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DATA EVALUATION RECORD

LAMBDA CYHALOTHRIN

Study Type: 82-2; 21-Day Dermal Toxicity Study in the Rat

Work Assignment No. 3-31A (MRID 44333802)

Prepared for
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Disclaimer

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treatment and control groups. No neoplastic tissue was observed. **The LOAEL is 50 mg/kg/day for both sexes, based on clinical signs of toxicity and decreased body weight and body weight gain. The NOAEL is 10 mg/kg/day for males and females.**

This dermal toxicity study is classified **acceptable (§82-2)** and satisfies the guideline requirement for a repeated dose dermal toxicity study.

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

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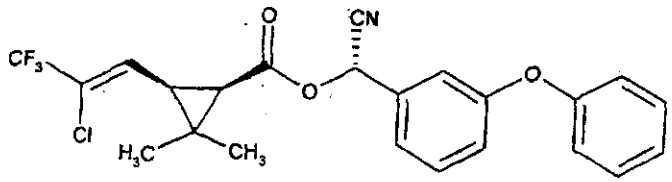
I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Lambda cyhalothrin
   Description: Light lumpy brown solid
   Lot/Batch #: YO2537/001/012
   Purity: 96.6% a.i.
   Stability of compound: Not reported
   CAS #: 91465-08-6
   Structure:



2. Vehicle and/or positive control: Olive oil

3. Test animals: Species: Rat
   Strain: Alpk:APfSD, Wistar-derived albino
   Age and weight at study initiation: Young adults (age not reported); males, 190-227 g; females, 194-226 g
   Source: Barriered Animal Breeding Unit, ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK
   Housing: Housed individually in suspended cages with solid stainless steel sides, a polycarbonate (MAKROLON) front, and stainless steel mesh floor and back. Each cage was partitioned into two equal compartments that each housed one animal.
   Diet: Porton Combined Diet, Special Diet Services Ltd., ad libitum
   Water: Not described, ad libitum
   Environmental conditions:
      Temperature: 15 - 24 C
      Humidity: 50 ± 10%
      Air Changes: 20-30/hour
      Photoperiod: 12-Hour light/dark cycle
   Acclimation period: ≥6 Days

B. STUDY DESIGN

1. In life dates - Not reported

2. Animal assignment

   Rats were assigned to the test groups in Table 1 immediately after receipt using computer-generated random numbers.

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Table 1. Study design.

Test Group	Dose to animal (mg/kg/day)	Animals assigned	
		Male	Female
1	0	5	5
2	1	5	5
3	10	5	5
4	100/50[a]	5	5

[a] The dose level was reduced to 50 mg/kg after two or three applications because two males dosed at 100 mg/kg were found dead.

3. Dose selection rationale

Dose levels were selected based on the results of a preliminary study in which groups of two male and two female rats were treated with four or five applications of undiluted lambda cyhalothrin at 10 or 100 mg/kg. Signs of slight toxicity in the high-dose group were the only observed effects. In the second part of the study, rats were treated with the test substance in olive oil at 10 or 100 mg/kg. Both dose groups exhibited slight toxicity; no irritation was observed.

4. Preparation and treatment of animal skin

Fresh dosing preparations of lambda cyhalothrin in olive oil were made approximately every 7 days. The chemical stability of the test substance in olive oil was confirmed in 0.5 and 50 mg/mL preparations following 13 days of room temperature storage (recoveries, 104% of nominal).

Eighteen to 24 hours before the first application of the test substance, the hair of each animal was clipped from the dorso-lumbar area of the trunk over an area approximately 10 cm x 5 cm of the body surface. The test substance in olive oil (2 mL/kg) was spread evenly onto the shorn backs of the animals using a 1 mL sterile disposable plastic syringe. Females were dosed one day later than males. The volume administered to the high-dose animals was reduced to 1 mL/kg after two or three applications because two males were found dead. The treated area was covered with a gauze patch that was covered with a patch of plastic film and held in place with adhesive bandage secured by two pieces of PVC tape wrapped around the animal. The rats were exposed to the test substance for 6 hours/day for 21 consecutive days, with an 18-hour rest period between each application. Plastic collars were put on the animals during the rest periods to prevent oral contamination. After each exposure, the dressings were removed and the application areas were cleaned with lukewarm water and absorbent cotton wool, and dried gently with clean tissue paper.

Rats in the control group were exposed to the vehicle in the same way.

5. Statistics

Mean body weight gain, hematology and clinical blood chemistry parameters, and absolute and relative organ weights for each treatment group were compared to the control group using a Student's t-test conducted at the 5 and 1% two-sided level.

C. METHODS

1. Observations

Animals were observed twice daily, prior to dosing and at decontamination, for gross signs of toxicity and for signs of irritation at the application site.

2. Body weight

Animals were weighed daily prior to dosing throughout the study period.

3. Food consumption and compound intake

Food consumption for each animal was estimated for a 24-hour period between days -1 and 1, 6 and 7, 13 and 14, and 20 and 21.

