.3	Andote administration	
3.3.3.1	Type	intraperitoneal
3.3.3.2	Concentration	atropine sulphate (mice): 2 x 50 mg/kg bw (at 20 min and 2 h p.a. of cyfluthrin) atropine sulphate (rats): 3 x 25 mg/kg bw (at 30 min, 3 and 24 h, p.a. of cyfluthrin) methocarbamol (mice): 2 x 100 mg/kg bw (at 20 min and 2 h p.a. of cyfluthrin) methocarbamol (rats): 3 x 50 mg/kg bw (1, 3 and 24 h p.a. of cyfluthrin) atropine + methocarbamol (mice): 2 x 50 mg/kg bw + 2 x 100 mg/kg bw (same time as above) atropine + methocarbamol (rats): 3 x 25 mg/kg bw + 3 x 50 mg/kg bw (same time as above)
3.3.4	Total volume applied	Not stated
3.4	**Examinations**	Clinical observations, mortality
3.5	**Method of determination of LD_{50}**	The mean lethal dose (LD_{50}) was determined by the method of Bliss.
3.6	**Further remarks**	None

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	The oral LD value of 5 % solution of FCR 1272 on mice was 660 mg/kg. Mice displayed salivation, titubation, athetosis as well as dyspnea. These symptoms occurred most severely 2 hours after the administration, and gradually disappeared in the next day post treatment. In rats, oral LD value of FCR 1272 - 5% SL was 2100 mg/kg. Poisoning symptoms in rats were similar to the mice.

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BPD Data set IIA/ Annex Point VI.6.9

Specific treatment in case of an accident or poisoning : first aid, antidotes and medical treatment, if known

4.2	**Antidote effects**	Results are summarised in table A6.12.17/01-1 and A6.12.17/01-2 Atropine treatment caused the slight elevation of LD value (840 mg/kg), indicating an antidotal effect. Methocarbamol treatment, by which LD value was 970 mg/kg, showed higher antidotal effects than single atropine treatments. Combined treatment of atropine and methocarbamol showed much higher antidotal effects, in which the LD value was 1280 mg/kg. Salivation was depressed by atropine, and athetosis temporarily reduced by methocabamol. In rats, atropine treatment slightly elevated the LD value (2600 mg/kg). Methocarbamol treatment elevated the LD value (2800 mg/kg) of 5 % solution of FCR 1272 on rats, as same as mice. This antidote did not affect salivation, but depress the athetosis and / or disorder of the respiration for 1 to 3 hours after every treatment. On the other hand, combined treatment was found to be more effective, in which LD value was 3100 mg/kg on rats. Reflecting an effect of each treatment, salivation, athetosis and disorder of the respiration were simultaneously depressed.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Groups of 10 male mice and rats received cyfluthrin via single oral administration. The doses were 350-2000 mg/kg bw for mice and 1000-5600 mg/kg bw for rats. Two antidotes were intraperitoneally injected in the following dosing schedule: - atropine sulphate (mice): 2 x 50 mg/kg bw (at 20 min and 2 h p.a. of cyfluthrin) - atropine sulphate (rats): 3 x 25 mg/kg bw (at 30 min, 3 and 24 h, p.a. of cyfluthrin) - methocarbamol (mice): 2 x 100 mg/kg bw (at 20 min and 2 h p.a. of cyfluthrin) - methocarbamol (rats): 3 x 50 mg/kg bw (1, 3 and 24 h p.a. of cyfluthrin) - atropine + methocarbamol (mice): 2 x 50 mg/kg bw + 2 x 100 mg/kg bw (same time as above) - atropine + methocarbamol (rats): 3 x 25 mg/kg bw + 3 x 50 mg/kg bw (same time as above) Recording period: 0 - 7 days.
5.2	**Results and discussion**	Atropine sulfate and methocarbamol, each had depressive effects on FCR 1272 – induced poisoning symptoms and elevated the LD value to slight degree. Therefore, it is considered that more effective results will be obtained, if the administrations of these antidotes are individually dependent on a type and a degree of poisoning symptoms.
5.3	**Conclusion**	
5.3.1	Reliability	2
5.3.2	Deficiencies	None

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Specific treatment in case of an accident or poisoning : first aid, antidotes and medical treatment, if known

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2010/07/21
Materials and Methods	Applicant's version is acceptable with the following amendment: *3.1* FCR 1272 (5% solution)
Results and discussion	Applicant's version is acceptable.
Conclusion	Applicant's version is acceptable.
Reliability	2 (reliable with restrictions)
Acceptability	Acceptable
Remarks	Low reliability, because: – no purity, no vehicle given. – LD_{50} of cyfluthrin up to 10 fold higher than in any other acute toxicity study (2100 mg/kg bw compared to 160-600 mg) but gross estimation of atropine and methylcarbamate effect possible. High atropine doses are not state-of-the-art treatment for cyfluthrin poisoning, in contrast they are contraindicated today (see Doc 6.12.5 Intoxication Treatment Database, updated in 2005)
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.12.17/01-1: LD50 values obtained in mice treated with FCR 1272 5% SL or atropine and methocarbamol as antidotes

Treatment mg/kg b.w.	FCR 1272 5% SL mg/kg b.w.	toxicol. results*	onset of death	LD50 (7 days) mg/kg b.w.
control	350	0/10	-	660
	500	2/10	2h	(560 - 770)
	700	6/10	lh-6 h	
	1000	9/10	lh-6 h	
	1400	10/10	lh-6 h	
Atropine 2x50 i.p.	500	1/10	3h	840
	700	4/10	2h-6h	(650 - 1070)
	1000	6/10	2h-6h	
	1400	9/10	lh-6h	
Methocarbamol 2x100 i.p.	500	0/10	-	1070
	700	3/10	2h-6h	(890-1260)
	1000	5/10	2h - 24h	
	1400	8/10	2h-6h	
Atropine + Methocarbamol	700	0/10	-	1280
	1000	2/10	3h-6h	(1090-1510)
	1400	7/10	2h - 24h	
	2000	9/10	lh-6h	

Table A6.12.17/01-2: LD50 values obtained in rats treated with FCR 1272 5% SL or Atropine and methocarebamol as antidotes

Treatment mg/kg b.w.	FCR 1272 5% SL mg/kg b.w.	toxicol. results*	onset of death	LD50 (7 days) mg/kg b.w.
control	1000	0/10		2100
	1400	1/10	2d	(1900 - 2300)
	2000	4/10	6h - 24h	
	2800	9/10	3h-2d	
	4000	10/10	2h-2d	
Atropine 3x25 i.p.	1400	1/10	24h	2600
	2000	3/10	24h	(2100 - 3200)
	2800	5/10	24h - 2d	
	4000	8/10	3h-2d	
	5600	10/10	3h-2d	
Methocarbamol 3x50 i.p.	1400	0/10		2800
	2000	2/10	24h	(2400 - 3300)
	2800	5/10	24h - 2d	
	4000	8/10	6h-3d	
	5600	10/10	2h-2d	
Atropine + Methocarbamol	1400	0/10		3100
	2000	1/10	24h	(2600 - 3700)
	2800	5/10	24h - 2d	
	4000	6/10	24h - 3d	
	5600	10/10	4h-2d	

* The entries in the "toxicological results" column in the tables mean:
1st figure = number of animals dying
2nd figure = number of animals used

Document IIIA/ Section A6.12.8

Prognosis following poisoning

BPD Data Set IIA/ Annex Point VI.6.9

Official use only

1 REFERENCE

1.1 Reference

[redacted] (2005); Cyfluthrin. Bayer Crop Sciences. Global QHSE. Intoxication treatment database.
BES N°M-258944-01-1

1.2 Data protection Yes

1.2.1 Data owner: Bayer CropScience AG

1.2.2 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 (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1 Test substance Cyfluthrin CAS No. 68359-37-5

4 INDICATIONS OF INTOXICATION

4.1 Clinical Signs

In cases of contact to pyrethroids the first sign of exposure is a specific paresthesia/irritation, often described as "cold burn". This may appear immediately or shortly after contact to the substance, may last up to 24 (rarely to 48) hours and often is reported to be worsened by warmth (e.g. showering). This "cold burn" is due to a stimulation of free nerve endings, and is dependant on concentration, not on dose. It is strictly a local symptom only and not a symptom of a general poisoning. The irritation can occur both on the skin and on the mucous membranes of the airways. In the latter case in sensible individuals an asthma-like unspecific response can be triggered. No late sequelae of pyrethroid poisoning have been described in the scientific literature.

