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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

EPA Reviewer: Pamela M. Hurley, PhD Pamela M Hurley, Date 2/2/2001
Registration Action Branch 2 (7509C)

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Registration Action Branch 2 (7509C)

DATA EVALUATION RECORD
Supplement to DER for MRID No.: 44435401 Cyfluthrin: [Chronic Oral Toxicity - Dogs]
This supplement includes days when clinical signs first observed and histopathology table

STUDY TYPE: 53-Week chronic toxicity [feeding] - dog
OPPTS Number: 870.4100 OPP Guideline Number: §83-1b

DP BARCODE: D243160
P.C. CODE: 128831
SUBMISSION CODE: S528018
TOX. CHEM. NO.: 266E

TEST MATERIAL (PURITY): Cyfluthrin (94.8-95.1% a.i.)

SYNONYMS: FCR 1272; (R,S)-α-cyano-4-fluoro-3-phenoxybenzyl-(1R,S)-cis, trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Jones, R.D. and Hastings, T.F. (1997) Technical Grade Cyfluthrin (FCR 1272): A Chronic Toxicity Feeding Study in the Beagle Dog. Bayer Corporation, Stilwell, KS. Laboratory Study number 94-276-ZR, November 10, 1997. MRID 44435401. Unpublished.

SPONSOR: Bayer Corporation, 17745 South Metcalf, Stilwell, KS

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 44435401), cyfluthrin (94.8-95.1% a.i., Lot # 4030059/BF9340-71) in corn oil was administered to beagle dogs (4/sex/dose) in the diet at dose levels of 0, 50, 100, 360, or 500 ppm in the diet (achieved doses of 0/0, 1.36/1.46, 2.43/3.61, 10.64/10.74, or 15.47/17.99 mg/kg/day [M/F], respectively) for 12 months. High-dose animals initially received 640 ppm, but the dose was reduced to 500 ppm at week 8 due to excessive toxicity.

One high-dose female was sacrificed on day 56 after exhibiting gait (including incoordination and increased stride width), postural, and behavioral abnormalities, convulsions, tremors, and cranial and peripheral nerve deficits. The high-dose was reduced to 500 ppm for the remainder of the study. One control male died on day 318 and one control female died on day 210 from asymptomatic idiopathic epilepsy.

In the 360 ppm animals, clinical signs (males and females combined) included abnormal posture (1/8 treated vs 0/8 controls, starting on day 183) and a higher incidence of vomiting (8/8 treated

vs 4/8 controls, starting on day 1). Gait abnormalities, including hypermetria, abnormal stride width, and reluctance to walk, were found at the 6 month (2/4 males; 1/4 females) and 12 month (1/4 males; 2/4 females) neurological examinations. Abnormal postural reactions, including "wheelbarrowing" with head position abnormal or dorsally flexed, abnormal front foot placement during lateral hopping, hemistanding, and abnormal foot placement or weight support during backward stepping, were also found at the 6 month (4/4 males; 3/4 females) and 12 month (4/4 males; 3/4 females) examinations. No postural or gait abnormalities were observed in controls.

At 500 ppm, clinical signs (males and females combined) included gait abnormalities such as reluctance/inability to walk, stiff-leggedness, ataxia, and abnormal stride width (1-2/8 treated vs 0/8 controls); seizures (2/8 treated vs 0/8 controls); convulsions and tremors (2/8 treated vs 0/8 controls); and abnormal posture (1/8 treated vs 0/8 controls). Vomiting (8/8 treated vs 4/8 controls), diarrhea (4/8 treated vs 0/8 controls) and soft feces (2/8 treated vs 0/8 controls) were also observed. Gait abnormalities similar to those observed in the 360 ppm group were found at the 6 month (3/4 males; 1/3 females) and 12 month (2/4 males; 1/3 females) examinations. Abnormal postural reactions similar to those observed in the 360 ppm group, but also including abnormal time to initiate front leg lateral hopping, were found at the 6 month (4/4 males; 3/3 females) and 12 month (4/4 males; 3/3 females) examinations. Again, no postural or gait abnormalities were observed in controls. Non-statistically significant decreases in body weights were observed in the males throughout the study (↓6-20%). Mean body weight gains, as calculated by the reviewers, were decreased at the end of treatment in the males (↓53%). Hepatic N-demethylase activity was increased in males at termination, the only interval tested (↑45%, $p \leq 0.05$).

There were no differences of toxicological concern observed in rectal body temperature, food consumption, electrocardiography, blood pressure, hematological, clinical chemistry or urinalysis parameters, ophthalmoscopic, necropsy, or histopathological findings, absolute or relative organ weights, and plasma cholinesterase, hepatic O-demethylase or cytochrome P450 activities. No neoplastic tissue was observed in dogs from any test group.

