Section A6.3.1 (01) Repeated dose toxicity

Annex Point IIA 6.3.1

Short-term repeated dose toxicity (oral) - Rat

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted]; Toxicity studies on the insecticide WL 43467 (cypermethrin): summary of results of preliminary experiments; [redacted].	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Chimac-Agriphar s.a.	
1.2.2			
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I authorisation	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No	
		Existing study comparable to method B7 of Directive 92/69/EEC	
2.2	**GLP**	No	
		GLP was not compulsory at the time the study was performed	
2.3	**Deviations**	Yes	
		Limited enquiries compared to a more modern study, no raw data included in report.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	WL 43467 (cypermethrin)	
		1:1 mixture of cis/trans isomers	
3.1.1	Lot/Batch number	19	
3.1.2	Specification	Deviating from specification given in section 2 as follows	
3.1.2.1	Description	Viscous liquid	
3.1.2.2	Purity	unknown	
3.1.2.3	Stability	Stable	X
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Not specified	
3.2.3	Source	[redacted]	
3.2.4	Sex	Males and females	
3.2.5	Age/weight at study initiation	5 weeks	
3.2.6	Number of animals per group	6 rats per sex, per group	
3.2.7	Control animals	Yes	

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3.3	**Administration/ Exposure**	Oral	
3.3.1	Duration of treatment	5 weeks	
3.3.2	Frequency of exposure	Not specified in report, dietary exposure.	
3.3.3	Postexposure period	None	
3.3.4	**Oral**		
3.3.4.1	Type	In diet	
3.3.4.2	Concentration	1.25, 5, 12.5, 37.5, 75 mg/kg /d (25, 100, 250, 750, 1500 ppm)	X
3.3.4.3	Vehicle	Not mentioned in report	
3.3.4.4	Concentration in vehicle	Not mentioned in report	
3.3.4.5	Total volume applied	Not mentioned in report	
3.3.4.6	Controls	Fed control diet only	
3.4	**Examinations**		
3.4.1	Observations		
3.4.1.1	Clinical signs	Yes	
3.4.1.2	Mortality	Yes	
3.4.2	Body weight	Yes (recorded weekly)	
3.4.3	Food consumption	Yes (recorded weekly)	
3.4.4	Water consumption	No	
3.4.5	Ophthalmoscopic examination	No	
3.4.6	Haematology	Yes (at necropsy) Packed cell volume, haemoglobin, erythrocyte count, leucocyte count, kaolin-cephalin coagulation time, prothombin time, differential leucocyte count	
3.4.7	Clinical Chemistry	Yes (at necropsy) Protein, urea, plasma alkaline phosphatase, plasma glutamic pyruvic transaminase, plasma glutamic oxaloacetic transaminase, sodium, potassium, chloride	
3.4.8	Urinalysis	No	
3.5	**Sacrifice and pathology**		
3.5.1	Organ Weights	Yes Organs: liver, kidneys, testes, spleen, brain, heart	

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3.5.2	Gross and histopathology	Yes Organs: brain, heart, kidney, lung, spleen, liver , oesophagus, stomach, intestine (small and large), urinary bladder, pancreas, salivary gland, thymus, lymph nodes, gonads, prostate or uterus, pituitary, adrenals, thyroid, eye, and peripheral nerve.
3.5.3	Other examinations	No
3.5.4	Statistics	Yes. Results were expressed as statistically significant but no further details of statistical methods detailed in the report.
3.6	**Further remarks**	
		4 RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical signs	Four out of 6 males and one out of six females fed 1500ppm cypermethrin (the top dose) exhibited piloerection, nervousness and uncoordinated movement from week 2 onwards. No signs of pyrethroid intoxication were seen in any other dose group.
4.1.2	Mortality	No mortalities recorded during the study.
4.2	**Body weight gain**	At 1500ppm, body weight gain and terminal body weight were reduced for both male and female rats.
4.3	**Food consumption and compound intake**	At 1500ppm, food intake was reduced for both male and female rats.
4.4	**Ophthalmoscopic examination**	Not performed
4.5	**Blood analysis**	
4.5.1	Haematology	Increase in hemoglobin in males in the 1500ppm group.
4.5.2	Clinical chemistry	At 1500ppm: Increase in blood urea concentration and hemoglobin in males and in plasma alkaline phosphatase activity in females
4.5.3	Urinalysis	Not performed
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	At 1500ppm : Significant increase in relative liver weight of females. A decrease in liver weight in male rats fed 250ppm cypermethrin was not considered to be of biological significance.
4.6.2	Gross and histopathology	No compound related histopathological effects at any dose level.

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4.7	**Other**	No other changes were observed which could be attributed to cypermethrin at any dose level.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	6 Charles River rats/sex/group were fed a diet containing cypermethrin (unknown purity) at 25, 100 250, 750 and 1500 ppm (converted doses 1.25, 5, 12.5, 37.5, 75 mg/kg bw/d.) for 5 weeks. 14 Animals/sex were used in the control group.	
5.2	**Results and discussion**	At 1500ppm (the top dose) body weight gain, food intake and terminal body weight were all reduced for both male and female rats. Clinical signs in this dose group were piloerection, nervousness, uncoordinated movement noted in 4/6 males and 1/6 female from week 2 onwards. An increase in blood urea concentration and hemoglobin was found in males in the 1500ppm group and an increase in plasma alkaline phosphatase activity was recorded in females. Significant increase in relative liver weight of females was also observed. No other changes were seen that could be attributed to the feeding of cypermethrin. No compound related histopathological effects were found. No signs of pyrethroid intoxication were seen in either male or female rats fed cypermethrin at concentrations of 750, 250, 100, or 25 ppm.	
5.3	**Conclusion**		
5.3.1	LO(A)EL		
5.3.2	NO(A)EL	NOAEL= 750 ppm (37.5 mg/kg bw/d)	
5.3.3	Other		
5.3.4	Reliability	2	X
5.3.5	Deficiencies	Yes. Deviations from official protocol – limited findings and no raw data were included in the brief summary report. However the study data is considered useful. Study evaluated and accepted under Directive 91/414/EC.	

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	March, 2007.
Materials and Methods	The applicants version is acceptable with the following amendments: 3.1.2.3. Stability: no data shown 3.3.4.2. Concentration: 25, 100, 250, 750, 1500 ppm
Results and discussion	The applicant’s version is adopted.

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Conclusion	LO(A)EL:1500 ppm NO(A)EL: 750 ppm However, this study is of poor validity: Results are only given in a (short) descriptive way. No data tables (means nor raw data) are made available.
Reliability	3
Acceptability	Acceptable, when considered as providing additional information for longer term repeated dose toxicity (e.g. 90d studies).
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	