4.2 Organ systems

Organ (system)	Signs/symptoms	Remarks (if any)
Skin/	Paresthesia/irritation ("cold burn")	Local only
Mucous membranes	Irritation, cough, sneezing	Local only
Lung	Chest tightness, airway hyperreaction, pulmonary oedema	
Heart/circulation	Tachycardia, hypotension, palpitations	
Gastrointestinal tract	Nausea, vomiting, diarrhoea, abdominal pain, salivation	
Central Nervous System	Dizziness, blurred vision, headache, listlessness, anorexia, somnolence/coma, seizures/convulsions; tremor, ataxia, choreoathetosis (observed in animals only); muscle fasciculation	

Document IIIA/ Section A6.12.8

BPD Data Set IIA/ Annex Point VI.6.9

Prognosis following poisoning

5 FIRST AID AND TREATMENT

5.1 First Aid

Remove patient from exposure/terminate exposure. Thorough skin decontamination with water and copious amounts of detergents/soap - pyrethroids are only slightly soluble in water. Note: Warm water may increase the subjective severity of irritation/paresthesia. Flush eyes with lukewarm water for 15 minutes, apply soothing eyedrops; if needed anesthetizing eyedrops. Induction of vomiting should only be considered if a significant amount has been swallowed (more than a mouthful), if the ingestion was less than one hour ago, and if the patient is fully conscious. Induced vomiting can remove maximum 50% of the ingested substance.

5.2 Treatment

Gastric lavage can be considered in cases of significant ingestions within the first (2) hour(s); it should be considered in cases of ingestion of water/surfactant formulations. However, the application of activated charcoal and sodium sulphate is always advisable in significant ingestions. There is no specific antidote for pyrethroids; any treatment thus can only be symptomatic.

Skin irritation may be painful and require the application of analgesics; anaesthetic eyedrops may be required in case of eye contamination after flushing. In cases of severe ingestions cardiac and respiratory function should be monitored. In case of convulsions diazepam is the anticonvulsant of choice. Thus seizure management should follow standard practice using benzodiazepines (with oxygen and airway protection), if insufficiently effective followed by phenobarbital infusion as required for status epilepticus. Recovery is spontaneous and without sequelae.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006-09-20
Materials and Methods	n/a.
Results and discussion	n/a
Conclusion	Prognosis: Treatment is symptomatic, Recovery is spontaneous and without sequelae
Remarks	-
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*

Document IIIA/ Section A6.12.8

Prognosis following poisoning

BPD Data Set IIA/ Annex Point VI.6.9

Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.13 BPD Data set IIIA/ Annex Point III-VI.2	Toxic effects on livestock and pets	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	Solfac® EW 50 is a 5% oil-in-water emulsion applied to animal housing buildings, to control flying and crawling insects. The product diluted in water is applied using a low pressure sprayer with a maximum application rate of 0.8 ml formulation/m2, which is equivalent to 0.04 g cyfluthrin/m2. Solfac® EW 50 may be applied on the walls as a strip of 1-2 m width, on window frames and to the ceiling. Solfac® EW 50 is recommended for use with the following general precautions: • Do not apply to surfaces on which food or feed are stored, prepared or supplied • Cover or remove feed, feed preparing equipment, water and feed suppliers with impermeable plastic sheets before application • Do not apply directly to animals Cyfluthrin isomers I, II, III and IV are classed as non-volatile (Vp 1.4 x 10-8 to 9.6 x 10-7 Pa at 20°C; mean 2.7 x 10-7 Pa). Therefore the exposure is unlikely via drinking water or feedstuffs. Furthermore poultry and ruminant metabolism and feeding studies were conducted with cyfluthrin active ingredient. No adverse effects were seen when poultry and cows were dosed up to 5 and 0.5 mg/kg bw per day for 5 successive days mg/kg bw respectively in metabolism studies and up to 20 ppm and 150 ppm in feed for 28 days respectively in feeding studies. From these results, livestock are not more sensitive than rats or rabbits, and the toxicology studies can be considered also relevant for livestock. In summary, ruminants and poultry will not be at risk from Solfac® EW50 uses when label recommendations are respected. Consequently, specific studies on toxic effects on livestock and pets are not needed and would be unethical for animal welfare reasons.	
	Raid® Cyfluthrin Foam containing 0.04% w/w cyfluthrin is formulated in a ready-to-use household product to be applied by non-professionals. Use will be intermittent and applications are localised. The product is formulated as a foam to create an active barrier that prevents insects from entering the home. Product application is targeted, being applied into cracks and crevices via a hollow delivery tube or wand from a pressurised ready-to-use can. The foam expands in to the crack or crevice and dries quickly. Raid Cyfluthrin Foam can be applied indoors or outdoors to joints, splits, clefts, etc around the perimeters of indoor rooms and the outside of the building, and around doors and windows.	

Document IIIA/ Section A6.13 BPD Data set IIIA/ Annex Point III-VI.2	Toxic effects on livestock and pets
	For a foam treatment, containing cyfluthrin which is non-volatile, specifically directed into a crack or crevice, that subsequently quickly dries in the crevice, emission to air during application of the product from evaporation is not considered a relevant route of exposure. Consequently, residues are restricted to the place of application and there will therefore be no condensed residues depositing on room surfaces or likely to come into contact with household pets (i.e. exposure via dislodgeable residues is predicted to be negligible). In addition, the following label restrictions apply: 'Do not spray on humans or domestic animals. Cover up or remove food or objects which can come into contact with food, as well as aquariums and animal cages'. Pyrethroids have a long history of direct use in veterinary medicines to control parasites such as fleas and ticks. These formulations are applied directly to the fur/coat of the animal to control the pest at a local level. The following pyrethroids have approval for veterinary use: Flumethrin: For treatment of sheep using a 6% EC solution Cattle dip and cattle tick spray at 75 g flumethrin/l Pour-on solution for cattle tick at 10g/l Deltamethrin: Dip/spray at 50g/l Pour-on at 7.5g/l (Source: www.fao.org) The levels of exposure associated with the other pyrethroid products listed above far exceed the potential exposures associated with the use of the cyfluthrin products. Toxicity testing is by principle conducted on several species and key reference values based on NOELs in the most sensitive of those species. Toxicology NOELs will therefore be in principle protective of most species of household pets. In summary there is very low potential risk to domestic pets through use of Raid® Cyfluthrin Foam.
Undertaking of intended data submission [ ]	Not applicable