The LOAEL is 360 ppm (equivalent to 10.64/10.74 mg/kg/day [M/F]), based on clinical signs, gait abnormalities, and abnormal postural reactions in males and females. The NOAEL is 100 ppm (equivalent to 2.43/3.61 mg/kg/day [M/F]).

This study is classified **acceptable (§83-1b)** and satisfies the guideline requirements for a chronic toxicity study in dogs.

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

Cyfluthrin Chronic Feeding Study in the Dog (1997): Microscopic Pathology of Selected Tissues

Organ and Lesion	Males					Females				
Dose Levels (mg/kg/day)	0	1.36	2.43	10.64	15.47	0	1.46	3.61	10.74	17.99
Brain										
Degeneration, Vacuolar	-	-	-	-	1 (1.0)	-	-	-	-	-
Mineralization	-	-	-	-	-	-	-	-	1 (2.0)	-
Satellitosis	-	-	-	-	1 (2.0)	-	-	-	-	-
Heart										
Myocardial Fibrosis/Atrophy/Inflammation	-	-	-	-	-	-	-	-	-	1 (2.0)
Hyperplasia, Mesothelium	-	-	-	-	-	-	1 (2.0)	-	-	-
Liver										
Hyperplasia/Fibrosis, Biliary	-	-	-	1 (2.0)	-	-	-	-	-	-
Degeneration, Vacuolar	-	-	-	-	1 (1.0)	-	-	-	-	-
Inflammation	-	1 (1.0)	-	-	-	-	-	-	-	-
Microgranuloma	-	-	-	-	-	-	-	1 (2.0)	-	1 (1.0)
Lungs										
Fibrosis	-	-	-	1 (3.0)	1 (3.0)	-	1 (3.0)	-	1 (2.0)	-
Hyperplasia, Adenomatous	-	-	-	1 (3.0)	-	-	-	-	-	-
Inflammation	1 (3.0)	-	-	2 (2.5)	1 (2.0)	1 (3.0)	-	-	1 (1.0)	1 (1.0)
Hyperplasia, Mesothelium	-	-	-	-	-	-	-	-	1 (1.0)	-
Mammary Gland										
Hemorrhage	-	-	-	-	-	1 (3.0)	-	-	-	-
Nerve, Sciatic										
Inflammation, Chronic	-	-	-	-	-	-	-	-	-	1 (3.0)
Skeletal Muscle, Protocol										
No Abnormality Detected	4	4	4	4	4	4	4	4	4	4
Spinal Cord										
Mineralization	2 (1.5)	2 (1.5)	2 (2.0)	3 (1.3)	2 (2.0)	4 (2.5)	4 (2.0)	4 (2.8)	2 (2.0)	3 (2.3)

() = Average severity of animals with lesion: 1 (minimal) to 5 (severe).

DATA EVALUATION RECORD

CYFLUTHRIN

Study Type: §83-1b; Chronic Oral Toxicity - Dogs

Work Assignment No. 2-01-73A (MRID 44435401)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
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Signature: Sharon A. Meyer
Date: 5/25/00

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

CYFLUTHRIN **Chronic oral toxicity (§83-1b)**

EPA Reviewer: William Greear, M.P.H., D.A.B.T. William Greear 7/28/00
Registration Action Branch 3/HED (7509C)
Work Assignment Manager: Marion Copley, D.V.M., D.A.B.T. mr Copley 8/14/00
Registration Action Branch 1/HED (7509C)

DATA EVALUATION RECORD

STUDY TYPE: 53-Week chronic toxicity [feeding] - dog
OPPTS Number: 870.4100 OPP Guideline Number: §83-1b

DP BARCODE: D243160 SUBMISSION CODE: S528018
P.C. CODE: 128831 TOX. CHEM. NO.: 266E

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One high-dose female was sacrificed on day 56 after exhibiting gait (including incoordination and increased stride width), postural, and behavioral abnormalities, convulsions, tremors, and cranial and peripheral nerve deficits. The high-dose was reduced to 500 ppm for the remainder of the study. One control male died on day 318 and one control female died on day 210 from asymptomatic idiopathic epilepsy.

In the 360 ppm animals, clinical signs (males and females combined) included abnormal posture (1/8 treated vs 0/8 controls), vomiting (8/8 treated vs 4/8 controls), diarrhea (1/8 treated vs 0/8 controls), and soft feces (1/8 treated vs 0/8 controls). Gait abnormalities, including hypermetria, abnormal stride width, and reluctance to walk, were found at the 6 month (2/4 males; 1/4 females) and 12 month (1/4 males; 2/4 females) examinations. Abnormal postural reactions,

including wheelbarrowing with head position abnormal or dorsally flexed, abnormal front foot placement during lateral hopping, hemistanding, and abnormal foot placement or weight support during backward stepping, were also found at the 6 month (4/4 males; 3/4 females) and 12 month (4/4 males; 3/4 females) examinations. No postural or gait abnormalities were observed in controls.