4. Clinical Pathology

Blood samples were taken from each rat by cardiac puncture immediately after death. It was not stated that the animals were fasted prior to blood collection. The CHECKED (X) parameters were examined in all samples analyzed.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)
X	Platelet count* (thrombocytes)	X	RBC morphology
	Blood clotting measurements*		
	(Partial thromboplastin time)		
	(Capillary clotting time)		
X	(Prothrombin time)		
X	(Kaolin-cephalin)		

* Required for repeated dose dermal toxicity studies based on Subdivision F guidelines.

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*	X	Cholesterol
X	Potassium*		Globulin
X	Sodium*	X	Glucose*
		X	Total bilirubin
	ENZYMES	X	Total serum protein (TP)*
X	Alkaline phosphatase	X	Triglycerides
	Cholinesterase (ChE)		
X	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine aminotransferase		
X	Serum aspartate aminotransferase		
	Gamma glutamyl transferase (GGT)		

* Required for repeated dose dermal toxicity studies based on Subdivision F guidelines.

6. Sacrifice and Pathology

Animals were anesthetized with excessive levels of halothane BP vapor, then euthanized by exsanguination. The bodies were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The skin, liver, kidney, adrenal, brain, heart, sciatic nerve, spinal cord, and spleen from all animals were examined microscopically. The (XX) organs, in addition, were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	X	Heart*	X	Sciatic nerve*
X	Esophagus*		Bone marrow*	X	Spinal cord*
X	Stomach*		(sternum)	X	Pituitary*
X	Duodenum*	X	Lymph nodes*	X	Eyes*
X	Jejunum*	X	Spleen*		
X	Ileum*	X	Thymus*		
X	Cecum*				
X	Colon*		UROGENITAL		GLANDULAR
X	Rectum*				
XX	Liver*	XX	Kidneys*	XX	Adrenal gland*
X	Pancreas*	X	Urinary bladder*		Lacrimal gland
		XX	Testes*		Mammary gland
		X	Epididymides	X	Thyroids* with
		X	Prostate		parathyroids*
	RESPIRATORY	X	Seminal vesicle	X	Harderian gland
		XX	Ovaries*		
	Trachea*	X	Uterus*		
X	Lungs*		Vagina		
	Pharynx				
	Larynx				OTHER
					Body (exsanguinated)
				X	Bone* (femur)
					Muscle*
				X	Skin* (treated and
					untreated)
				X	All gross lesions and
					masses*

* Required for repeated dose dermal toxicity studies based on Subdivision F guidelines.

II. RESULTS

A. Observations

1. Mortality - Two males treated at 100 mg/kg/day were found dead prior to dosing on Day 4. No other animals died during the study.

2. Toxicity - Males dosed at 50 mg/kg/day exhibited reduced splay reflex (5/5), bizarre behavior (3/5), pinched in sides (3/5), dehydration (3/5), reduced stability (2/5), and thin appearance (2/5); these clinical signs were unique to this dose level (refer to Attachment to this DER). The 50 mg/kg/day group males also exhibited an increased incidence (number of animals affected and/or observations) of tip toe gait (5/5), upward curvature of the spine (5/5), signs of urinary incontinence (4/5) downward curvature of the spine (4/5), and splayed gait (4/5) compared to the other male test groups. Females dosed at 50 mg/kg/day exhibited an increased incidence in signs and occurrence of urinary incontinence (5/5), upward curvature of the spine (5/5), tip toe gait (4/5), chromodacryorrhea (4/5), and reduced splay reflex (3/5) compared to the other female test groups (Attachment). There was no indication of an increase in dermal irritation. No signs of clinical toxicity or dermal irritation in the 10 or 1 mg/kg/day treatment groups were considered to be treatment-related.

B. Body weight and weight gain

Males dosed at 50 mg/kg/day had significantly ($p<0.05$ or $p<0.01$) lower mean body

weight gains than the control gains during most study days, and a final mean body weight gain 58% lower than the controls. Females dosed at 50 mg/kg/day had reduced mean body weight gains that differed statistically from the control gains only during the first 3 days of the study. Mean body weight gain for the 10 mg/kg/day group males was ≥20% lower ($p<0.05$) than the control gain on most days through day 14, and thereafter remained between 9-19% lower than the control group. Although the final body weight gain was still 19% less than the control group, the final mean body weight for this dose group was within 4% of the mean control value. Statistical significance for body weight gain disappeared by day 14. No treatment-related differences in body weight gains were observed between the 10 mg/kg/day female treatment group or the 1 mg/kg/day treatment groups compared to the controls.