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2010/07/22
Evaluation of applicant's justification	Acceptable
Conclusion	Acceptable
Remarks	None
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.14 **BPD Data set IIIA/ Annex Point III-XI.2**	**Other tests related to the exposure of humans**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	According to the technical guidance document in support of directive 98/8/EC, other tests related to humans covers the toxicity of degradation products, by-products and reaction products (other than mammalian metabolites). The major degradation products of cyfluthrin are permethric acid and fluorophenoxybenzoic acid; which are also the major mammalian metabolites. As such, any toxicity would be accounted for in tests on the parent compound. Additional testing is therefore unwarranted.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2010/07/21	
Evaluation of applicant's justification	Applicant's justification is acceptable.	
Conclusion	Applicant's justification is acceptable.	
Remarks	None	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Document IIIA/ Section A6.15.1 **BPD Data set IIIA/ Annex Point III-XI.2**	**Identification of the residues (identity and concentrations), degradation and reaction products and of metabolites of the active substance in contaminated foods or feedingstuffs.**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	**Official use only**
Other existing data [X] **Limited exposure [ ]**	**Technically not feasible [ ] Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	Solfac® EW 050 is a 5% oil-in-water emulsion applied to animal housing buildings, to control flying and crawling insects. The product diluted in water is applied using a low pressure sprayer with a maximum application rate of 0.04 g cyfluthrin/m2. Solfac® EW 50 may be applied on the walls as a strip of 1-2 m width, on window frames and to the ceiling. The following precautions are recommended on the label : • Do not apply to surfaces on which food or feed are stored, prepared or supplied • Cover or remove feed, feed preparing equipment, water and feed suppliers with impermeable plastic sheets before application • Do not apply directly to animals • Do not contaminate ground, water bodies or watercourses with remaining spray liquid or unused insecticide, cleaning water or used container Therefore, no food or feedstuffs contamination is expected when Solfac® EW 050 is used as recommended on the label.	
	Raid® Cyfluthrin Foam uses will be intermittent and applications are localised. Product application is targeted, being applied into cracks and crevices via a hollow delivery tube or wand from a pressurised ready-to-use can. The foam expands in to the crack or crevice and dries quickly. Raid Cyfluthrin Foam can be applied indoors or outdoors to joints, splits, clefts, etc around the perimeters of indoor rooms and the outside of the building, and around doors and windows. Therefore, no food or feedstuffs contamination is expected.	
Undertaking of intended data submission [ ]	Not applicable	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007-01-30
Evaluation of applicant's justification	The justification is reasonable under consideration of the recommended precautions on the label.
Conclusion	The justification provided by the applicant is considered acceptable. Under consideration of the recommended precautions on the label no relevant residues are expected in plant or animal food items.
Remarks	none
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.15.2 **BPD Data set IIIA/ Annex Point III-XI.2**	**Behaviour of the residues of the active substance, its degradation and reaction products and where relevant, its metabolites on the treated or contaminated food or feedingstuffs including the kinetics of disappearance**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	**Official use only**
Other existing data [X] **Limited exposure [ ]**	**Technically not feasible [ ] Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	Solfac® EW 050 is a 5% oil-in-water emulsion applied to animal housing buildings, to control flying and crawling insects. The product diluted in water is applied using a low pressure sprayer with a maximum application rate of 0.04 g cyfluthrin/m². Solfac® EW 050 may be applied on the walls as a strip of 1-2 m width, on window frames and to the ceiling. The following precautions are recommended on the label : • Do not apply to surfaces on which food or feed are stored, prepared or supplied • Cover or remove feed, feed preparing equipment, water and feed suppliers with impermeable plastic sheets before application • Do not apply directly to animals • Do not contaminate ground, water bodies or watercourses with remaining spray liquid or unused insecticide, cleaning water or used container No food or feedstuffs contamination is expected when Solfac® EW 050 is used as recommended on the label. Therefore information on degradation is not necessary.	
	Raid® Cyfluthrin Foam uses will be intermittent and applications are localised. Product application is targeted, being applied into cracks and crevices via a hollow delivery tube or wand from a pressurised ready-to-use can. The foam expands in to the crack or crevice and dries quickly. Raid Cyfluthrin Foam can be applied indoors or outdoors to joints, splits, clefts, etc around the perimeters of indoor rooms and the outside of the building, and around doors and windows. No food or feedstuffs contamination is expected. Therefore information on degradation is not necessary.	
Undertaking of intended data submission [ ]	Not applicable	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007-01-31
Evaluation of applicant's justification	The justification is reasonable under consideration of the recommended precautions on the label.
Conclusion	The justification provided by the applicant is considered acceptable. Under consideration of the recommended precautions on the label no relevant residues are expected in plant or animal food items.
Remarks	none
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.15.3 — Estimation of potential or actual exposure of the active substance to humans trough diet and other means

BPD Data set IIIA/ Annex Point XI.1 — Rotational Crop study

Official use only

		1 REFERENCE
1.1	**Reference**	Leslie, W.L (1989) Baythroid® - residues in field rotational cereal crops, Mobay Corporation, Stanley Research Center, Stilwell, Kansas, USA Report N°MR98429 BES Ref M-067638-01-1 July 12, 1989 Unpublished Addendum N°1 Baythroid® - residues in field rotational cereal crops, Mobay Corporation, Stanley Research Center, Stilwell, Kansas, USA Report N°MR98429-I BES Ref M-067604-01-1 July 12, 1989 Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2	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**	EPA Pesticide Assessment Guidelines, Series 165-2
2.2	**GLP**	No, When the study was performed, GLP was not compulsory
2.3	**Deviations**	none
		3 MATERIALS AND METHODS
3.1	**Test material**	Baythroid 240 EC (240 g a.i./l cyfluthrin)
3.1.1	Lot/Batch number	Not stated
3.1.2	Specification	not relevant (pure a.i. measured)
3.1.3	Description	emulsifiable concentrate
3.1.4	Purity	240 g a.i./l cyfluthrin
3.1.5	Stability	product was used within its shelf life according to storage stability test
3.1.6	Further relevant properties	none
3.2	**Reference substances**	none
3.3	**Test solution**	Solvesso = aromatic hydrocarbon mixture 240 g a.i./l cyfluthrin
3.4	**Testing procedure**	

Document IIIA/ Section A6.15.3	**Estimation of potential or actual exposure of the active substance to humans trough diet and other means**
BPD Data set IIIA/ Annex Point XI.1	Rotational Crop study

3.4.1	soils	Benoit, Mississipi: silt loam, pH 5.6, 1.4 % organic matter, Stilwell, Kansas, 1: silty clay loam, pH 5.3,4.6 % organic matter, Stilwell, Kansas, 2: silty clay loam, pH 5.7, 4.4 % organic matter
3.4.2	Test system	Plants : wheat Application : to soil, broadcast spray Rate : a.i.: 0.025 Ibs/acre/application, spray volume: 6.5 to 24 gallons per acre corresponding to: 28 g a.i./ha/application, spray volume: 60 - 225 Ltr./ha number of application : 10 application interval : 4 - 12 days planting time : 38, 105 and 135 days after last application planting to sampling : 45-48 days, 195 days, 241-255 days Wheat samples harvested at maturity
3.4.3	Conditions of test:	In field
3.4.4	Number of replicates	Two replicates per sampling day.
3.4.5	Extraction and identification	
3.4.6	Crop	Crop sample were extracted with methanol/water (4:1), re-extracted with methanol and acetonitrile, followed by a liquid-liquid partition with chloroform and saturated sodium chloride, and a final cleanup using a florisil column. Quantitation was done via gas chromatography utilizing a Nickel-63 electron capture detector (ECD).
3.4.7	soil	Soil sample were extracted with extractions using methanol/water (4:1), methanol, and 1.0 N hydrochloric acid, followed by an acid/base liquid-liquid partition cleanup. Final quantitation was performed by gas-liquid chromatography.

4 RESULTS

4.1	**Method validation**	Recovery data in cereal grain (dry corn grain) : Three replicates at the 0.05 ppm fortification level were analyzed with percent recoveries of 76% to 110%. Recovery data in green forage (corn green forage): Duplicate determinations at the 0.05 ppm fortification level were done with percent recoveries of 82% and 86%. Recovery data in wheat straw, generated at the 0.01, 0.02, and 0.05 ppm fortification levels produced percent recoveries that ranged from 95% to 110%.. Duplicate concurrent recovery samples at the 0.05 ppm fortification level produced percent recoveries of 82% and 86%. Recovery data in test plot soil : Triplicate concurrent recoveries at the0.05 ppm fortification level produced percent recoveries of 90% to 102%.
4.2	**Linear response of the gas**	The linear response of the gas chromatograph detector for cyfluthrin in the presence of cereal grain, green forage, straw, and soil were

	chromatography	demonstrated. Separate curves for each matrix were generated with the following correlation coefficients resulting, when calculated by the linear least squares regression analysis program: 0.9990, corn grain; 0.9990, corn forage; 0.9930, wheat straw; and 0.9930, soil.
4.3	**Residue**	No detectable residues were found at the 38, 105 and 135 days plant-back interval in the mature wheat crop components (green forage, threshed grain and straw). See table A6.15.3-1 Soil samples (0-15 cm depth) taken at the time of sowing never contained residues above 0.03 mg cyfluthrin/kg soil. At harvest soil residues were always < 0.01 mg Cyfluthrin /kg soil. See table A6.15.3-2
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Rotational cereal crop field trials following pretreatment of the soil at 10 applications of BAYTHROID 2 formulation at the rate of 28 g a.i./ha/application. At intervals of approximately 30 and 120 days post-treatment, i.e., one and four months, winter wheat was planted and grown to maturity at two test sites. These intervals represent an emergency (one month) and intermediate planting (four month) situation for field rotational crops. Residues of cyfluthrin were determined on the mature wheat crop components (green forage, threshed grain, and straw), as well as in the field soil samples taken at the times of last treatment, planting, and harvest.
5.2	**Results and discussion**	No detectable residues were found at the 38, 105 and 135 days plant-back interval in the mature wheat crop components (green forage, threshed grain and straw). Soil samples (0-15 cm depth) taken at the time of sowing never contained residues above 0.03 mg cyfluthrin/kg soil. At harvest soil residues were always < 0.01 mg Cyfluthrin /kg soil.
5.3	**Conclusion**	It can be concluded that cereals planted at least 38 days after the last soil treatment with Cyfluthrin, contain no detectable residues.
5.3.1	Reliability	2
5.3.2	Deficiencies	None