At 500 ppm, clinical signs (males and females combined) included gait abnormalities such as reluctance/inability to walk, stiff-leggedness, ataxia, and abnormal stride width (1-2/8 treated vs 0/8 controls); seizures (2/8 treated vs 0/8 controls); convulsions and tremors (2/8 treated vs 0/8 controls); and abnormal posture (1/8 treated vs 0/8 controls). Vomiting (8/8 treated vs 4/8 controls), diarrhea (4/8 treated vs 0/8 controls) and soft feces (2/8 treated vs 0/8 controls) were also observed. Gait abnormalities similar to those observed in the 360 ppm group were found at the 6 month (3/4 males; 1/3 females) and 12 month (2/4 males; 1/3 females) examinations. Abnormal postural reactions similar to those observed in the 360 ppm group, but also including abnormal time to initiate front leg lateral hopping, were found at the 6 month (4/4 males; 3/3 females) and 12 month (4/4 males; 3/3 females) examinations. Non-statistically significant decreases in body weights were observed in the males throughout the study (↓6-20%). Mean body weight gains, as calculated by the reviewers, were decreased at the end of treatment in the males (↓53%). Hepatic N-demethylase activity was increased in males at termination, the only interval tested (↑45%, $p \leq 0.05$).

There were no differences of toxicological concern observed in rectal body temperature, food consumption, electrocardiography, blood pressure, hematological, clinical chemistry or urinalysis parameters, ophthalmoscopic, necropsy, or histopathological findings, absolute or relative organ weights, and plasma cholinesterase, hepatic O-demethylase or cytochrome P450 activities. No neoplastic tissue was observed in dogs from any test group.

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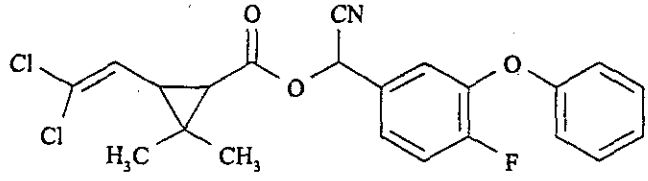
This study is classified **acceptable (§83-1b)** and satisfies the guideline requirements for a chronic toxicity study in dogs.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Cyfluthrin
   Description: Viscous brown liquid
   Lot/Batch #: 4030059/BF9340-71
   Purity: 94.8-95.1% a.i.
   Stability of compound: Dietary formulations were stable when stored at room temperature for up to 14 days or frozen for 28 days.
   CAS #: 68359-37-5
   Structure:



2. Vehicle and/or positive control: Corn oil

3. Test animals: Species: Dog
   Strain: Purebred Beagle
   Age and weight range at treatment initiation: approximately 27 weeks; males, 8231.0 - 10729.0 g; females 6040.0-9772.0 g
   Source: White Eagle Laboratories, Doylestown, PA
   Housing: Individually in stainless steel runs
   Diet: Lab Canine Diet 5006-3 (Purina Mills, Inc. St. Louis, MO), ad libitum
   Water: Municipal water, ad libitum
   Environmental conditions:
   Temperature: 18-29°C
   Humidity: 30-70%
   Air Changes: Not reported
   Photoperiod: 12-hr light/dark cycle
   Acclimation period: ≥12 days

B. STUDY DESIGN:

1. In life dates - start: September/94 end: October/95

2. Animal assignment - Four dogs of each sex were randomly assigned (stratified by body weight) to the test groups shown in Table 1.

Table 1. Study design.[a]

Test Group	Concentration (ppm)	Achieved Doses (mg/kg/day) [M/F]	Animals assigned	
			Male	Female
Control	0	0	4	4
Low	50	1.36/1.46	4	4
Mid	100	2.43/3.61	4	4
Mid-High	360	10.64/10.74	4	4
High	500	15.47/17.99[b]	4	4

a Data extracted from the Study Report, pages 19 and 43.
b Animals initially received 640 ppm, but the dose was reduced to 500 ppm at week 8 due to excessive toxicity. Calculated intake was time-weighted for this change.

3. Dose rationale - Selection of doses was primarily based on a subchronic and chronic dog study. In the subchronic study, male and female dogs received cyfluthrin at 0, 65, 200, and 600 ppm for 6 months. No toxicity was observed at 65 ppm. Decreased food consumption was observed in both sexes at 200 and 600 ppm; decreased thymus weight was observed in males at 200 ppm and both sexes at 600 ppm; transient hind limb motor dysfunction, trembling, arching of the back, and impaired coordination was observed in the 600 ppm males. In the chronic study, dogs received cyfluthrin at 0, 40, 160, and 640 ppm. No toxicity was observed at ≤160 ppm. Hind limb motor dysfunction was observed in 2 males in the 640 ppm group. In addition to these studies, the report cites a 2-year chronic rat study in which animals received cyfluthrin at 0, 50, 150, or 450 ppm. Reduced body weights were observed at 150 ppm. There were no liver, kidney, hematology, or histopathology lesions and no neoplasia.