Lambda-Cyhalothrin: 21-Day Dermal Toxicity Study in Rats: Body Weight and Body Weight Gains (g)								
Day	Males				Females			
Dose (mg/kg)	0	1	10	100/50	0	1	10	100/50
Initial Body Weight	206.2 ± 13.8	207.4 ± 11.4	209.6 ± 10.8	200.2 ± 9.7	201.6 ± 9.6	209.8 ± 9.2	215.8 ± 2.3*	216.2 ± 7.8*
2	2.0 ± 5.0	3.4 ± 7.9	-1.2 ± 4.8	-26.2 ± 10.5**	5.4 ± 5.3	-0.2 ± 6.7	-3.4 ± 5.4*	-14.4 ± 6.3**
5	11.0 ± 4.5	10.8 ± 6.1	5.4 ± 3.2	-12.0 ± 13.2*	7.4 ± 9.2	6.4 ± 2.6	7.0 ± 6.9	5.0 ± 11.6
10	38.4 ± 7.0	35.4 ± 11.7	29.4 ± 2.6*	12.3 ± 12.1**	26.0 ± 12.8	22.2 ± 5.8	19.8 ± 2.5	16.4 ± 12.8
15	56.2 ± 29.5	58.0 ± 15.9	46.0± 4.4	20.0 ± 25.5	30.6 ± 11.1	24.4 ± 13.6	27.0± 5.4	25.2 ± 14.8
22	80.8 ± 12.8	76.4 ± 20.4	65.6 ± 8.8	34.3 ± 33.9*	42.4 ± 14.0	35.8 ± 13.4	41.4 ± 2.3	42.6 ± 18.3
Final Body Weight	287.0 ± 14.7	283.8 ± 29.6	275.2 ± 10.4	233.3 ± 42.8*	244.0 ± 14.2	245.6 ± 17.8	257.2 ± 3.8	258.8 ± 13.8

C. Food consumption

Males in the 50 mg/kg/day treatment group consumed 14-28% less food than the controls throughout the study; the decreases were not statistically significant. No other differences in food consumption were observed between the treatment and control groups.

D. Clinical Pathology

1. Hematology - No treatment-related effects in hematology parameters were observed between the treated and control groups. Minor differences in hematology parameters observed between rats in the treated and control groups (female control values were high) remained within normal limits for this strain and age of rat.

2. Clinical Chemistry - No treatment-related differences in clinical chemistry were observed between the treated and control groups. Differences that showed statistical significance were small and/or not dose-related or were due to high individual control values.

E. Sacrifice and Pathology

1. Organ weight - No treatment-related biologically significant differences in absolute or relative organ weights were observed between the treatment and control groups. A decreased mean absolute liver weight for the 50 mg/kg group males ($p < 0.05$) was due to one very low individual body weight. A decreased mean relative kidney weight for the 50 mg/kg group females ($p < 0.01$) differed by $< 10\%$ of the control weight and lacked associated pathological findings.

2. Gross pathology - In the two males treated at 50/100 mg/kg/day that died prematurely, seminal vesicles were reduced. No other gross post-mortem differences were observed between the treated and control groups.

3. Microscopic pathology

a) Non-neoplastic - In the two males treated at 50/100 mg/kg/day that died prematurely, seminal vesicles were moderately atrophied and spleens were slightly atrophied. No other microscopic differences were observed between the treated and control groups.

b) Neoplastic - No neoplastic tissue was observed in the treated or control rats.

III. DISCUSSION

A. Investigator's Conclusions

The study author concluded that the NOAEL for systemic toxicity of lambda cyhalothrin is 10 mg/kg, based on clinical signs of slight general toxicity observed in males and females dosed at 100 mg/kg (reduced to 50 mg/kg after two or three applications) for 21 consecutive days. Abnormalities observed after application of 50 mg/kg were bizarre behavior, reduced stability, pinched in sides, reduced splay reflex, thin appearance, and dehydration. No significant signs of skin irritation were observed in any treatment group. Premature deaths of two males initially treated with two or three applications of

100 mg/kg were likely the result of pyrethroid toxicity.

B. Reviewer's Discussion

We agree with the study author's conclusion that clinical signs of general toxicity were observed in rats dermally treated with 50 mg/kg of the lambda cyhalothrin. Most of the clinical signs were unique to this treatment group or exhibited an increased incidence compared to the other test groups. Males exhibited reduced splay reflex, downward curvature of the spine, splayed gait, bizarre behavior, pinched in sides, dehydration, reduced stability, and thin appearance. Females exhibited an increased incidence of tip toe gait, upward curvature of the spine, an increased incidence in signs of urinary incontinence, urinary incontinence, chromodacryorrhea, and reduced splay reflex. Body weight gain and food consumption were more severely affected in males than females. For males, body weight gains were significantly ($p < 0.05$ or $p < 0.01$) reduced and food consumption was depressed throughout the study. For females, decreases in body weight gains during the first half of the study were eventually recovered, and food consumption was similar to the controls. No dermal irritation was observed at 100/50 mg/kg/day. No signs of clinical toxicity or dermal irritation in the 10 or 1 mg/kg/day treatment groups were considered to be treatment-related.

In conclusion, we agree that the LOAEL for this study is 50 mg/kg/day, based on clinical signs in both sexes, and that the NOAEL is 10 mg/kg/day.

IV. STUDY DEFICIENCIES

No significant deficiencies were noted in this study.

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