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007-01-30
Materials and Methods	Acceptable

Document IIIA/ Section A6.15.3	**Estimation of potential or actual exposure of the active substance to humans trough diet and other means**
BPD Data set IIIA/ Annex Point XI.1	Rotational Crop study

Results and discussion	No detectable residues were found at the 38, 105 and 135 days plant-back interval in the mature wheat crop components (green forage, threshed grain and straw). Soil samples (0-15 cm depth) taken at the time of sowing never contained residues above 0.03 mg cyfluthrin/kg soil. At harvest soil residues were always < 0.01 mg Cyfluthrin /kg soil.
Conclusion	Cyfluthrin is not likely to produce detectable residues in plant grown in contaminated soil. Under consideration of the recommended precautions on the label a direct contamination of food items or lifestock animals can be excluded. An additional exposure to humans through diet arising from the use of cyfluthrin as a biocide can be excluded.
Reliability	1
Acceptability	Acceptable
Remarks	None

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.15.3-1: Cyfluthrin residues in wheat samples

Location	sample type	plant-back interval (days)	planting to sampling interval (days)	gross residue (ppm)
Kansas 1	forage	38	48	<0.01
	grain	38	255	<0.01
	straw	38	255	<0.01
Kansas 2	forage	105	45	<0.01
	grain	105	241	<0.01
	straw	105	241	<0.01
Mississippi	grain	135	195	<0.01
	straw	135	195	<0.01

Table A6.15.3-2: Cyfluthrin residues in soil samples

Location	plant-back interval (days)	Sampling interval	PHI (days)	gross residue (ppm)
Kansas 1 Clay loam	38	Last treatment	0	0.06
		At planting	38	0.03
		At harvest	293	<0.01
Kansas 2 Clay loam	105	Last treatment	0	0.24
		At planting	105	0.02
		At harvest	346	<0.01
Mississippi Silty Clay	135	Last treatment	1	0.36
		At planting	135	<0.01
		At harvest	330	<0.01

Section A6.15.5/01 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in Hen

Official use only

1 REFERENCE

1.1 Reference

[redacted] (1984).
A 28 day Baythroid TM poultry feeding study, [redacted]
Bayer AG Report No.: MR86046, Edition Number: M-060241-02-1
Report Date: 14.09.1983, Amended: 05.07.1984
Unpublished

Methods of analysis :
[redacted] 1985)
An analytical method for Baythroid in bovine and poultry tissues, milk and eggs, [redacted]
Method No.: 85883, Edition Number: M-066143-01-1
Date: 02.04.1985
unpublished
[redacted] (1985)
An analytical method for quantitating Baythroid metabolite residues in animal tissues, [redacted]
Bayer AG Report No.: 86212, Edition Number: M-066384-01-1
Report Date: 14.11.1983
Unpublished

1.2 Data protection Yes

1.2.1 Data owner: Bayer CropScience AG

1.2.2 Companies with letters of access:

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.

At the time the study was undertaken, no particular method was compulsory.

2.2 GLP No.

When the study was performed, GLP was not compulsory.

2.3 Deviations Not relevant.

3 MATERIALS AND METHODS

3.1 Test material

3.1.1 Unlabelled material: Cyfluthrin (Baythroid)

3.1.2 Lot/Batch number: Not stated

3.1.3 Specification: As given in Sections 2

3.1.4 Description: Not given

Section A6.15.5/01 Any other available information that is relevant

Annex Point IIIA.XI.1.8

		Feeding study in Hen
3.1.5	Purity	94.3%
3.1.6	Stability	stable 28 days after fortification with 2 ppm, triplicate analysis yielded 1.8, 1.9 and 1.8 ppm.
3.2	**Reference substances**	Not used
3.3	**Test Animals**	
3.3.1	Species	Gallus gallus
3.3.2	Strain	white Leghorn
3.3.3	Sex	hens
3.3.4	Age/weight at study initiation	1364 - 1481 g (averages)
3.3.5	Number of animals per group	Four groups of 10 hens each
3.3.6	Control animals	Yes, one control group
3.4	**Administration/ Exposure**	
3.4.1	administration	Cyfluthrin administered with the feed over 28 days
3.4.2	Concentration of test substance	0, 2, 6 and 20 ppm diet
3.4.3	Volume administered	Not stated.
1.1.1	Sampling	The eggs were collected daily and after removal of the shells, the eggs of each group were combined to a mixed sample. The animals were sacrificed after 28 days and samples of the tissues (liver, meat, heart, gizzard, fat, kidney and skin) were taken.
3.5	**Extraction and preparation of samples**	Tissue and egg samples were extracted according to the method of Shaw, *et al* (MR85883). Cyfluthrin is removed from the sample matrix, by organic hexane or acetone/chloroform extraction. The organo-soluble extract is partitioned with various solvents to remove lipids and polar and non-polar interferences. The final purification step is a chromatography of the sample on either a silica gel column or a Florisil Sep-Pak.
3.6	**Separation and isolation of metabolites**	Sample materials of fat, meat, liver, gizzard and skin were later analysed for COOH-cyfluthrin (FCR 2728), FPB-alc (FCR 1261), FPB-ald (FCR 1260) and FBP-acid (COE 538/78) according to method of Shaw, *et al* (MR86217) : Cyfluthrin and metabolites are extracted from animal tissues with acetone/chloroform. The sample extract is purified to eliminate some naturally occurring compounds by methanol/water, ethyl acetate partitioning. The sample extract is divided after a gel permeation column clean-up. One-fourth of the sample extract is subjected to column chromatography to separate cyfluthrin from 'acid'-cyfluthrin. The other three-fourths of the sample extract is subjected to column chromatographic clean-up, oxidation where 'acid'-cyfluthrin is degraded to unknown, non-interfering compounds , partitioning where cyfluthrin is removed.

Section A6.15.5/01 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in Hen

3.7	**Analysis and identification of samples**	Tissue and egg samples were analyzed for cyfluthrin residue according to the methods of Shaw, *et al*: Cyfluthrin: method MR85883 : The purified sample is subjected to gas chromatography with an electron capture detector Metabolites: method MR86217: COOH-cyfluthrin fraction (after methylation) is subjected to gas liquid chromatographic analysis, while FPB-acid fraction is subjected to high pressure liquid chromatographic analysis after methylation.

4 RESULTS AND DISCUSSION

4.1	**Somatic and behavioural effects**	All hens exhibited normal behaviour throughout the study. Egg production and body weight appeared to decline in all groups during the study. These declines may have been influenced by the relatively high temperatures of 29 to 33°C inside the experiment room for the last 3 weeks of the study when the outside temperatures were near 38°C.
4.2	**Residues identification**	Due to the fact that the eggs of the 6-20 ppm dose groups did not show any quantifiable residues (<0.01 mg/kg), the eggs of the low dose group (2 ppm) were not analysed. In addition, no residues exceeding the limit of determination of 0.01 mg/kg could be found in tissues with the exception of the fatty tissue and the skin in the highest dose group (20 ppm). The residues amounted to 0.05 mg/kg in the fat and to 0.01 mg/kg in the skin (see table 6.15.5/01-1).
4.3	**Metabolites identification**	Residues of 'acid'-cyfluthrin (FCR 2728), FCR 1261, FCR 1260 or COE 538/78 could not be found in any dose group and in any tissue above the limit of determination (0.01 mg/kg) with the exception of the liver. In the dose groups 6 and 20 ppm 0.02 mg/kg cyfluthrin equivalents was detected, whereas it was <0.01 mg/kg in the low dose group (2 ppm) (see table 6.15.5/01-2).

