Section A6.3.1 (02) Repeated dose toxicity

Annex Point IIA 6.3.1 **Short-term repeated dose toxicity (oral) - Dog**

			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	X
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	Dog	
3.2.2	Strain	beagle	
3.2.3	Source	Not specified in report	
3.2.4	Sex	Males and females	
3.2.5	Age/weight at study initiation	Not specified in report	
3.2.6	Number of animals per group	3 dogs 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, dietary exposure.	
3.3.3	Postexposure period	None	
3.3.4	**Oral**		
3.3.4.1	Type	In diet	
3.3.4.2	Concentration	0, 0.375, 3.75 and 37.5 mg/kg /d (0, 15, 150 and 1500 ppm)	X
3.3.4.3	Vehicle	Not mentioned in report	X
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 (observed daily)	
3.4.1.2	Mortality	Yes (observed daily)	
3.4.2	Body weight	Yes (recorded weekly)	
3.4.3	Food consumption	Yes (observed daily)	
3.4.4	Water consumption	No	
3.4.5	Ophthalmoscopic examination	Yes, in the top dose and control group animals at the start and end of the study.	
3.4.6	Haematology	Yes (at intervals throughout the study and at the end of the study) Packed cell volume, haemoglobin, erythrocyte count, leucocyte count, kaolin-cephalin coagulation time, prothombin time, differential leucocyte count	
3.4.7	Clinical Chemisty	Yes (at intervals throughout the study and at the end of the study) Protein, urea, plasma alkaline phosphatase, plasma glutamic pyruvic transaminase, plasma glutamic oxaloacetic transaminase, sodium, potassium, chloride, glucose.	
3.4.8	Urinalysis	No	
3.5	**Sacrifice and pathology**		
3.5.1	Organ Weights	Yes Organs: liver, kidneys, testes, spleen, brain, heart, thyroid.	

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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, peripheral nerve, gall bladder, aorta.
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	In the 1500ppm group (the top dose) animals exhibited apprehension, diarrhoea and vomiting, licking and chewing of the paws, whole body tremors and stiff exaggerated hind leg gait, and ataxia. Two animals (1 female, 1 male) convulsed during week 1 and 5 respectively. 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**	Significantly reduced at 1500ppm due to the observed loss of apetite exhibited by animals in this dose group.
4.3	**Food consumption and compound intake**	At 1500ppm animals exhibited a loss of apetite.
4.4	**Ophthalmoscopic examination**	No ocular abnormalities were found in the 1500ppm and control groups examined.
4.5	**Blood analysis**	
4.5.1	Haematology	In the 1500ppm group, male dogs showed an increase in WBC and Kaolin-cephalin coagulation time (KCCT) values at week 5 of the study.
4.5.2	Clinical chemistry	At 1500ppm: Female blood urea concentrations were increased and blood glucose levels decreased at week 5 of the study.
4.5.3	Urinalysis	Not performed
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	At 1500ppm : Increased relative thyroid weight in both males and females.
4.6.2	Gross and histopathology	No compound related gross pathological and 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**	3 Beagle dogs/sex/group were fed a diet containing cypermethrin (unknown puritiy) at 0, 15, 150 and 1500 ppm (0.375, 3.75 and 37.5 mg/kg bw/d) for 5 weeks.
5.2	**Results and discussion**	At 1500ppm: *Body weight gain, food intake and terminal body weight*: loss of appetite, the latter accounting for a significantly decreased body weight gain . *Clinical signs*: apprehension, diarrhoea and vomiting, licking and chewing of the paws, whole body tremors and stiff exaggerated hind leg gait, ataxia . Two animals convulsed during week 1 and 5 respectively. *Haematology/Clinical chemistry*: at week 5, female blood urea levels were increased and blood glucose levels decreased. Male dogs showed an increase in WBC and Kaolin-cephalin coagulation time (KCCT) values. *Organ weight*: Male and female relative thyroid weight were increased. 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 dogs fed cypermethrin at concentrations of 150 or 15 ppm.
5.3	**Conclusion**	
5.3.1	LO(A)EL	
5.3.2	NO(A)EL	NOAEL= 150 ppm (3.75 mg/kg bw/d)
5.3.3	Other	
5.3.4	Reliability	2
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 as dogs are a more sensitive species compared to rats. 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.

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Materials and Methods	The applicant's version is acceptable with the following amendments: 3.1.1. Lot/Batch: not mentioned 3.1.2.3. Stability: no data shown 3.3.4.2. Concentration: 0, 15, 150, 1500 ppm 3.3.4.3. Vehicle: aceton
Results and discussion	*The applicant's version is adopted.*
Conclusion	LO(A)EL: 1500 ppm NO(A)EL: 150 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	