   Based on the results of these studies, the doses presented in Table 1 were selected for the subsequent chronic study.

4. Diet preparation and analysis - Fresh diets were prepared once weekly. A solution of corn oil and the required amount of test substance was prepared and appropriate amounts of the solution were mixed with untreated diet. Diets were stored frozen. Stability and homogeneity analyses were performed in a prior study. For stability analyses, 25 and 800 ppm diets were stored at room temperature for up to 14 days and frozen for 28 days. Homogeneity (top, middle, bottom) analyses of the 25 and 800 ppm diet formulations (in triplicate) were performed prior to study initiation. Concentration analyses were performed on all concentrations approximately every quarter.

Results -

Homogeneity analyses (range as mean % of nominal ± C.V.): 92.6-108% ± 5-7.2%

Stability analyses (range as % nominal at 14 [room temperature] or 28 [frozen] days): 14 days - 101-103%; 28 days - 104-105%

Concentration analyses (mean % of nominal ± C.V.): 98.2-99.6% ± 2.5-9.8%

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

5. Statistics - Continuous data were analyzed by an analysis of variance (ANOVA). If significance was observed, each treatment group was compared to the control using Student's t-test. Frequency data were analyzed using a Chi-Square test. If significance was observed, each treatment group was compared to the control using a Fisher's Exact test.

C. METHODS:

1. Observations - All animals were observed for mortality and clinical signs of toxicity at least once daily. Each animal received a detailed clinical examination at pretest and weekly during the treatment period.

2. Body weight - All animals were weighed prior to study initiation, weekly during treatment, and at study termination.

3. Food consumption and compound intake - Food consumption was measured in all animals daily and reported as g/animal/day. The amount of test substance consumed was reported as mg/kg/day.

4. Ophthalmoscopic examination - Ophthalmological examinations were performed in all animals prior to study initiation and at study termination. Examinations included tests of anterior pressure and fluid dynamic conditions and corneal pachymetric measurements.

5. Neurological examination - Prior to study initiation, at 6 months after study start, and at study termination, the following neurological assessments were conducted on all animals:

Mental status/behavior	Postural status	Gait
Arousal	Reluctant to stand	Ataxia
Motor Activity	Tremors	Knuckling
Startle response	Fasciculations	Circling
Auditory response	Wide-based stance	Stiff/stilted
Cowering/apprehension	Flat-footed	Hypermetria
Aggression	Head position	Hypometria
	Tail position	Stride length
	Back position	Stride width
	Head tilt	
Postural reaction	**Spinal/cranial reflexes**	**Other parameters**
Hemihop	Patellar	Pulmonary rales
Hemiwalk	Bicep	Rectal temperature
Hemistanding	Tricep	Heart murmurs
Wheel-barrow/head normal or dorsal	Gastrocnemius	
Visual placing	Pupillary/direct and indirect	
Tactile placing	Perineal	
Proprioceptive placing		
Withdrawal response		

In addition, thoracic auscultation of the heart and lungs was performed, and rectal body temperatures were measured.

6. Electrocardiogram/blood pressure assessment - Electrocardiogram Lead II measurements of the P wave, QRS complex, and T wave and measurements of heart rate and systolic, diastolic, and mean arterial pressure were made on all animals prior to study initiation and at study termination.

7. Blood - Blood was collected from the cephalic or jugular vein of all animals after overnight fasting twice pretest, and at 3, 6, 9, and 12 months for hematology and clinical chemistry analyses. The following checked (X) parameters were examined.

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*	X	Reticulocyte count
X	Blood clotting measurements*	X	Erythrocyte morphology
	(Thromboplastin time)	X	Heinz bodies
	(Clotting time)		
	(Prothrombin time)		
X	(Activated partial thromboplastin time)		

* Required for chronic toxicity studies.

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Bile acids
X	Magnesium	X	Blood creatinine*
X	Phosphorus*	X	Blood urea nitrogen*
X	Potassium*	X	Total Cholesterol
X	Sodium*	X	Globulins
		X	Glucose*
		X	Total bilirubin
	ENZYMES	X	Total serum protein (TP)*
			A/G ratio
X	Alkaline phosphatase (ALP)	X	Methemoglobin
X	Cholinesterase (ChE)	X	Thyroxine - total (T_4)
X	Creatine phosphokinase	X	Triiodothyronine - total (T_3)
X	Lactic acid dehydrogenase (LDH)	X	T_3 uptake
X	Serum alanine aminotransferase*	X	Uric acid
X	Serum aspartate aminotransferase*		
X	Gamma glutamyl transferase (GGT)		
X	N-Demethylase [1]		
X	O-Demethylase [1]		
X	Cytochrome P450 [1]		

* Required for chronic toxicity studies.

