Reviewed By: Pamela Hurley, Ph.D. Pamela M. Hurley Date: 4/18/2001
Section I, Tox. Branch, IRS (H7509C)
Secondary Reviewer: Roger L. Gardner Date:
Section I, Tox. Branch, IRS (H7509C)

DATA EVALUATION REPORT
This is an updated DER for MRID 41387702 (lambda-cyhalothrin). Since an electronic copy was available, the changes were made in the original DER. They include an updated first page, a new executive summary and tables.

STUDY TYPE: 21-day inhalation - rat (82-4)
OPPTS Number: N/A
OPP Guideline Number: § N/A

DP BARCODE: N/A
P.C. CODE: 128867, 128897
SUBMISSION CODE: N/A
TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Lambda - cyhalothrin Technical (81.5% a.i.)

SYNONYMS: [(RS) α-cyano-3-phenoxybenzyl (z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane-carboxylate]; PP321, Karate, Commodore, Saber

CITATION: Hext, P. (1990) Lambda-Cyhalothrin Production Material: 21-day Sub-acute Inhalation Toxicity Study in the Rat: Lab Project Number: CTL/P/2772: MR0135. Unpublished study prepared by ICI Central Toxicology Laboratory. 102 p. MRID 41387702

SPONSOR: ICI Americas, Inc., Agricultural Products, Wilmington, Delaware 19897

EXECUTIVE SUMMARY: In a 21-day inhalation study, 10/sex/dose SPF Alpk:APfSD Wistar-derived) albino rats were exposed nose-only 6 hours/day, 5 days/week for 21 days to lambda-cyhalothrin (81.5% pure) at 0, 0.3, 3.3, or 16.7 µg/L (estimated to be approximately 0, 0.08, 0.90 or 4.5 mg/kg/day). The MMAD ranged from 1.47 to 1.91µm and the GSD ranged from 1.02 to 2.24 µm.

No treatment-related effects were observed at 0.3 µg/L. At 3.3 µg/L, the following was observed: salivation, lachrymation, paw flicking (males only), tail erections and splayed gait (males only); decreased body weight (94-95%, $p < 0.05$) and body weight gain (53-65%, $p < 0.01$) of control values; an increased incidence of punctate foci on the cornea; slight reductions in cholesterol levels in females ($p < 0.05$); decreased urine volume in males, slightly raised specific gravity of the urine in both sexes and reductions in urinary protein levels in males. At 16.7 µg/L, the following was observed: salivation, lachrymation, auditory hypoaesthesia, paw flicking, tail erection, splayed gait, decreased activity, reduced foot withdrawal (males only), head flicking, reduced righting reflex, shaking (males only), sides pinched in, reduced splay reflex, decreased visual placing response, absent pinna reflex (females only), ungroomed appearance (females only), tiptoe gait (males only), respiratory noise; decreased body weight (85-88%, $p < 0.01$) and body weight gain (<3-14%, $p < 0.01$) of control values); decreased food consumption (46-91% (♂), 56-87% (♀) of controls); changes in selected clinical chemistry values, particularly in

(08/30/2001 HIARC)

females; decreased urine volume, increased urine specific gravity, and decreased urinary protein. There was also a slight increase in the incidence of alveolitis in high dose females.

The NOAEL is 0.3 µg/L (0.08 mg/kg/day) and the LOAEL is 3.3 µg/L (0.90 mg/kg/day) based on clinical signs of neurotoxicity, decreased body weight gains, increased incidence of punctate foci in the cornea, slight reductions in cholesterol in females and slight changes in selected urinalysis parameters.

This inhalation toxicity study is classified as **acceptable nonguideline** and does not satisfy any particular guideline requirement. The study is too short for a guideline study and individual animal data were not provided.

COMPLIANCE: Signed and dated Data Confidentiality, GLP, Quality Assurance, and Flagging statements were provided.

