Section A6.8.1 (01) Teratogenicity Study

Annex Point IIA6.8.1. (01) **Teratogenicity test – rat, oral route**

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted]; WL 43467 (Cypermethrin) – Effects upon the progress and outcome of pregnancy in the rat; [redacted] Dates of experimental work: 8 August 1978 – 4 October 1978	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Chimac-Agriphar s.a.	
1.2.2	Companies with letter 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 authorisation	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No guidelines mentioned in report, however protocol is in compliance with method B.31 of Directive 87/302/EEC, corresponding OECD guideline 414 (1981).	
2.2	**GLP**	No. GLP was not compulsory at the time the study was performed.	
2.3	**Deviations**	No	
		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	Not specified in report	
3.1.2.2	Purity	98.2 % w/w	
3.1.2.3	Stability	Not mentioned in report	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	CD	
3.2.3	Source	[redacted]	
3.2.4	Sex	Female	
3.2.5	Age/weight at study initiation	Not specified in report	
3.2.6	Number of animals per group	25	
3.2.7	Control animals	Yes	
3.2.8	Mating period	Not specified in report, however the day on which a sperm positive smear or vaginal plug was detected was designated day 1 of pregnancy.	
3.3	**Administration/ Exposure**	Oral	

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3.3.1	Duration of exposure	Rats were dosed from days 6 to 15 of pregnancy
3.3.2	Postexposure period	Females killed on day 21 of gestation (i.e. post exposure period = 6 days)
		Oral
3.3.3	Type	Gavage
3.3.4	Concentration	0, 17.5, 35 or 70 mg/kg bw/d
		Based on the results of a preliminary range finding study to identify suitable dose levels for the main study.
3.3.5	Vehicle	corn oil
3.3.6	Concentration in vehicle	1% w/v
3.3.7	Total volume applied	Appropriate dosage volume
3.3.8	Controls	Vehicle (corn oil)
3.4	**Examinations**	
3.4.1	Body weight	Yes
3.4.2	Food consumption	No
3.4.3	Clinical signs	Yes
3.4.4	Examination of uterine content	Number of corpora lutea, number of implantations, number of resorption sites, number and distribution of live and dead foetus in each uterine horn.
3.4.5	Examination of foetuses	
3.4.5.1	General	Litter size, number of dead foetuses, foetal weight, sex.
3.4.5.2	Skeletal processing	Yes
3.4.5.3	Soft tissue	Yes
3.5	**Further remarks**	Pre-implantation and Post-implantation % loss calculated.
3.6	**Statistics**	Significance of inter group differences were examined by analysis of variance.

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4 RESULTS AND DISCUSSION

4.1 Maternal toxic Effects

Appearance and general condition of females in the 17.5 and 35 mg/kg dose groups was similar to that of the control animals throughout the study.

In the top dose group (70 mg/kg), 11 out of the 25 females displayed transient neurological disturbances after a minimum of three doses. Signs commenced 4-7 hours after dosing and ranged from slight splaying of the hind legs whilst walking to severe splaying of all limbs, involountary jaw movements, convulsive spasms and hypersensitivity to noise. Animals appeared to recover when observed the following morning before dosing and effects were not observed after the treatment period had been completed. One female from the top dose group was killed in extremis following severe convulsions on day 14 of gestation and a second was found dead on day 15. Both had received a total of nine doses.

Bodyweight changes in the 17.5 mg/kg were similar to the controls througout gestation. A slight dose-related depression of weight gain was noted in the 35 and 70 mg/kg groups during the dosing period ($P < 0.05$ and $P < 0.001$ respectively) however subsequently their performance was slightly better than the controls.

Examination of all females at necropsy on day 21 of gestation revealed no macroscopic changes that could be related to treatment with cypermethrin. Litter responses were unaffected by treatment of the dams (see table A6_8_1_01-1).

4.2 Teratogenic / embryotoxic effects

Examination of foetuses at necropsy, revealed a small number of abnormalities in all groups; the type and the incidences of which have previously been found to occur spontaneously in this strain of rats. No cypermethrin treatment related effects were found (see table A6_8_1_01-1).

4.3 Other effects

Litter responses were unaffected by treatment of the dams with cypermethrin.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

25 adult female CD strain rats/group were dosed with cypermethrin (B.n°30; 98.2 %) by gavage (0, 17.5, 35 and 70 mg/kg bw/d in corn oil) from day 6 of pregnancy to day 15 inclusive. All animals were examined daily for signs of adverse effects. On day 21 of gestation the females were killed and examined macroscopically for signs of adverse reactions to the treatment. Foetuses were removed for skeletal and visceral examination.

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5.2	**Results and discussion**	General condition of the dams in the two lower dose groups was similar to the controls. Transient neurological disturbances were observed in the top dose group (70 mg/kg) which in two cases resulted in death. Remaining affected animals were seen to recover the next day and showed no signs after the treatment period had ended. Slight retardation of maternal bodyweight gain was observed at the 35 and 70 mg/kg dose levels with performance improving once the treatment period had ended. No macroscopic changes were observed in females at day 21 of gestation. Litter responses were unaffected. No foetal abnormalities were observed which could be attributed to treatment with cypermethrin at any dose level. A small number of foetal abnormalities in all groups were noted at necropsy, however these were not treatment related.	
5.3	**Conclusion**	There was no embryotoxicity or teratogenicity associated with oral administration of cypermethrin.	
5.3.1	LO(A)EL maternal toxic effects	35 mg/kg bw/d	X
5.3.2	NO(A)EL maternal toxic effects	17.5 mg/kg bw/d	
5.3.3	LO(A)EL embryotoxic / teratogenic effects		
5.3.4	NO(A)EL embryotoxic / teratogenic effects	>70 mg/kg bw/d	
5.3.5	Reliability	2	
5.3.6	Deficiencies	No. Study is not GLP, however it is considered robust and was performed at a recognised facility and using test substance of known purity. Study has been evaluated and accepted under Directive 91/414/EC.	

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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	April, 2007.
Materials and Methods	The applicant's version is acceptable.
Results and discussion	The applicant's version is adopted (minor changes in table A6_8_1_01-1).
Conclusion	The applicant's version is adopted.
	LOAEL maternal = ~~30~~ 35 mg/kg bw
	NOAEL maternal = 17.5 mg/kg bw
	NOAEL embryotoxic/teratogenic effects > 70 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	

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Table A6_8_1_01-1 Teratogenicity of cypermethrin in rat – maternal and foetal effects

Endpoints/dose	**0 mg/kg bw/d**	**17.5 mg/kg bw/d**	**35 mg/kg bw/d**	**70 mg/kg bw/d**
Mortality				2/25 (after 9 doses)
Clinical signs				11/25 Slight to severe neurological disturbances after receiving 3 doses. Signs started 4-7 hours after dosing and regressed by the following morning.
Body weight changes:				
day 6-15			↘ *	↘ **
day 6-21				↘ *
nb. pregnant females	25	25	25	25
corpora lutea count	16.4	15.4	16	16.5
implantations	14.3	14.0	14.1	14.3
viable young ♂/♀	6.7/7.1	6.6/6.6	6.7/6.7	7.3/6.7
resorptions early/late	0.6/0.0	0.7/0.1	0.6/0.1	0.4/0.0
implantation loss % pre/post	12.7/3.9	8.6/6.0	11.8/4.8	13.5/2.5
Litter weight g	48.9	48.0	48.7	50.8
Foetal weight g	3.6	3.7	3.6	3.6

↘ significantly different from control (analysis of variance : * $p<0.05$; ** $p< 0.001$)