1 Quantified in liver tissue at termination. The substrates for the demethylase assays were not reported.

8. Urinalysis - Urine was collected from all animals prior to study initiation and at 3, 6, 9, and 12 months. The checked (X) parameters were examined.

X	Appearance (including color and turbidity)	X	Glucose
	Volume	X	Ketones
X	Specific Gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)	X	Nitrite
X	Protein	X	Urobilinogen
		X	Leukocytes

* Urinalysis is required for chronic toxicity studies.

9. Plasma cholinesterase activity - Plasma cholinesterase activity was determined twice pre-study and at 3, 6, 9, and 12 months in all animals.

10. Sacrifice and pathology - All surviving animals were euthanized at study termination. The animals were subjected to gross pathological examination and the checked (X) tissues were collected for histological examination. Animals sacrificed moribund or found dead also received a complete postmortem examination. In addition, the (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta*	XX	Brain* (3 levels)
X	Salivary glands*	XX	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)[a]*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen*	X	Eyes (optic n.)*
X	Jejunum*	XX	Thymus*	X	Ears with internal structure
X	Ileum*				
X	Cecum*				GLANDULAR
X	Colon*		UROGENITAL		
X	Rectum*			XX	Adrenal gland*
XX	Liver*[+]	XX	Kidneys*[+]	X	Lacrimal gland[T]
X	Gallbladder*	X	Urinary bladder*	X	Mammary gland[T]
X	Pancreas*	XX	Testes*[+] with epididymides	XX	Thyroids with parathyroids*[++]
		X	Prostate		
		XX	Ovaries*[+]		OTHER
	RESPIRATORY	X	Uterus* (body, horns,		
			cervix)	X	Bone* with joint
X	Trachea*			X	Skeletal muscle*
XX	Lungs*			X	Skin*
X	Nose			X	All gross lesions and masses*
X	Pharynx				
X	Larynx				

* Required for chronic toxicity studies.
[+] Organ weight required in chronic studies.
[++] Organ weight required for non-rodent studies.
T = required only when target tissue.

II. RESULTS

A. Observations

1. Mortality - One high-dose female (# ZR4103) was sacrificed on day 56 after exhibiting gait (including incoordination and increased stride width), postural, and behavioral abnormalities, convulsions, tremors, and cranial and peripheral nerve deficits. The high-dose was reduced to 500 ppm for the remainder of the study. One control male (# ZR0004) died on day 318 and one control female (# ZR0102) died on day 210 from asymptomatic idiopathic epilepsy. No other premature deaths occurred.

2. Clinical signs - No treatment-related clinical signs were observed in the 50 or 100 ppm groups. Clinical signs were apparent in the 360 and 500 ppm groups (Table 2). Clinical signs in the 500 ppm animals (males and females combined) included gait abnormalities such as reluctance/inability to walk, stiff-leggedness, ataxia, and abnormal stride width (1-2/8 treated vs 0/8 controls); seizures (2/8 treated vs 0/8 controls); convulsions and tremors (2/8 treated vs 0/8 controls); and abnormal posture (1/8 treated vs 0/8 controls). Vomiting (8/8 treated vs 4/8 controls), diarrhea (4/8 treated vs 0/8 controls) and soft feces (2/8 treated vs 0/8 controls) were also observed. In the 360 ppm animals, neurological signs included abnormal posture (1/8 treated vs 0/8 controls), vomiting (8/8 treated vs 4/8 controls), diarrhea (1/8 treated vs 0/8 controls), and soft feces (1/8 treated vs 0/8 controls).

Table 2. Selected clinical signs (incidence) in males and females treated with cyfluthrin for up to 376 days.[a]

Observation	Combined Sexes				
	Dose (ppm)				
	0	50	100	360	500
Reluctant to walk	0	0	0	0	1
Unable to walk	0	0	0	0	1
Stiff-leggedness	0	0	0	0	1
Ataxia	0	0	0	0	2
Abnormal stride width	0	0	0	0	2
Soft feces	0	0	0	1	2
Diarrhea	0	0	0	1	4
Seizures	0	0	0	0	2
Convulsions	0	0	0	0	1
Tremors	0	0	0	0	1
Abnormal posture	0	0	0	1	1
Vomitus (all types)	4	2	4	8	8

a Data obtained from the study report Table CO-SUM, pages 375 through 389. N=8 (males and females, combined)