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: [1 alpha (S*), 3 alpha (Z)]-(+/-)-cyano(3-phenoxyphenyl)methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate

Description: Brown/black viscous liquid
Batch #(s), Other #(s): ADH 553 225, Batch 367
Purity: Total pyrethroid content 91.6%, cis B content 81.5%
Source: ICI Agrochemicals, Fernhurst, Surrey, UK
Vehicle (if applicable): None
Positive Control(s) (if applicable): None

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Male and female SPF Alpk:APfSD Wistar-derived) albino rats
Age: 8 weeks
Weight(s): 238-297 g (males), 195-241 g (females)
Source(s): Alderley Park, Cheshire, UK

3. Procedure:

a. Atmosphere Generation: The test material was warmed to 70°C. The report stated that the "atmospheres were generated into a reservoir chamber using a glass concentric jet atomiser with a size-selective cyclone. The test compound was delivered to the atomiser using a peristaltic pump. A glass concentric jet atomiser was used above each exposure chamber to create a venturi, which pulled test atmosphere from the reservoir chamber, along a delivery tube and into the exposure chamber. Variation of flow rate through the atomiser was used to control the exposure chamber concentrations. Clean, dry air...was supplied to the exposure chamber via the atomiser and also directly as diluting air. Air flow rates were measured using variable area flowmeters".

Measurement of Particulate Concentrations: Particulate concentrations of the test atmospheres were measured gravimetrically (close to the animals breathing zone) at least 3 times during each exposure. The test atmosphere was drawn through a VM-1 filter at a flow rate of 2 liters/minute for a known time and the filter was weighed before and after sampling.

Measurement of Aerodynamic Particle Size Distributions: The particle size of the test atmosphere was measured daily for the first 3 days and once a week thereafter by means of a Marple Cascade Impactor. The mean amount of aerosol, by weight, in each size range, was then used to calculate the aerodynamic particle size distribution of the aerosol. The mass median aerodynamic diameter (D_{50}) and the geometric standard deviation (GSD) were calculated.

Determination of Atmospheric Concentrations: The atmospheric concentration of lambda-cyhalothrin was determined by dissolving the formulation deposited on the VM-1 filters and the stages of the cascade Impactor in ethyl acetate and then diluting further with ethyl acetate where necessary. The resultant solutions were then analysed by gas chromatography.

Exposure System: The animals were exposed nose-only for 6 hours/day for 5 days/week, giving a total of 15 days out of a 21-day period. Temperature and relative humidity were measured within each chamber during exposure.

b. Basis for Selection of Dose Levels: Dose levels were selected on the basis of the results from a 3-day preliminary inhalation study.

c. Animal Assignment and Dose Levels:

Table 1: Target Concentrations

Test Group	Target Exposure Level	Study Length 15/21 days	
	µg/L	Male	Female
Control	0	10	10
1	0.25	10	10
2	2.5	10	10
3	15.0	10	10

d. Clinical Observations and Mortality: Animals were examined daily every 30 minutes during exposure and following each exposure, and also daily on non-exposure days. Detailed clinical examinations were given following exposure days 1, 2, and 3 (males) and days 1, 2, and 5 (females), and on days 7, 11, 15, 18 and 22 (prior to post mortem).

e. Body Weight Determinations: Bodyweights were recorded prior to exposure on the same days as the detailed clinical examinations.

f. Food and/or Water Consumption: Weekly food consumption was calculated for each cage of rats from measurements made at the same time as bodyweights.

g. Ophthalmological Examinations (if applicable): The eyes of all animals were examined prior to exposure using a Fisons indirect ophthalmoscope after instillation of 0.5% tropicamide. Following exposure on day 21, the eyes of all animals were again examined.

h. Clinical Pathology: (*) recommended by Guidelines

1) Hematology:

Collection times for blood (including # of animals): Cardiac blood samples were taken at post mortem examination from all animals.

The following CHECKED (X) parameters were examined:

X		X	
x	Hematocrit (HCT)*	x	Mean corpuscular HGB (MCH)
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB conc. (MCHC)
x	Leukocyte count (WBC)*	x	Mean corpuscular volume (MCV)
x	Erythrocyte count (RBC)*		Reticulocytes
x	Platelet count*		
	Total plasma protein (TP)		
	Leukocyte differential count*		

2) Clinical Chemistry:

The following CHECKED (X) parameters were examined:

X		X	
	Electrolytes:		Other:
x	Calcium*	x	Albumin*
	Chloride*	x	Blood creatinine*
	Magnesium*		Blood urea nitrogen*
x	Phosphorus*	x	Cholesterol*
x	Potassium*		Globulins
x	Sodium*	x	Glucose*
	Enzymes:	x	Total bilirubin*
x	Alkaline phosphatase	x	Total protein*
	Cholinesterase	x	Triglycerides
x	Creatine phosphokinase*		A/G Ratio
	Lactic acid dehydrogenase	x	Plasma Urea
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		
	Gamma-glutamyl transpeptidase (GGTP)		

3) Urinalysis:

Collection times for urine (including # of animals): Urine samples were collected from five males and five females in each group after exposure day 20. The animals were deprived of food and water for 14 hours while the urine samples were being collected.