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	A poultry feeding was conducted to determine the transfer of cyfluthrin to eggs and tissues of laying hens. Four groups of 10 hens each (white Leghorn) were administered cyfluthrin with the feed over 28 days. The dose corresponded to 0 (control), 2, 6 and 20 ppm cyfluthrin in feed. The eggs were collected daily and after removal of the shells, the eggs of each group were combined to a mixed sample. The animals were sacrificed after 28 days and samples of the tissues (liver, meat, heart, gizzard, fat, kidney and skin) were taken.
5.2	**Results and discussion**	Due to the fact that the eggs of the 6-20 ppm dose groups did not show any quantifiable cyfluthrin residues (<0.01 mg/kg), the eggs of the low dose group (2 ppm) were not analysed. In addition, no cyfluthrin residues exceeding the limit of determination of 0.01 mg/kg could be found in tissues with the exception of the fatty tissue and the skin in the highest dose group (20 ppm). The cyfluthrin residues amounted to 0.05 mg/kg in the fat and to 0.01 mg/kg in the skin (see table 6.15.5/01-1) Residues of 'acid'-cyfluthrin (FCR 2728), FCR 1261, FCR 1260 or COE 538/78 could not be found in any dose group and in any tissue above the limit of determination (0.01 mg/kg) with the exception of the liver. In the dose groups 6 and 20 ppm 0.02 mg/kg cyfluthrin equivalents was detected, whereas it was <0.01 mg/kg in the low dose group (2 ppm) (see Table 6.15.5/01-2).

Section A6.15.5/01 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in Hen

5.3	**Conclusion**	In eggs and poultry tissues after feeding of 2, 6 and 20 ppm in feed for 28 days, no residues exceeding 0.01 mg/kg could be found with the exception of the fatty tissue and the skin in the highest dose group. The residues amounted to 0.05 mg/kg in the fat and to 0.01 mg/kg in the skin.
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	2007/01/30
Materials and Methods	Acceptable
Results and discussion	Due to the fact that the eggs of the 6-20 ppm dose groups did not show any quantifiable cyfluthrin residues (<0.01 mg/kg), the eggs of the low dose group (2 ppm) were not analysed. In addition, no cyfluthrin residues exceeding the limit of determination of 0.01 mg/kg could be found in tissues with the exception of the fatty tissue and the skin in the highest dose group (20 ppm). The cyfluthrin residues amounted to 0.05 mg/kg in the fat and to 0.01 mg/kg in the skin (see table 6.15.5/01-1) Residues of 'acid'-cyfluthrin (FCR 2728), FCR 1261, FCR 1260 or COE 538/78 could not be found in any dose group and in any tissue above the limit of determination (0.01 mg/kg) with the exception of the liver. In the dose groups 6 and 20 ppm, 0.02 mg/kg cyfluthrin equivalents was detected, whereas it was <0.01 mg/kg in the low dose group (2 ppm)
Conclusion	The feeding study on laying hens shows a cyfluthrin transfer in fat rich tissues after oral application. Under consideration of the recommended precautions on the label no additional contribution to the intake of livestock animal is expected. Since the residues in animal matrices are low, it can be assumed that the established MRLs for cyfluthrin are also sufficient in combination with the use as a biocide.
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.15.5/01 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in Hen

Table A6.15.5/01-1 Cyfluthrin residues in eggs and tissues of hens after daily feeding with cyfluthrin (28 days)

Dose ppm	Cyfluthrin residue mg/kg					
	Eggs	Fat	Muscle	Liver	Gizzard	Skin
Control	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
6	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
6	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
20	<0.01	0.05	<0.01	<0.01	<0.01	0.01
20	<0.01	0.05	<0.01	<0.01	<0.01	0.01

Table A6.15.5/01-2: Residues of cyfluthrin metabolites in eggs and tissues of hens after daily feeding with cyfluthrin (28 days)

Metabolites	Dose ppm	Cyfluthrin equivalent mg/kg				
		Fat	Muscle	Liver	Gizzard	Skin
COOH-cyfluthrin	Control	<0.01	<0.01	<0.01	<0.01	<0.01
	20	<0.01	<0.01	<0.01	<0.01	<0.01
	6	na	na	<0.01	na	na
	2	na	na	<0.01	na	na
FBP-acid +FBPalc +FBPald	Control	<0.01	<0.01	<0.01	<0.01	<0.01
	20	<0.01	<0.01	0.02	<0.01	<0.01
	6	na	na	0.02	na	na
	2	na	na	<0.01	na	na

na = not analysed

Section A6.15.5/02 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in cow

Official use only

1 REFERENCE

1.1 Reference

[redacted] (1983)
Baythroid 28 day feeding study, [redacted]
Bayer Report No.: MR-86045, BES Ref.: M-055028-02-1
Report Date: 14.09.1983, Amended: 23.01.1984
Unpublished

Re-analysis :
[redacted] (1985)
Baythroid - Identity of major components in cow liver, [redacted]
Bayer Report No.: MR-88970, BES Ref.: M-053789-01-1
Report Date: 05.03.1985
Unpublished

Methods of analysis :
[redacted] 1983)
An analytical method for Baythroid in bovine and poultry tissues, milk and eggs, [redacted]
Bayer Report No.: 85883, BES Ref.: M-066143-01-1
Report Date: 02.04.1985
Unpublished

[redacted] (1985)
An analytical method for quantitating Baythroid metabolite residues in animal tissues, [redacted]
Bayer Report No.: 86217, BES Ref.: M-066384-01-1
Report Date: 14.11.1983
Unpublished

1.2 Data protection Yes

1.2.1 Data owner Bayer CropScience

1.2.2 Companies with letters of access

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.

At the time the study was undertaken, no particular method was compulsory.

2.2 GLP No.

When the study was performed, GLP was not compulsory.

2.3 Deviations Not relevant.

Section A6.15.5/02 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in cow

3 MATERIALS AND METHODS

3.1	**Test material**	
3.1.1	Unlabelled material	Cyfluthrin (Baythroid)
3.1.2	Lot/Batch number	not stated
3.1.3	Specification	As given in Sections 2 and 3 of Doc IIIA
3.1.4	Description	As given in Sections 2 and 3 of Doc IIIA
3.1.5	Purity	91%
3.1.6	Stability	Known to be stable from other studies cited in.
3.2	**Reference substances**	Not used.
3.3	**Test Animals**	
3.3.1	Species/strain	Holstein
3.3.2	Sex	Dairy cows
3.3.3	Age/weight at study initiation	345-630 kg
3.3.4	Number of animals per group	12 lactating cows in four groups, 3 cows per dose level
3.3.5	Control animals	yes
3.4	**Administration/ Exposure**	
3.4.1	Administration	Daily after milking in the morning over a period of 29 days by oral administration in capsules.
3.4.2	Concentration of test substance	The dose corresponded to 0 (control), 5, 15 and 50 ppm cyfluthrin in dry feed.
3.4.3	Volume administered	Capsule pre-filled with 9.0 g of a-lactose.
3.4.4	Sampling	The animals were milked twice daily. Aliquots of the milk of the evening and the following morning were mixed and considered as sample of 1 day. The animals were sacrificed after 29 days shortly after administration of the last capsule and samples of the respective tissues (fat, meat, liver and kidney) were taken.
3.5	**Extraction and preparation of samples**	Tissue and milk samples were extracted according to the method of Shaw, *et al* (MR85883). Cyfluthrin is removed from the sample matrix, by organic hexane or acetone/chloroform extraction. The organo-soluble extract is partitioned with various solvents to remove lipids and polar and non-polar interferences. The final purification step is a chromatography of the sample on either a silica gel column or a Florisil Sep-Pak.