3. Neurological examination - At the 6 and 12 month neurological exam, neurotoxicity signs were observed in the 360 and 500 ppm groups (Table 3). In the 360 ppm group, gait abnormalities, including hypermetria, abnormal stride width, and reluctance to walk, were found at the 6 month (2/4 males; 1/4 females) and 12 month (1/4 males; 2/4 females) examinations. Abnormal postural reactions, including wheelbarrowing with head position abnormal or dorsally flexed, abnormal front foot placement during lateral hopping, hemistanding, and abnormal foot placement or weight support during backward stepping, were also found at the 6 month (4/4 males; 3/4 females) and 12 month (4/4 males; 3/4 females) examinations. In the 500 ppm group, gait abnormalities similar to those observed in the 360 ppm group were found at the 6 month (3/4 males; 1/3 females) and 12 month (2/4 males; 1/3 females) examinations. Abnormal postural reactions similar to those observed in the 360 ppm group, but also including abnormal time to initiate front leg lateral hopping,

were found at the 6 month (4/4 males; 3/3 females) and 12 month (4/4 males; 3/3 females) examinations. There were no differences in rectal body temperature.

Table 3. Neurotoxicity signs (incidence) in males and females treated with cyfluthrin for up to 376 days.[a]

Observation		Study Day	
		183	370
360 ppm group; n=8			
Posture	Unsteady	1	-
Gait	Hypermetria	2	2
	Stride width	-	2
	Reluctant to walk	1	-
Postural reactions	Wheelbarrowing, head position abnormal	6	7
	Wheelbarrowing, head dorsally flexed	2	5
	Front leg lateral hopping, foot placement abnormal	3	3
	Backward stepping, foot placement abnormal	3	3
	Backward stepping, weight support abnormal	1	1
	Hemistanding	3	1
500 ppm group; n=7			
Posture	Unsteady	-	-
Gait	Hypermetria	3	2
	Stride width	-	-
	Reluctant to walk	2	2
Postural reactions	Wheelbarrowing, head position abnormal	4	5
	Wheelbarrowing, head dorsally flexed	3	7
	Front leg lateral hopping, foot placement abnormal	4	4
	Front leg lateral hopping, time to initiate abnormal	2	2
	Backward stepping, foot placement abnormal	6	5
	Backward stepping, weight support abnormal	2	4
	Hemistanding	4	4

a Data extracted from the study report, pages 403 through 412. No neurotoxicity was observed at the pretreatment exam.

\- No observations made.

B. Body weight and weight gain - There were no statistically significant differences in mean body weights (Table 4) in any of the treatment groups; however, body weights were decreased throughout the study in the 500 ppm males 6-20%. Body weights were also decreased in all female treatment groups, although not dose-dependently. The smallest control female died during the study, causing the mean body weight of the remaining control animals to be biased upward. Therefore, the differences in body weight observed in the female treatment groups were considered of equivocal toxicological concern.

Mean body weight gains, as calculated by the reviewers, were decreased at the end of treatment in the 500 (↓53%) and the 50 (↓18%) ppm males. Because of the lack of dose-dependence, the decrease in the 50 ppm males was considered not treatment-related. Mean body weight gains were also decreased at the end of treatment in all female treatment groups (↓40-57%). The differences were not dose-dependent and in part attributable to the death of the smallest control female, and therefore were considered of equivocal toxicological concern.

Table 4. Selected mean body weights and body weight gains in dogs treated with cyfluthrin for up 12 months (g).[a]

Interval	Dose in ppm				
	0	50	100	360	500
Males					
Day 0	8780.3	9241.3	9089.5	9872.8	9131.5
Day 7	9331.0	9958.0	9439.0	10089.0	8739.8(↓6)
Day 91	12394.0	12254.5	12136.0	13385.8	10760.8(↓13)
Day 182	13663.3	12761.8	13117.5	14280.5	11481.5(↓16)
Day 245	13355.0	12901.3	12993.0	14230.3	11355.3(↓15)
Day 343	13774.3	13015.3	13391.0	14726.8	10966.5(↓20)
Day 371	13969.3	13484.0	13887.8	14747.5	11575.3(↓17)
Gain (Day 0-371)[b]	5189.0	4242.7	4798.3	4874.7	2443.8(↓53)
Females					
Day 0	8034.3	7830.8	8024.5	7730.0	7991.3
Day 91	10654.8	9676.5	10077.5	9568.8	8911.3
Day 182	11709.3	9740.3	10964.0	10305.8	9796.0
Day 245	12543.0	10068.8	10955.8	10501.8	9781.0
Day 371	13588.3	10411.8	11384.5	10721.3	10382.0
Gain (Day 0-371)[b]	5554.0	2581.0	3360.0	2991.3	2390.7

a Data extracted from the study report Table BW-MEAN, pages 225 through 230, n=2-4/dose.
b Body weight gain data were calculated by the reviewers.

C. Food consumption and compound intake

1. Food consumption - Mean weekly food consumption (g/animal/day) was unaffected by treatment at all dose levels. Occasional sporadic differences ($p \leq 0.05$) occurred, but these were considered not of toxicological concern.