The following CHECKED (X) parameters were examined:

X		X	
| |	Appearance*	|x|	Glucose*
|x|	Volume*	|x|	Ketones*
|x|	Specific gravity*	| |	Bilirubin*
|x|	pH	|x|	Blood*
|x|	Sediment (microscopic)*	| |	Nitrate
|x|	Protein*	|x|	Urobilinogen

i. Gross Necropsy:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to end of exposure period and were subjected to complete gross pathological examinations: None.

Animals (groups) sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations: All animals.

j. Histopathology:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to the end of the exposure period and were subjected to microscopic examination: None.

Animals (groups) which were sacrificed at the end of the treatment/observation period and were subjected to microscopic examination: Tissues were removed from all animals and preserved. Tissues from the control and high dose group were prepared and examined microscopically, except the eye, Harderian gland, mammary gland, skin, spinal cord and voluntary muscle. Lung and abnormal tissues were prepared and examined in the low and mid-dose groups as well.

CHECKED (X) tissues were preserved for histopathological examination and (XX) tissues were weighed upon removal from the animal. The (*) tissues were recommended by the Guidelines. Paired organs were weighed together.

X		X		X	
	Digestive system		Cardiovasc./Hemat		Neurologic
	Tongue	x	Aorta*	xx	Brain*
x	Salivary glands*	xx	Heart*	x	Periph. nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord
					(3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	x	Spleen*		Eyes (optic n.)*
x	Jejunum*	x	Thymus*		Glandular
x	Ileum*		Urogenital	xx	Adrenals*
x	Cecum*	xx	Kidneys*		Lacrimal gland
x	Colon*	xx	Urinary bladder		Mammary gland*
x	Rectum*	x	Testes*	x	Parathyroids*
xx	Liver		Epididymides	x	Thyroids*
	Gall bladder*	x	Prostate		Other
x	Pancreas*	x	Seminal vesicle	x	Bone* (femur, sternum)
	Respiratory	x	Ovaries	x	Skeletal muscle*
xx	Trachea*	x	Uterus*		Skin
xx	Lung*	x	Cervix	x	All gross lesions and masses
x	Larynx				
x	Nasal cavity				

k. Statistical Analyses: The following types of statistically analyses were conducted: analysis of variance, analysis of covariance and two-sided Student's t-test.

B. RESULTS:

1. Atmospheric Generation and Measurements: The following table summarizes the study mean (mean of daily means) concentrations of the test chemical determined both gravimetrically and analytically.

Table 2: Concentrations of Test Chemical

Group	Target Concentration (Lambda-Cyhalothrin) (µg/l)	Mean Particulate Concentration +/- SD (µg/l)	Mean Analysed Lambda-Cyhalothrin Concentration +/- SD (µg/l)
1	0	-	None detected
2	0.25	0.3 +/- 0.06	0.21 +/- 0.05
3	2.5	3.3 +/- 0.7	2.64 +/- 0.58
4	15.0	16.7 +/- 2.9	12.80 +/- 2.65

The report stated that "the analyzed lambda-cyhalothrin content of the total particulate represented an average of approximately 76% and was close to the

analysed purity of the production material. The particulate was therefore considered to represent lambda-cyhalothrin production material."

The following table summarizes the mean aerodynamic particle size distribution of the total particulate.

Table 3: Mean Particle Size Distribution

Group	Particulate Concentration Lambda-Cyhalothrin Production Material (µg/l)	MMAD (+/- SD) micrometers	GSD (+/- SD)
2	0.3	1.91 +/- 0.47	2.24 +/- 0.41
3	3.3	1.48 +/- 0.21	1.82 +/- 0.14
4	16.7	1.47 +/- 0.10	1.68 +/- 0.10

MMAD = Mass median aerodynamic diameter
GSD = Geometric standard deviation

The report stated that "the percentages on the stages of the cascade impactor were similar when calculated using the particulate data and the analysed concentrations".

2. Clinical Observations and Mortality: Observation results were divided into three categories: during exposure, immediately following exposure and observation on non-exposure days.

Observations During Exposure: These included clinical signs generally associated with restraint (stains around the snout, wet fur and chromodacryorrhea). These signs were seen in both test and control animals. Salivation and lachrymation were observed in some animals exposed to 3.3 and 16.7 µg/l of the test material, and auditory hypoaesthesia was present in most animals exposed to 16.7 µg/l.