Section A6.15.5/02 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in cow

3.6	**Separation and isolation of metabolites**	Sample materials of liver and kidney were later analysed for COOH-cyfluthrin (FCR 2728), FPB-alc (FCR 1261), FPB-ald (FCR 1260) and FBP-acid (COE 538/78) according to method of Shaw, *et al* (MR86217) : Cyfluthrin and metabolites are extracted from animal tissues and milk with acetone/chloroform. The sample extract is purified to eliminate some naturally occurring compounds by methanol/water, ethyl acetate partitioning. The sample extract is divided after a gel permeation column clean-up. One-fourth of the sample extract is subjected to column chromatography to separate cyfluthrin from 'acid'-cyfluthrin. The other three-fourths of the sample extract is subjected to column chromatographic clean-up, oxidation where 'acid'-cyfluthrin is degraded to unknown, non-interfering compounds , partitioning where cyfluthrin is removed.
3.7	**Analysis and identification of samples**	Tissue and milk samples were analyzed for cyfluthrin residue according to the methods of Shaw, *et al*: Cyfluthrin: method MR85883 : The purified sample is subjected to gas chromatography with an electron capture detector Metabolites: method MR86217: COOH-cyfluthrin fraction (after methylation) is subjected to gas liquid chromatographic analysis, while FPB-acid fraction is subjected to high pressure liquid chromatographic analysis after methylation.
		4 RESULTS AND DISCUSSION
4.1	**Somatic and behavioural effects**	The animals exhibited normal behavior throughout the study. Weekly milk production did not vary significantly during the course of the test. The slight increases in bodyweight in all groups corresponded to the slightly increased feed consumption. The increases are not considered significant.
4.2	**Residues identification**	The highest cyfluthrin residues were found with 0.26 mg/kg after 14 days feeding in the milk of the highest dose group. After 29 days they decreased to 0.1 - 0.17 mg/kg. The milk of the 15 ppm medium dose group contained residues ranging from 0.03 - 0.08 mg/kg and that of the lowest dose group (5 ppm) contained a maximum 0.02 mg/kg after 29 days of feeding. (see Table A6.15.5/02-1) The highest average residues in the highest dose group were 2.6 mg/kg in fat, 0.03 mg/kg in meat. The samples for liver and kindney were re-analysed by Murphy (1985, MR88970) and 0.13 mg/kg in the liver and 0.17 mg/kg in the kidney could be determined. Kidney and liver samples of the low dose group were not analysed since residues were <0.01 mg/kg in the 15 ppm dose group. A maximum of 0.02 mg/kg of cyfluthrin were found in the meat and 0.73 mg/kg in the fat of the 15 ppm dose group, while the samples of the low dose group contained <0.01 mg/kg (meat) and 0.21 - 0.3 mg/kg (fat). (see Table A6.15.5/02-2 and A6.15.5/02-4)

Section A6.15.5/02 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in cow

4.3	**Metabolites identification**	COOH-cyfluthrin (FCR 2728) could not be detected in any of the dose groups in the liver or the kidney at levels exceeding the limit of determination (0.01 mg/kg). In the medium dose group (15 ppm) the residue of FPB acid (COE 538/78) was found at a maximum of 0.01 mg/kg (cyfluthrin equivalents) in the kidney (average <0.01 mg/kg) and below the limit of determination (<0.01 mg/kg) in the liver. Samples from animals in the highest dose group (50 ppm) contained an average of 0.03 mg/kg FPB acid (COE 538/78), cyfluthrin equivalents, in the liver and in the kidney, respectively. (see Table A6.15.5/02-3)

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	A dairy cattle feeding study was conducted where twelve lactating cows in four groups were given cyfluthrin daily after milking in the morning over a period of 29 days by oral administration in capsules. The dose corresponded to 0 (control), 5, 15 and 50 ppm cyfluthrin in dry feed. The animals were milked twice daily. Aliquots of the milk of the evening and the following morning were mixed and considered as sample of 1 day. The animals were sacrificed after 29 days shortly after administration of the last capsule and samples of the respective tissues were taken.
5.2	**Results and discussion**	The highest cyfluthrin residues were found with 0.26 mg/kg after 14 days feeding in the milk of the highest dose group. After 29 days they decreased to 0.1 - 0.17 mg/kg. The milk of the 15 ppm medium dose group contained cyfluthrin residues ranging from 0.03 - 0.08 mg/kg and that of the lowest dose group (5 ppm) contained a maximum 0.02 mg/kg after 29 days of feeding. The highest average residues in the highest dose group were 2.6 mg/kg in fat, 0.03 mg/kg in meat. The samples for liver and kidney were re-analysed by Murphy (1985, MR88970) and 0.13 mg/kg in the liver and 0.17 mg/kg in the kidney could be determined. Kidney and liver samples of the low dose group were not analysed since residues were <0.01 mg/kg in the 15 ppm dose group. A maximum of 0.02 mg/kg of cyfluthrin were found in the meat and 0.73 mg/kg in the fat of the 15 ppm dose group, while the samples of the low dose group contained <0.01 mg/kg (meat) and 0.21 - 0.3 mg/kg (fat). 'Acid'-cyfluthrin (FCR 2728) could not be detected in any of the dose groups in the liver or the kidney at levels exceeding the limit of determination (0.01 mg/kg). In the medium dose group (15 ppm) the residue of FPB acid (COE 538/78) was found at a maximum of 0.01 mg/kg (cyfluthrin equivalents) in the kidney (average <0.01 mg/kg) and below the limit of determination (<0.01 mg/kg) in the liver. Samples from animals in the highest dose group (50 ppm) contained an average of 0.03 mg/kg COE 538/78 (cyfluthrin equivalents) in the liver and in the kidney, respectively.
5.3	**Conclusion**	The results show that in case of residues of 5 ppm cyfluthrin in dry feed, measurable residues were only found in the milk (maximum 0.02 mg/kg) and the fat (max. 0.3 mg/kg) but the residues were proportional to the feeding levels. All metabolites determined in liver and kidney were <0.01 mg/kg.
5.3.1	Reliability	2
5.3.2	Deficiencies	No

Section A6.15.5/02 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in cow

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007-01-30
Materials and Methods	Acceptable.
Results and discussion	The highest cyfluthrin residues were found with 0.26 mg/kg after 14 days feeding in the milk of the highest dose group. After 29 days they decreased to 0.1 - 0.17 mg/kg. The milk of the 15 ppm medium dose group contained cyfluthrin residues ranging from 0.03 - 0.08 mg/kg and that of the lowest dose group (5 ppm) contained a maximum 0.02 mg/kg after 29 days of feeding. The highest average residues in the highest dose group were 2.6 mg/kg in fat, 0.03 mg/kg in meat. The samples for liver and kidney were re-analysed by Murphy (1985, MR88970) and 0.13 mg/kg in the liver and 0.17 mg/kg in the kidney could be determined. Kidney and liver samples of the low dose group were not analysed since residues were <0.01 mg/kg in the 15 ppm dose group. A maximum of 0.02 mg/kg of cyfluthrin were found in the meat and 0.73 mg/kg in the fat of the 15 ppm dose group, while the samples of the low dose group contained <0.01 mg/kg (meat) and 0.21 - 0.3 mg/kg (fat). 'Acid'-cyfluthrin (FCR 2728) could not be detected in any of the dose groups in the liver or the kidney at levels exceeding the limit of determination (0.01 mg/kg). In the medium dose group (15 ppm) the residue of FPB acid (COE 538/78) was found at a maximum of 0.01 mg/kg (cyfluthrin equivalents) in the kidney (average <0.01 mg/kg) and below the limit of determination (<0.01 mg/kg) in the liver. Samples from animals in the highest dose group (50 ppm) contained an average of 0.03 mg/kg COE 538/78 (cyfluthrin equivalents) in the liver and in the kidney, respectively.
Conclusion	The feeding study on cows shows a cyfluthrin transfer in fat rich tissues and milk after oral application. Under consideration of the recommended precautions on the label no additional contribution to the intake of livestock animal is expected. It can be assumed that the established MRLs for cyfluthrin are also sufficient in combination with the use as a biocide.
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*

Section A6.15.5/02 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in cow

Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

A6.15.5/02-1 : Cyfluthrin residues in Milk from dairy cows dosed daily with cyfluthrin for 28 days

Cow No	Dose level	Cyfluthrin (ppm)			
		Day 7	Day 14	Day 21	Day 28
218	control	<0.01	<0.01	<0.01	<0.01
219	control	<0.01	<0.01	<0.01	<0.01
223	control	<0.01	<0.01	<0.01	<0.01
216	5	NA*	NA*	NA*	0.02
225	5	NA*	NA*	NA*	0.02
226	5	NA*	NA*	NA*	0.01
217	15	NA*	NA*	NA*	0.03
222	15	NA*	NA*	NA*	0.03
227	15	NA*	NA*	NA*	0.08
215	50	0.16	0.25	0.21	0.17
220	50	0.19	0.26	0.21	0.16
221	50	0.08	0.16	0.12	0.10

NA* : not analysed.