2. Compound intake - Average consumption of cyfluthrin is presented in Table 1.

D. Ophthalmoscopic examination - No direct treatment-related ophthalmoscopic abnormalities were observed in any of the treatment groups. The high-dose female (ZR4103) that was sacrificed on day 56 exhibited ptosis, direct and indirect pupillary response deficits, and a protruding nictitating membrane; however, there were no macroscopic or microscopic pathology findings in the ocular structures of this high-dose female, and therefore these findings were attributed to a neurological condition that contributed indirectly to the ophthalmological findings.

E. Electrocardiography and blood pressure - No treatment-related differences in electrocardiography or blood pressure were observed in any of the treatment groups.

F. Blood work

1. Hematology - There were no differences of toxicological concern in hematological parameters in any of the treatment groups. A decrease ($p \leq 0.05$) in lymphocyte count was observed in the 50, 360, and 500 ppm male dogs at 281 days (↓19-33%) and at 372 days (↓23-33%). An increase ($p \leq 0.05$) was observed in segmented neutrophil count at 281 days in the 50, 360, and 500 ppm males (↑15-25%). These effects were not dose-dependent and/or not observed at termination, and so were considered not of toxicological concern. Platelet counts were increased ($p \leq 0.05$) at 281 days in the 100, 360, and 500 ppm females (↑32-64%) and at 372 days in the 360 and 500 ppm females (↑17-34%). The values (261-345 x 10^3/mm) were within historical control ranges (206-413 x 10^3/mm^3 at nine months and 188-455 x 10^3/mm^3 at 12 months) and there were no associated changes in activated partial thromboplastin times (APTT), gross findings, or histopathologic findings, and therefore the observation was considered not of toxicological concern.

2. Clinical Chemistry - No treatment-related differences in blood clinical chemistry parameters were observed in any of the treatment groups. Increased mean alkaline phosphatase activity was observed in the 500 ppm females at 372 days (↑77%, $p \leq 0.05$), but there were no associated histopathological findings, and therefore this observation was considered incidental.

Hepatic N-demethylase activity (Table 5) was increased in the 500 ppm males at termination, the only interval tested (↑45%, $p \leq 0.05$). No significant differences were observed in O-demethylase or cytochrome P450 activities.

Table 5. Liver N-demethylase (nmol/min /mg protein), O-demethylase (nmol/min /mg protein), and cytochrome P450 (nmol/mg protein) activities in dogs treated with cyfluthrin for up to 376 days.

Interval	Dose in ppm				
	0	50	100	360	500
Males					
N-Demethylase	1.10	0.97	0.83	1.24	1.60*(↑45)
O-Demethylase	0.16	0.14	0.17	0.15	0.20
Cytochrome P450	0.26	0.29	0.21	0.40	0.39
Females					
N-Demethylase	1.61	1.32	1.19	1.43	1.63
O-Demethylase	0.21	0.22	0.18	0.22	0.22
Cytochrome P450	0.32	0.45	0.40	0.33	0.49

a Data extracted from the study report Table SC1-SUM, pages 505 and 506, n=3-4/dose.

F. Urinalysis - No treatment-related differences in urinalysis parameters were observed in any of the treatment groups. Urine specific gravity was increased (↑1%, $p \leq 0.05$) in the high-dose females at day 278, put the difference was minor and not considered of toxicological concern.

G. Plasma cholinesterase activity - No differences from controls were observed in plasma cholinesterase activity (Table 6).

Table 6. Plasma cholinesterase activity (IU/mL) in dogs treated with cyfluthrin for up to 376 days.

Timepoint	Dose in ppm				
	0	50	100	360	500
Males					
Day -28	1.95	1.68	1.67	1.53	1.91
Day -7	1.96	1.67	1.63	1.69	1.78
Day 99	1.66	1.58	1.50	1.62	1.56
Day 190	1.67	1.52	1.61	1.52	1.57
Day 281	1.82	1.80	1.63	1.65	1.62
Day 372	1.60	1.63	1.51	1.51	1.63
Females					
Day -28	1.74	1.66	1.81	1.50	1.98
Day -7	1.70	1.63	1.86	1.60	1.89
Day 99	1.52	1.56	1.56	1.46	1.84
Day 190	1.70	1.82	1.60	1.52	1.76
Day 281	1.50	1.81	1.68	1.75	2.06
Day 372	1.37	2.16	1.69	1.45	1.83

a Data extracted from the study report Table CHE1-SUM, pages 492 through 503, n=3-4/dose.

H. Sacrifice and Pathology

1. Organ weight - No treatment-related differences in absolute or relative (to body) weights were observed between the treated and control groups. Absolute ovary weights were decreased in all female treatment groups (↓37-59%, $p \leq 0.05$). The decreases were not dose-dependent and there were no differences in relative ovary weights, and therefore this observation was attributed to decreased body weights.

2. Gross pathology - No treatment-related differences in gross postmortem findings were observed in any of the treatment groups.