Observations Immediately Following Exposure: Again, clinical signs generally associated with restraint were observed in all groups, including controls (hunched posture, piloerection, stains around the nose, chromodacryorrhea and wet fur). No toxicologically significant effects were seen at the 0.3µg/l dose level. Treatment-related effects were seen at both the mid- and high dose levels. These effects were either neurological in nature (i.e. paw flicking or tail erections) or indicative of irritancy (i.e. lachrymation or salivation). The effects were more severe and were of a greater range in the high dose animals (See Table 4).

Table 4: 21-Day Inhalation Study with Lambda-Cyhalothrin: Incidences of Clinical Signs Following Exposure								
Clinical Sign	Males (10/dose)				Females (10/dose)			
Concentration µg/L	0	0.3	3.3	16.7	0	0.3	3.3	16.7
Paw flicking			2 (3)	9 (1)				10 (1)
Tail Erection			3 (3)	8 (1)	1 (15)		5 (5)	10 (1)
Lachrymation			2 (3)	8 (1)	1 (7)		5 (1)	10 (1)
Salivation			8 (1)	10 (1)			3 (2)	10 (1)
Splayed gait			2 (3)	10 (1)				10 (1)
Activity decreased				7 (1)				9 (2)
Reduced foot withdrawal				1 (1)				
Head flicking				2 (1)				1 (7)
Reduced righting reflex				3 (1)				1 (2)
Shaking				3 (1)				
Sides pinched in				1 (11)				3 (7)
Reduced splay reflex				3 (1)				2 (5)
Tip toe gait				8 (1)			3 (7)	10 (1)
Dec/SD Visual Plac. Resp.				2 (1)				
Incr./SD response to touch					2 (7)		1 (15)	1 (7)
Pinna reflex absent								1 (15)
Ungroomed								2 (11)

* Highest number of animals affected on any one day (day sign first observed)

01

Observations on Non-Exposure Days: The authors stated that "the only significant effects were tail erections and tiptoe gait in some animals exposed to " the 16.7 µg/l dose level.

The authors also stated that respiratory noise was present in a few animals from all test groups throughout the study and was possibly due to irritancy caused by deposition of the test compound in the upper respiratory tract. There were no histological findings in these regions. Therefore, these effects were not considered to be of toxicological significance.

3. Body Weight Determinations: At the highest dose level, body weight and body weight gain were reduced in both sexes when compared to controls. By the end of the study, mean body weights were 15% and 12% and mean body weight gains were 14% and less than 3% of the mean control values for males and females, respectively. The authors stated that the effects on bodyweight gain in females appeared to be dependent on whether or not the bodyweights were recorded on an exposure day or on a non-exposure day since there appeared to be some recovery in bodyweight gain in females on non-exposure days. Males appeared to have a steady but reduced bodyweight gain over the duration of the study, but in females, the overall pattern was an approximate maintenance of the starting weight. The effects at the mid-dose level were similar but at a reduced level. At this dose level, the final mean body weights were 5% and 6% and the final mean body weight gains were 65% and 53% of the mean control levels for males and females, respectively. There were no effects in either bodyweight or bodyweight gain at the low dose level. The following table summarizes the results.

Table 5. Bodyweight Gain (g) in a 21-Day Inhalation Study

	Exposure Level (µg/l)			
	Males			
Day	0 (Contr.)	0.3	3.3	16.7
1 Initial Weight	258.0	261.6 (101%)	266.1 (103%)	266.1 (103%)
7	24.7	23.1	5.8**	-8.4**
15	55.1	54.1	26.9**	1.2**
22	64.8	67.6	42.1**	9.3**
Final Weight	322.8	329.2 (102%)	308.2 (95%)	275.4** (85%)

Females

1 Initial Weight	216.8	218.0 (101%)	216.4 (100%)	219.7 (101%)
7	8.4	9.4	0.2**	-6.8**
15	23.1	22.7	11.5**	-6.5**
22	29.7	30.4	15.8**	-3.2**
Final Weight	246.5	248.4 (101%)	232.2* (94%)	216.5** (88%)

** Statistically significant $p<0.01$.
* Statistically significant $p<0.05$.

4. Food and/or Water Consumption: A statistically significant reduction in food consumption over control values was observed in both sexes at the high dose up to day 18 and a slight reduction between days 18 to 22. At the mid-dose level reduced food consumption was observed in males during the first week of the study, statistically significant on days 1-2, 3-7, and 7-11. In females, significant reductions in food consumption were observed on days 2-5 and 11-15.