A6.15.5/02-2 : Cyfluthrin residues in tissue from dairy cows dosed daily with cyfluthrin for 28 days

Cow No	Dose level	Cyfluthrin (ppm)			
		Fat	Meat	Liver	Kidney
218	control	<0.01	<0.01	<0.01	<0.01
216	5	0.30	<0.01	NA*	NA*
225	5	0.24	<0.01	NA*	NA*
226	5	0.21	<0.01	NA*	NA*
217	15	0.66	<0.01	<0.01	<0.01
222	15	0.71	<0.01	<0.01	<0.01
227	15	0.73	0.02	<0.01	<0.01
215	50	2.38	0.03	<0.01	0.01
220	50	2.54	0.03	<0.01	<0.01
221	50	3.00	0.03	<0.01	0.02

NA* : not analysed.

A6.15.5/02-3 : Cyfluthrin metabolite residues in tissues from dairy cows dosed daily with cyfluthrin for 28 days

Cow No	Dose level	ppm (Cyfluthrin equivalents)			
		COOH-Cyfluthrin		FBP-acid , FBP-alc and FBP-ald as FBP- acid	
		Kidney	Liver	Kidney	Liver
218	control	<0.01	<0.01	<0.01	<0.01
216	5	<0.01	<0.01	<0.01	<0.01
225	5	<0.01	<0.01	<0.01	<0.01
226	5	<0.01	<0.01	<0.01	<0.01
217	15	<0.01	<0.01	<0.01	<0.01
222	15	<0.01	<0.01	<0.01	<0.01
227	15	<0.01	<0.01	0.01	<0.01
215	50	<0.01	<0.01	0.05	0.03
220	50	<0.01	<0.01	<0.01	0.02
221	50	<0.01	<0.01	0.02	0.02

A6.15.5/02-4 : Cyfluthrin residues in liver and kidney sample from dairy cows fed 50 ppm cyfluthrin for 28 days : re-analysis using Tekmar tissuemizer extractraction instead of omni-mixer.

Cow No	Dose level	Cyfluthrin (ppm)	
		Liver	Kidney
215	50	0.14	0.18
220	50	0.13	0.16
221	50	0.13	0.16
control	0	<0.01	0.01

Section A6.15.5/03 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in cow

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (1994). Cyfluthrin - A 28 - day dairy cattle feeding study, [redacted] Report No.: 106628, Edition Number: M-054521-01-1 Date: 13.12.1994 unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Bayer CropScience AG
1.2.2	1.2.2 Companies with letters of access	
1.2.3	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 2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No. At the time the study was undertaken, no particular method was compulsory.
2.2	**GLP**	No. When the study was performed, GLP was not compulsory.
2.3	**Deviations**	Not relevant.

3 MATERIALS AND METHODS

3.1	**Test material**	
3.1.1	Unlabelled material	Cyfluthrin (Baythroid)
3.1.2	Lot/Batch number	40302777
3.1.3	Specification	As given in Sections 2 and 3 of Doc IIIA
3.1.4	Description	As given in Sections 2 and 3 of Doc IIIA
3.1.5	Purity	92%
3.1.6	Stability	stable during the course of the study under ambient temperature
3.2	**Reference substances**	Not used.
3.3	**Test Animals**	
1.1.1	Species/strain	Holstein/Fresian
3.3.1	Sex	Dairy cows
3.3.2	Age/weight at study initiation	329-508 kg
3.3.3	Number of animals per group	Four groups of dairy cows, three cows/treatment group

Section A6.15.5/03 Any other available information that is relevant

Annex Point IIIA.XI.1.8

		Feeding study in cow
3.3.4	Control animals	Yes, one cow as control
3.4	**Administration/ Exposure**	
3.4.1	administration	Daily with capsules containing cyfluthrin at levels equivalent to 0, 15, 50 and 150 ppm for 28 consecutive days.
3.4.2	Concentration of test substance	The dose corresponded to 0 (control), 5, 15 and 50 ppm cyfluthrin in dry feed.
3.4.3	Volume administered	Capsule pre-filled with 5.0 g of α-lactose.
3.4.4	Sampling	Milk samples were collected in the morning and in the evening. Aliquots of the milk of the evening and the following morning were mixed and considered as sample of 1 day. After 28-day feeding period, animals were sacrificed, and composite fat (omental, renal, and subcutaneous), composite muscle (round, flank, and loin), liver, and kidney tissues were collected and cut into small chunks and frozen immediately after collection.
3.5	**Extraction and preparation of samples**	Tissue and milk samples were extracted according to the method of Shaw, *et al* (MR85883) Cyfluthrin is removed from the sample matrix, by organic hexane or acetone/chloroform extraction. The organo-soluble extract is partitioned with various solvents to remove lipids and polar and non-polar interferences. The final purification step is a chromatography of the sample on either a silica gel column or a Florisil Sep-Pak.
3.6	**Separation and isolation of metabolites**	Not performed
3.7	**Analysis and identification of samples**	Tissue and milk samples are subjected to gas chromatography with an electron capture detector.
		4 RESULTS AND DISCUSSION
4.1	**Somatic and behavioral effects**	No major changes in milk production or body weights were seen among treatment groups.
4.2	**~~Metabolites~~ Residues identification**	No major changes in milk production or body weights were seen among treatment groups. Cyfluthrin average residue in milk reached a maximum of 0.08 mg/kg at 14 days in the 15 ppm group, 0.24 mg/kg at 14 days in the 50 ppm group, and 0.7 mg/kg at 21 days in the 150 ppm group.(See table 6.15.5/03-1). Cyfluthrin average residue in the fat was 1.16 mg/kg in the 15 ppm group, 2.69 mg/kg in the 50 ppm group, and 6.81 mg/kg in the 150 ppm group. All other tissues (muscle, liver and kidney) in the 15 ppm group contained ≤0.01 mg/kg cyfluthrin. Average residues in the 50 ppm group were 0.04, <0.01, and 0.03 mg/kg for muscle, liver, and kidney, respectively. Tissues from the 150 ppm group contained cyfluthrin average residues of 0.07, 0.02, and 0.05 mg/kg for muscle, liver, and kidney, respectively.(See Table 6.15.5/03-2)

Section A6.15.5/03 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in cow

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Four groups of dairy cows (three cows/treatment group and one cow as control) were fed daily with capsules containing cyfluthrin at levels equivalent to 0, 15, 50 and 150 ppm in feed for 28 consecutive days. Milk samples were collected in the morning and in the evening during the course of the study. After 28-day feeding period, animals were sacrificed, and tissues (fat, muscle, liver and kidney) were collected
5.2	**Results and discussion**	No major changes in milk production or body weights were seen among treatment groups. Cyfluthrin average residue in milk reached a maximum of 0.08 mg/kg at 14 days in the 15 ppm group, 0.24 mg/kg at 14 days in the 50 ppm group, and 0.7 mg/kg at 21 days in the 150 ppm group. Cyfluthrin average residue in the fat was 1.16 mg/kg in the 15 ppm group, 2.69 mg/kg in the 50 ppm group, and 6.81 mg/kg in the 150 ppm group. All other tissues (muscle, liver and kidney) in the 15 ppm group contained ≤0.01 mg/kg cyfluthrin. Average residues in the 50 ppm group were 0.04, <0.01, and 0.03 mg/kg for muscle, liver, and kidney, respectively. Tissues from the 150 ppm group contained cyfluthrin average residues of 0.07, 0.02, and 0.05 mg/kg for muscle, liver, and kidney, respectively.
5.3	**Conclusion**	The results show that in case of residues of 150 ppm cyfluthrin in dry feed, cyfluthrin average residues are below 0.1 mg/kg except in fat and milk. Furthermore as the residues were proportional to the feeding levels.
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	2009/02/19
Materials and Methods	Acceptable
Results and discussion	Acceptable
Conclusion	The feeding study on lactating cows shows a cyfluthrin transfer into fatty tissue and milk after oral application. Under consideration of the recommended precautions on the product label, no additional contribution to the cyfluthrin-intake of livestock animals is expected from the proposed use of Raid Cyfluthrin Foam and Solfac EW 050. It can be assumed that the MRLs established under the plant protection regulation are sufficient to also cover the biocidal use under PT 18
Reliability	1
Acceptability	Acceptable
Remarks	-
COMMENTS FROM ...	