3. Microscopic pathology

   a) Non-neoplastic - No treatment-related differences in microscopic pathology were observed in any of the treatment groups.

   b) Neoplastic - No neoplastic tissue was observed in dogs from any test group.

III. DISCUSSION

A. Investigator's Conclusions - Administration of cyfluthrin caused gait abnormalities and postural reaction deficits at 360 ppm. The severity and extent of neurological abnormalities and deficits were increased in the 500 ppm groups. The NOAEL is 100 ppm and the LOAEL is 360 ppm.

B. Reviewer's Discussion - Cyfluthrin was administered to Beagle dogs (4/sex/group) at concentrations of 0, 50, 100, 360, or 500 ppm in the diet (achieved doses of 0/0, 1.36/1.46, 2.43/3.61, 10.64/10.74, or 15.47/17.99 mg/kg/day [M/F], respectively) for approximately 12 months. The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

One high-dose female was sacrificed on day 56 after exhibiting gait (including incoordination and increased stride width), postural, and behavioral abnormalities, convulsions, tremors, and cranial and peripheral nerve deficits. The high-dose was reduced to 500 ppm for the remainder of the study. One control male died on day 318 and one control female died on day 210 from asymptomatic idiopathic epilepsy.

In the 360 ppm animals, clinical signs (males and females combined) included abnormal posture (1/8 treated vs 0/8 controls), vomiting (8/8 treated vs 4/8 controls), diarrhea (1/8 treated vs 0/8 controls), and soft feces (1/8 treated vs 0/8 controls). Gait abnormalities, including hypermetria, abnormal stride width, and reluctance to walk, were found at the 6 month (2/4 males; 1/4 females) and 12 month (1/4 males; 2/4 females) examinations. Abnormal postural reactions, including wheelbarrowing with head position abnormal or dorsally flexed, abnormal front foot placement during lateral hopping, hemistanding, and abnormal foot placement or weight support during backward stepping, were also found at the 6 month (4/4 males; 3/4 females) and 12 month (4/4 males; 3/4 females) examinations. No

postural or gait abnormalities were observed in controls.

At 500 ppm, clinical signs (males and females combined) included gait abnormalities such as reluctance/inability to walk, stiff-leggedness, ataxia, and abnormal stride width (1-2/8 treated vs 0/8 controls); seizures (2/8 treated vs 0/8 controls); convulsions and tremors (2/8 treated vs 0/8 controls); and abnormal posture (1/8 treated vs 0/8 controls). Vomiting (8/8 treated vs 4/8 controls), diarrhea (4/8 treated vs 0/8 controls) and soft feces (2/8 treated vs 0/8 controls) were also observed. Gait abnormalities similar to those observed in the 360 ppm group were found at the 6 month (3/4 males; 1/3 females) and 12 month (2/4 males; 1/3 females) examinations. Abnormal postural reactions similar to those observed in the 360 ppm group, but also including abnormal time to initiate front leg lateral hopping, were found at the 6 month (4/4 males; 3/3 females) and 12 month (4/4 males; 3/3 females) examinations. Non-statistically significant decreases in body weights were observed in the males throughout the study (↓6-20%). Mean body weight gains, as calculated by the reviewers, were decreased at the end of treatment in the males (↓53%). Hepatic N-demethylase activity was increased in males at termination, the only interval tested (↑45%, $p \leq 0.05$).

There were no differences of toxicological concern observed in rectal body temperature, food consumption, electrocardiography, blood pressure, hematological, clinical chemistry, or urinalysis parameters, ophthalmoscopic, necropsy, or histopathological findings, absolute or relative organ weights, and plasma cholinesterase, hepatic O-demethylase or cytochrome P450 activities. No neoplastic tissue was observed in dogs from any test group.

Body weights (↓6-16% at day 182 and ↓16-24% at day 371, p=not significant) and mean body weight gains as calculated by the reviewers (↓40-57%) were decreased in all female treatment groups. The decreases were not dose-dependent and were in part attributable to the death of the smallest control female, and therefore were considered of equivocal toxicological concern.

The LOAEL is 360 ppm (equivalent to 10.64/10.74 mg/kg/day [M/F]), based on clinical signs, gait abnormalities, and abnormal postural reactions in males and females. The NOAEL is 100 ppm (equivalent to 2.43/3.61 mg/kg/day [M/F]).

This study is classified **acceptable (§83-1b)** and satisfies the guideline requirements for a chronic toxicity study in dogs.

C. Study Deficiencies - There were no deficiencies noted.

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R058379

Chemical:	**Cyfluthrin**
PC Code:	**128831**
HED File Code	**13000 Tox Reviews**
Memo Date:	**02/02/2001 12:00:00 AM**
File ID:	**DPD243160**
Accession Number:	**412-04-0046**

HED Records Reference Center
03/25/2004