Table 6: 21-Day Inhalation Study with Lambda-Cyhalothrin: Food Consumption (g/rat/day)								
Period (Days)	Males				Females			
Concentration µg/L	0	0.3	3.3	16.7	0	0.3	3.3	16.7
-1 to 1	24.0	21.5*	24.0	24.5	19.0	18.0	19.0	20.5
1-2	26.0	24.5	20.0**	12.0**	21.5	18.5	18.0	12.0**
2-3	27.0	24.5	23.5	17.5**	23.5	23.0	21.5*	20.5**
3-7	29.5	28.0	25.0*	23.5*	22.0	22.5	20.0	13.5**
7-11	29.5	29.0	25.5*	20.5**	23.0	23.5	21.0	19.5*
11-15	32.0	30.5	28.5	27.0*	25.0	24.0	23.5*	18.5*
15-18	30.0	29.5	26.0	22.5*	24.0	25.0	23.5	21.0*
18-22	28.5	28.5	28.5	26.0	23.5	23.0	20.0	18.5*

* $p < 0.05$
** $p < 0.01$

5. Ophthalmological Examinations: The authors stated that there was a dose-related increase in the incidence of punctate foci on the cornea in both sexes exposed to the mid- and high dose levels. No effects were observed at the low dose level or on histological examination of the eyes. The incidences were as follows: 0, 0, 3 and 5 out of 10/dose in males and 1, 1, 3 and 7 out of 10/dose in females.

6. Hematology: The report stated that "the platelet count was reduced in all female treated groups and the prothrombin time was slightly raised in top dose females. There were changes in other hematological parameters although these, together with the changes in the platelet count of females, are considered to be of no toxicological significance."

7. Clinical Chemistry: At the high dose level, reductions in plasma urea, albumin, cholesterol and total protein were observed as well as increases in aspartate transaminase and alkaline phosphatase activities in females. In males, small reductions were seen in triglyceride levels at this dose level. At the mid-dose level, slight reductions in plasma albumin, total protein and cholesterol levels were observed in females as well as minimal reductions in albumin and total protein levels in males. All of these values were statistically significant over control values. No other biologically significant changes were seen.

14.

Table 7: 21-Day Inhalation Study with Lambda-Cyhalothrin: Selected Clinical Chemistry Values								
Clinical Chemistry Parameter	Males (4/dose)				Females (4/dose)			
Concentration µg/L	0	0.3	3.3	16.7	0	0.3	3.3	16.7
Urea (mg/100 ml)	47.9	47.1	50.8	45.7	54.7	51.5	50.5	42.8**
Albumin (g/100 ml)	4.43	4.40	4.17**	4.39	4.44	4.32	4.20**	4.05**
Cholesterol (mg/100 ml)	72.2	70.1	68.7	72.0	74.5	78.9	62.5*	59.5*
Total Protein (g/100 ml)	6.42	6.40	6.16*	6.21	6.48	6.44	6.11**	5.95**
Aspartate transaminase (mU/ml)	64.7	59.1	63.4	70.6	69.4	73.2	78.6	82.6*
Alkaline phosphatase (mU/ml)	258	242	239	245	151	169	165	184*
Triglycerides (mg/100 ml)	129	133	129	105*	101	99	102	107

* $p < 0.05$, ** $p < 0.01$

8. Urinalysis (Table 8): The urine volume was reduced in all treated groups in males and in high dose females. The apparent reduction in volume in low dose males was considered to reflect a few extreme control values giving rise to a high control mean and was not considered to be of any toxicological significance. The specific gravity was slightly raised in both sexes at the mid- and high dose levels and there were reductions in protein levels in mid- and high dose males and in high dose females (not statistically significant). All values were statistically significant over control values unless otherwise noted.