Section A6.15.5/03 Any other available information that is relevant

Annex Point IIIA.XI.1.8

Feeding study in cow

Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

A6.15.5/03-1 : Cyfluthrin residues in Milk from dairy cows dosed daily with cyfluthrin for 28 days

Cow No	Dose level	Cyfluthrin (ppm)			
		Day 7	Day 14	Day 21	Day 28
230	0	<0.01	0.01	<0.01	<0.01
39	15	0.07	0.07	0.04	0.06
97	15	0.08	0.10	0.07	0.06
228	15	0.07	0.06	0.05	0.06
	average	0.07	0.08	0.05	0.06
230	0	<0.01	0.02	<0.01	<0.01
238	50	0.21	0.24	0.22	0.13
239	50	0.26	0.27	0.20	0.16
241	50	0.20	0.20	0.16	0.08
	average	0.22	0.24	0.19	0.12
230	0	<0.01	<0.01	<0.01	<0.01
229	150	0.49	0.56	0.50	0.44
235	150	0.68	0.89	0.96	0.49
240	150	0.50	0.41	0.65	0.43
	average	0.56	0.62	0.70	0.45

A6.15.5/03-2 : Cyfluthrin residues in tissue from dairy cows dosed daily with cyfluthrin for 28 days

Cow No	Dose level	Cyfluthrin (ppm)			
		Fat	Muscle	Liver	Kidney
230	0	0.09	<0.01	<0.01	<0.01
39	15	1.15	0.01	<0.01	0.01
97	15	1.36	<0.01	<0.01	<0.01
228	15	0.98	<0.01	<0.01	<0.01
	average	1.16	<0.01	<0.01	<0.01
230	0	NA	<0.01	<0.01	<0.01
238	50	3.30	0.07	<0.01	0.07
239	50	2.18	0.02	<0.01	0.02
241	50	2.58	0.03	<0.01	<0.01
	average	2.69	0.04	<0.01	0.03
230	0	0.08	<0.01	<0.01	<0.01
229	150	6.49	0.05	0.01	0.05
235	150	3.99	0.04	0.03	0.02
240	150	9.94	0.11	<0.01	0.07
	average	6.81	0.07	0.02	0.05

NA: not available

Document IIIA/ Section A6.15.6 BPD Data set IIIA/ Annex Point III-XI.2	Summary and evaluation of data submitted under point 6.15	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	Solfac® EW 050 is a 5% oil-in-water emulsion applied to animal housing buildings, to control flying and crawling insects. The product diluted in water is applied using a low pressure sprayer with a maximum application rate of 0.04 g cyfluthrin/m^2. Solfac® EW 050 is applied on the walls as a strip of 1-2 m width, on window frames and to the ceiling. The following precautions are recommended on the label : • Do not apply to surfaces on which food or feed are stored, prepared or supplied • Cover or remove feed, feed preparing equipment, water and feed suppliers with impermeable plastic sheets before application • Do not apply directly to animals • Do not contaminate ground, water bodies or watercourses with remaining spray liquid or unused insecticide, cleaning water or used container Cattle graze on grassland at least 4 to 6 weeks after treatment with manure. Otherwise the animals will not feed on grass. Furthermore, when manure is sprayed on grassland, cyfluthrin residues, which are adsorbed on organic matter of manure, are unlikely to contaminate plants leaves since manure particles will be swept into the soil by rainfall. The crop rotational study demonstrated that no residues were detected on forage, straw and grain of plants grown on treated soil (10 applications at the rate of 28 g cyfluthrin./ha/application). Therefore, it is unlikely that cattle will be exposed to cyfluthrin residues when grazing on treated grassland. Exposure of cattle and poultry to cyfluthrin after the use of Solfac® EW 050 in animals housing is addressed in the report titled “Assessment of Cattle and Poultry Exposure to and Risk From Application of Solfac® EW 050 in Animal Housing” given in appendix 2 of document IIB_Solfac. No detectable residues (<0.01 mg/kg) are expected in products of poultry and cattle origin, except for cattle fat. Residues in cattle fat are expected to be below the MRL laid down under crop protection directive and by the European Medicines Agency (EMEA). Therefore, when Solfac® EW 050 is used as recommended on the label, no food or feedstuffs contamination is expected. The use of Solfac® EW is not expected to raise any concern regarding residues of cyfluthrin in animal edible tissues.	

Document IIIA/ Section A6.15.6 BPD Data set IIIA/ Annex Point III-XI.2	Summary and evaluation of data submitted under point 6.15
	Raid® Cyfluthrin Foam uses will be intermittent and applications are localised. Product application is targeted, being applied into cracks and crevices via a hollow delivery tube or wand from a pressurised ready-to-use can. The foam expands in to the crack or crevice and dries quickly. Raid Cyfluthrin Foam can be applied indoors or outdoors to joints, splits, clefts, etc around the perimeters of indoor rooms and the outside of the building, and around doors and windows. Therefore, neither food or feedstuffs contamination nor potential exposure to humans or animals is expected.
Undertaking of intended data submission [ ]	Not applicable
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2007-01-30
Evaluation of applicant's justification	The justification provided by the applicant is acceptable.
Conclusion	Based on the justifications, the succeeding crop study and the feeding studies provided by the applicant additional residues are not expected in plant and animal commodities arising from the use as a biocidal substance. The already established MRLs for cyfluthrin are sufficient to cover the combined cyfluthrin residues from pesticidal, veterinary or biocidal uses. The following residue definitions are set of cyfluthrin residues: Plant matrices: Cyfluthrin including other mixtures of constituent isomers (sum of isomers) Animal matrices: Cyfluthrin (sum of isomers)
Remarks	none
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Document IIIA/ Section A6.16 **BPD Data set IIIA/ Annex Point III-VI.3.5**	**Any other tests related to the exposure of the active substance to humans, in its proposed biocidal products, that are considered necessary**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [ ]**	
Detailed justification:	No additional tests are necessary related to exposure of the active substance in its proposed biocidal products. The nature of the potential toxic effects is adequately understood based upon the studies detailed in Doc IIIA, section 6 and the exposure is adequately expressed in the Doc IIBs.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2010/08/02	
Evaluation of applicant's justification	Applicant's version is adopted.	
Conclusion	Non-submission is acceptable.	
Remarks	None	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Document IIIA/ Section A6.17 **BPD Data set IIIA/ Annex Point III-VI.6**	**If the active substance is to be used in products for action against plants then tests to assess toxic effects of metabolites from treated plants, if any, where different from those identified in animals shall be required**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X]**	
Detailed justification:	The active substance will not be used in biocidal products for action against plants. However cyfluthrin was reviewed under Directive 91/414/EEC and cyfluthrin is listed on Annex I of the Directive 91/414/EEC (COMMISSION DIRECTIVE 2003/31/EC of 11 April 2003 amending Council Directive 91/414/EEC to include 2,4-DB, beta-cyfluthrin, cyfluthrin, iprodione, linuron, maleic hydrazide and pendimethalin as active substances).	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2007-01-30	
Evaluation of applicant's justification	The justification provided by the applicant is acceptable.	
Conclusion	Cyfluthrin is not intended for action against plants. Nevertheless during the listing into Annex I of 91/414/EEC data for the metabolism of cyfluthrin in plants and animals was evaluated. No relevant differences in the metabolism patterns between plants and animals could be observed.	
Remarks	none	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		