Section A6.1.3 Acute Inhalation Toxicity - Rat

Annex Point IIA 6.1.3

Rat, cypermethrin, Inhalation Exposure (LC50)

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted]; Acute Aerosol Inhalation Toxicity in the Rat of CGA 55186 Tech. (cypermethrin); [redacted] Dates of experimental work: 31 July 1984 – 5 December 1984	
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**	Yes Existing study with protocol based on method B.2. of Directive 92/69/EEC (corresponding OECD guideline 403)	
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**	CGA 55186 tech (cypermethrin cis:trans/40:60)	
3.1.1	Lot/Batch number	307046	
3.1.2	Specification	Deviating from specification given in section 2 as follows	
3.1.2.1	Description	Liquid, viscous	
3.1.2.2	Purity	92.6%	
3.1.2.3	Stability	Stable at room temperature	X
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Tif: RAI f (SPF), F3-crosses of RII 1/Tif x RII 2/Tif	
3.2.3	Source	[redacted]	
3.2.4	Sex	Males and females	
3.2.5	Age/weight at study initiation	Young adults, 229±29g (males) and 212±13g (females)	
3.2.6	Number of animals per group	5 males, 5 females	
3.2.7	Control animals	Yes	

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3.3	**Administration/ Exposure**	Inhalation	
3.3.1	Postexposure period	14 days	
		Inhalation	
3.3.2	Concentrations	Nominal concentration : 0, 2217, 3119, 3478, 5170 mg/m^3 Analytical concentration: 0, 970, 1926, 3462, 5328 mg/m^3	
3.3.3	Particle size	MMAD 1.6-2.9 µm, 82-94% of airborn particles had a diameter smaller than 7 µm.	X
3.3.4	Type or preparation of particles	Aerosol generated in a pneumatic nebulizer	
3.3.5	Type of exposure	Nose only	
3.3.6	Vehicle	Ethanol	
3.3.7	Concentration in vehicle	20 % w/w cypermethrin	
3.3.8	Duration of exposure	4 hours	
3.3.9	Controls	Ethanol (nominal concentration 32.4 g/m$^{3)}$	
3.4	**Examinations**	Mortality and clinical symptoms observed during exposure at 1, 2 and 4 hours, as well as 2 hours after exposure and then daily thereafter for 14 days. Dead animals removed twice daily on working days. Body weight recorded on days 7, 14 and at death. Gross necropsy at death and on all survivors at the end of the observation period.	
3.5	**Method of determination of LD_{50}**	Logit method (J. Berkson, J.Am.Stat. Ass. 39. 357-65, 1944)	
3.6	**Further remarks**	-	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Dyspnoea, sedation, exophthlamos, ruffled fur, curved and ventral body position, tremor, convulsions were seen in both sexes to a similar extent but with a dose-dependent increase in intensity and duration. In addition, the high dosed males showed extreme irritability and hyperkinetic behaviour. Surviving animals recovered within 9 days.	X
4.2	**Pathology**	About half of the animals in the two higher dose groups showed mottled, hemorrhagic, or edematous lungs, as well as dilatation of the stomach. In 2 males and 1 female exposed to 3462 mg/m^3, dilatations of the heart were found.	
4.3	**Other**	*Body weight*: male rats showed significantly lower weight gain during the first week after exposure and compensated with increased gain in the second week. Females were not significantly affected.	
4.4	**LD_{50}**	LC_{50} male : 3281 mg/m^3 (= 291 mg/kg bw) LC_{50} female : 5038 mg/m^3 (= 448 mg/kg bw) LC_{50} : 3894 mg/m^3 (= 327 mg/kg bw)	X

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		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Acute (4 hr) inhalation exposure in rat with 14 day post-treatment observation, based on EC method B.2.
5.2	**Results and discussion**	An LC50 of 3894 mg/m^3 (with 95% confidence limits) was calculated for both sexes.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	No, study was 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	March, 2007.
Materials and Methods	The applicant's version is adopted with the following amendments: 3.1.2.3 Stability: stable at room temperature. Guaranteed by sponsor, but data not shown. 3.3.3 Particle size: MMAD 1.6-2.9 µm, GSD 2.3-2.7, 82-94% of airborn particles with diameter < 7 µm (w/w).
Results and discussion	The applicant's version is adopted with the following amendments: 4.1 Clinical signs and Mortality: In the test groups, dyspnea, ruffled fur, curved body position, and convulsions were observed for both sexes to a similar extent but with a dose-dependent increase in intensity and duration. In addition, the high dosed males showed extreme irritability and hyperkinetic behaviour. Surviving animals recovered within 9 days. In the control (ethanol) group, sedation, dyspea, exophthalmos, and ruffled fur were observed at the day of application. All deaths occurred during the exposure period or within 2 hours thereafter. LC_{50} male: 3281 (2181-7102) mg/m³ air LC_{50} female: 5038 (lower: 2640) mg/m³ air LC_{50} both sexes: 3894 (2884-6607) mg/m³ air Table A6.1.3_1: Table for Acute Inhalation Toxicity
Conclusion	An LC50 (4 h) of 3894 mg/m³ (with 95% confidence limits) was calculated for both sexes. Nevertheless, the LC50 (4h) males = 3281 mg/m³ will be used for risk characterization purposes.
Reliability	2 (not GLP)
Acceptability	acceptable
Remarks	

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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	

Table A6.1.3_1: Table for Acute Inhalation Toxicity

Conc. [mg/km³]	*Number of dead / number of investigated*	*Time of death (range)*	*Observations*
0	0/10 (♂ 0/5;♀ 0/5)	-	Dyspnea, exophthalmus, ruffled fur, sedation. All animals recovered 1 day post-exposure.
970	0/10 (♂ 0/5;♀ 0/5)	-	Dyspnea, ruffled fur, curved body position. All animals recovered by day 5.
1926	1/10 (♂ 0/5;♀ 1/5)	Within 2 hours after exposure	Dyspnea, ruffled fur, curved body position. All animals recovered by day 7.
3462	3/10 (♂ 2/5;♀ 1/5)	During exposure	Dyspnea, ruffled fur, curved body position, convulsions. All animals recovered by day 9.
5328	8/10 (♂ 5/5;♀ 3/5)	During exposure and within 2 hours after expsore	Dyspnea, ruffled fur, curved body position, convulsions. All animals recovered by day 7.
LD_{50} value	1945 (1449-2676) mg/kg bw		