Section A6.4.1 (02) Repeated dose toxicity

Annex Point IIA 6.4.1 **Subchronic Oral Toxicity - Dog**

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted]; A 13 week feeding study of WL 43467 (cypermethrin) in dogs; [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 B of Directive 87/302/EEC (corresponding OECD guideline 408)	X
2.2	**GLP**	No	
		GLP was not compulsory at the time the study was performed	
2.3	**Deviations**	Yes	
		Means: standard deviations not given	
		3 MATERIALS AND METHODS	
3.1	**Test material**	WL 43467 (cypermethrin)	
3.1.1	Lot/Batch number	30	
3.1.2	Specification	Deviating from specification given in section 2 as follows	
3.1.2.1	Description	liquid	
3.1.2.2	Purity	98.%	
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	Accredited breeder	
3.2.4	Sex	Males and females	
3.2.5	Age/weight at study initiation	8 – 11 months	
3.2.6	Number of animals per group	4 male, 4 female	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Oral	

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3.3.1	Duration of treatment	90 days
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	None
3.3.4	**Oral**	
3.3.4.1	Type	In food
3.3.4.2	Concentration	0, 0.125, 1.25, 12.5, 37.5 mg/kg /d ad libitum (0, 5, 50, 500, 1500 ppm)
3.3.4.3	Vehicle	A.R. grade acetone
3.3.4.4	Concentration in vehicle	Not mentioned in report
3.3.4.5	Total volume applied	400g daily of powdered diet moistened with 400ml water
3.3.4.6	Controls	Powdered diet plus equivalent volume of vehicle
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes (daily observation)
3.4.1.2	Mortality	Yes (recorded daily)
3.4.2	Body weight	Yes (recorded weekly)
3.4.3	Food consumption	Yes (daily observation)
3.4.4	Water consumption	No
3.4.5	Ophthalmoscopic examination	Yes (at start and end of the study)
3.4.6	Haematology	Yes (weeks 0, 1, 4, 8 and 13)
3.4.7	Clinical Chemisty	Yes (weeks 0, 1, 4, 8 and 13)
3.4.8	Urinalysis	No
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	Yes organs: liver, kidneys, testes, adrenal, brain, heart, thyroid
3.5.2	Gross and histopathology	Yes All dose groups organs: brain, heart, liver, aorta, spleen, kidneys, gonads, stomach, pancreas, lymph nodes, prostate/uterus, thyroid, thymus, eye, lungs, pituatry, adrenals, intestine, sciatic nerve, posterior tibial nerve, salivary glands, urinary bladder, gall bladder.
3.5.3	Other examinations	None

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3.5.4	Statistics	Yes, Body and organ weights analysed by covariance. Chemical and haematological parameters examined using analysis of variance.	
3.6	**Further remarks**	-	
		4 RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	Feeding 1500 ppm caused diarrhoea, licking and chewing of the paws, whole body tremors, a stiff exagegerated hind leg gait, ataxia, incoordination and hyperaesthesia in all except one female animal (which refused to eat the whole of her daily ration) in the dose group.	
4.1.2	Mortality	In the high dose group, 2 males and 2 females were sacrificed during week 6 and 10, 10 and 12 for humane reasons.	
4.2	**Body weight gain**	loss of 17-18% in the top dose group. This is though to be due to the inappetence oberved in intoxicated dogs at the 1500 ppm dose level.	X
4.3	**Food consumption and compound intake**	Reduced food intake in the top dose group.	X
4.4	**Ophtalmoscopic examination**	No compound related effects.	
4.5	**Blood analysis**		
4.5.1	Haematology	RBC count (↘ 6%) and and KCCT (↘ 21%) were significantly reduced in females at the top dose . Other minor differences were not attributable to the compound.	
4.5.2	Clinical chemistry	Minor difference not attributable to the test compound.	
4.5.3	Urinalysis	Minor difference not attributable to the test compound.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	No effects on organ weights which could be attributed to the test compound up to the 500 ppm dose level.	
4.6.2	Gross and histopathology	In the top dose group, animals showed non-specific pathological changes, mainly in the lungs, where focal bronchopneumonia was seen in several animals. Such changes can be expected in severe intoxication from any cause.	
4.7	**Other**		
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	4 Beagle dogs/sex/dose were fed a diet containing cypermethrin, WL43467(cypermethrin) (B.n°.30; 98%) at concentrations of 0, 5, 50, 500 or 1500 ppm over a period of 13 weeks. Converted dose : 0, 0.125, 1.25, 12.5, 37.5 mg/kg/d.	
5.2	**Results and discussion**	Clinical signs, were observed in the high dose group only along with reduced food consumption and bodyweight. No significant histopathological changes were attributed to the test compound.	

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5.3	**Conclusion**	
5.3.1	LO(A)EL	
5.3.2	NO(A)EL	500 ppm = 12.5 mg/kg bw
5.3.3	Other	
5.3.4	Reliability	2
5.3.5	Deficiencies	Yes. Protocol not fully in compliance with the method B of Directive 87/302/EEC or OECD 408(1981). Minor deviations from the official protocol. However the study is considered acceptable as it was conducted at an established research facility and used cypermethrin of known purity 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	April, 2007.
Materials and Methods	The applicant's version is acceptable with the following amendments: *2.1 Guideline:* The study is partly in compliance with method B.27 of Directive 87/302/EEC and OECD guideline 409 (1981). *3.1.2.3 Stability:* The stability of the test substance in the diet was not confirmed.
Results and discussion	The applicant's version is adopted with the following amendments: *4.2 Body weight gain and 4.3 Food consumption and compound intake:* The BE CA cannot verify the results because the data (table I) were not included in the report made available. *4.5.1 Haematology:* RBC count (↘ 6%) and and KCCT (↘ 15%) were significantly reduced in females at the 500 ppm dose at the end of the study (13 weeks). Other minor differences were not attributable to the compound. However, the KCCT values of the female dogs fed 500 ppm were consistently lower throughout the study (also at the start of the study) compared with the controls. No significant differences were found for male animals.
Conclusion	NO(A)EL: 12.5 mg/kg bw (500 ppm) The applicant's version is adopted.
Reliability	3 (2 when requested data is provided)
Acceptability	Will be acceptable when the body weight and food intake data will be provided.
Remarks	The data concerning body weight and food intake (nor raw data, nor mean ±SD) were not made available to the BE CA. These data were not included in the report made available.

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	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	