Table 8: 21-Day Inhalation Study with Lambda-Cyhalothrin: Selected Urinalysis Values								
Uninalysis Parameter	Males (5/dose)				Females (5/dose)			
Concentration µg/L	0	0.3	3.3	16.7	0	0.3	3.3	16.7
Urine volume (ml)	7.50	5.08*	3.02**	2.72**	5.34	4.48	3.32	2.28**
Specific gravity	1.041	1.048	1.061**	1.064**	1.045	1.047	1.053*	1.060**
Protein (mg/TPV)	13.78	10.36	7.80**	6.01**	1.18	0.92	1.06	0.56

* $p < 0.05$, ** $p < 0.01$

Table 9: 21-Day Inhalation Study with Lambda-Cyhalothrin: Mean Liver Weights (Absolute and Adjusted for Body Weight; g)								
	Males (10/dose)				Females (10/dose)			
Concentration µg/L	0	0.3	3.3	16.7	0	0.3	3.3	16.7
Absolute Liver Weight	13.9	13.8	13.9	12.4*	10.8	10.8	9.6**	9.4**
Adjusted for Body Weight	13.0	12.4	13.9*	14.6**	10.3	10.1	9.8	10.4

* $p < 0.05$, ** $p < 0.01$

Table 10: 21-Day Inhalation Study with Lambda-Cyhalothrin: Microscopic Examination: Selected Tissues								
	Males (10/dose)				Females (10/dose)			
Concentration µg/L	0	0.3	3.3	16.7	0	0.3	3.3	16.7
Kidney (# examined) Unilateral hydronephrosis Intratubular microlithiasis	10 4 0	0 - -	0 - -	10 6 0	10 2 7	0 - -	0 - -	10 0 10
Adrenal Gland (# examined) Enlarged Pale	Did not find anything				10 0 1	10 0 0	10 0 1	10 2 4
Brain (# examined) Meningioma	10 0	0 -	0 -	10 1	Did not find anything			
Heart (# examined) Degenerative myocarditis	10 0	0 -	0 -	10 1	Did not find anything			
Lung (# examined) Alveolitis	10 1	10 4	10 3	10 1	10 1	10 1	10 2	10 7

* $p < 0.05$, ** $p < 0.01$

9. Gross Pathology: No treatment-related macroscopic findings were observed.

10. Organ Weights (Table 9): Statistically significant decreases in absolute liver weights over controls were observed in high dose males and in mid- and high dose females. Statistically significant increases in relative liver weights over controls were observed for mid- and high dose males. Since these do not correlate with each other, the changes are not considered to be biologically significant.

11. Histopathology (Table 10): There was a slight increase in the incidence of alveolitis in high dose females. The report stated that one high dose male had a benign meningioma in the brain. They also stated that "this is a rare tumor, especially in a young rat, but it is considered highly unlikely that this tumor was caused by exposure to lambda-cyhalothrin production material."

C. DISCUSSION: The mean particulate concentrations were 0.3, 3.3 and 16.7 µg/l for the low, lid- and high dose groups, respectively. The target concentrations were 0.25, 2.5 and 15.0 µg/l for the low, mid- and high dose groups, respectively. Therefore, the measured concentration values were fairly close to the target values. The mass median aerodynamic diameters (MMAD) were 1.91, 1.48 and 1.47 µm for the low, mid- and high dose groups, respectively. These are close to 1 µm which is the respirable value accepted by the Agency at present. The NOAEL for systemic effects is 0.3 µg/l and the LOAEL was 3.3 µg/l based on decreased bodyweight gains; clinical signs of neurotoxicity; punctate foci on the cornea and changes in clinical chemistry and urinalysis. The authors provided the following statements about the observed effects:

"The major clinical effects seen...were either neurological in nature or indicated irritancy. This is consistent with the known effects of synthetic pyrethroids. On non-exposure days throughout the study, the majority of the abnormalities had disappeared, again consistent with the effects of synthetic pyrethroids....The small increases in [the relative] liver weight[s]...in male rats...in the absence of any histopathological findings, are considered to be an adaptive response to exposure to the test material and of no toxicological significance...The changes seen in some clinical chemistry and haematological parameters in both sexes suggest a minimal effect on liver metabolism and together with the other changes in the urine profile and plasma urea, probably reflect the general toxicity of lambda-cyhalothrin...The presence of an increased incidence of punctate foci on the cornea in ...[both sexes]...indicates a dose response to treatment. In view of the clinical observation of excess lachrymation during exposure, the absence of histopathological change and the nature of the ophthalmoscopic effect, it is considered likely that this treatment-related increase represented an abnormal pre-corneal film due to excessive lachrymation. As such, it is of no toxicological significance...The slight increase in the incidence of alveolitis in top dose females was possibly due to an irritant effect of the test material depositing in the lung." The Agency notes that these explanations are all plausible. With the exception of length of exposure (days) and the exclusion of individual animal data, this study appears to be within guideline requirements for a repeated dose inhalation study. The study is classified as acceptable nonguideline.