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

DATA EVALUATION RECORD

BETA-CYFLUTHRIN

Study Type: §82-7a, Subchronic Neurotoxicity Screening Battery in Rats

Work Assignment No. 2-01-73D (MRID 44296001)

Prepared for

Health Effects Division
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DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Neurotoxicity [Feeding] - rat
OPPTS Number: 870.6200 ✓ OPP Guideline Number: §82-7a

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

TEST MATERIAL (PURITY): Beta-cyfluthrin (≥96.5% a.i.)

SYNONYMS: FCR 4545, Cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropanecarboxylate

CITATION: Sheets, L.P., (1997). An Subchronic Dietary Neurotoxicity Screening Study with Technical Grade FCR 4545 (β-Cyfluthrin) in Fischer 344 Rats. Bayer Corporation Agriculture Division Toxicology, Stilwell, KS. Laboratory Study Number 95-472-FG. May 9, 1997. MRID 44296001. Unpublished.

SPONSOR: Bayer Corporation Agriculture Division, Kansas City, MO

EXECUTIVE SUMMARY: In this subchronic neurotoxicity study (MRID 44296001), beta-cyfluthrin (≥96.5% a.i., Lot/batch # 3030125) was administered continuously in the diet for 90 days to 12 Fischer 344 rats/sex/dose at doses of 0, 30, 125, or 400 ppm (equivalent to [M/F] 0/0, 2.02/2.34, 7.99/9.40, and 26.81/30.83 mg/kg/day). After 13 weeks, six animals/sex/group were perfused for neurohistological examination and animals from the control and high-dose groups were examined microscopically. The functional observational battery (FOB) and motor activity measurements were conducted during weeks -1, 4, 8, and 13. No treatment-related findings were observed in the 30 ppm group. No mortalities occurred during the study. Handling observations of the FOB, motor activity, brain weights, and neuropathology were unaffected by the test substance.

At 400 ppm, ataxia was observed in all of the animals (24/24 treated vs. 0/24 controls) beginning on day 11 and continuing throughout most of the study. Red crusty zones on one or both ears were observed in the males and females (13/24 treated vs. 0/24 controls). Repetitive chewing movements were observed in the males (2/12 vs. 0/12 controls) on day 25 only. In the females, increased reactivity (4/12), increased activity (1/12), pawing at the bottom of the cage (2/12) and red nasal staining (2/12) were observed (vs. 0/12 controls). During the home cage observations of the FOB, slight gait incoordination was observed in the males at weeks 4 (4/12) and 8 (1/12) and in the females at weeks 4 (4/12) and 13 (1/12). Moderate to severe gait incoordination (1/12)

and increased reactivity (3/12) were observed in the females at week 4 only. None of these home cage observations were noted in any control animal at any time point. During the open field observations of the FOB, slight repetitive chewing was observed in the males and females at weeks 4 (2/12 and 7/12, respectively) and 8 (2/12 and 5/12, respectively). Slight gait incoordination was observed in the males at weeks 4 (6/12) and 8 (5/12) and in the females at weeks 4 (10/12), 8 (5/12), and 13 (1/12). In addition, moderate to severe gait incoordination was observed in the high-dose females at week 4 only (1/12). None of these open field observations were noted in any control animal at any time point. During the reflex and physiological observations of the FOB, righting response was adversely affected (slight incoordination or lands on back) in the females at weeks 4 (5/12 treated vs. 0/12 controls) and 13 (6/12 treated vs. 1/12 controls) and in the males at week 4 only (1/12 treated vs. 0/12 controls). In addition, forelimb grip strength was decreased ($p \leq 0.05$) in the males at weeks 4 (↓19%) and 8 (↓21%) and in the females at weeks 4 (↓19%), 8 (↓12%), and 13 (↓14%). Hindlimb grip strength was decreased ($p \leq 0.05$) in the males at weeks 4 (↓26%) and 13 (↓20%) and in the females at weeks 4 (↓18%) and 8 (↓17%). Food consumption was decreased ($p \leq 0.05$) in the males and females throughout most of the study (↓6-42 and 10-38%, respectively); however, the magnitude of decreased food consumption appeared to lessen over time. Body weights were decreased ($p \leq 0.05$) in the males (↓14-21%) and females (↓13-19%) throughout the study. Overall (day 0-91) body weight gains (calculated by reviewers) were decreased in both sexes (↓31-39%). It is likely that the decreases observed in body weights, body weight gains, and food consumption were due to unpalatability of the test substance and not a toxicological effect.

The only adverse finding noted at 125 ppm was red crusty zones on one or both ears of the males (3/12 treated vs. 0/12 controls).

Evidence, including clinical signs and changes in FOB parameters, suggests that the test substance is neurotoxic at 400 ppm (equivalent to 26.81 mg/kg/day in males and 30.83 mg/kg/day in females).

The LOAEL for this study was 400 ppm (equivalent to 26.81 mg/kg/day in males and 30.83 mg/kg/day in females) based on clinical signs, changes in FOB parameters, and possibly decreased body weights, body weight gains, and food consumption.

The NOAEL for this study is 125 ppm (equivalent to 7.99 mg/kg/day in males and 9.40 mg/kg/day in females).

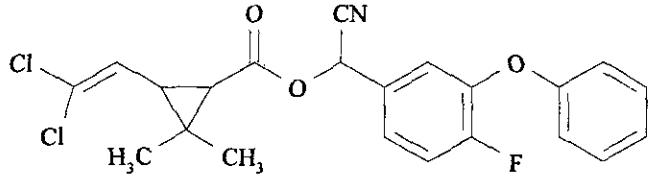
The submitted study is classified as **acceptable/guideline (§82-7[a])** and satisfies the requirements for a subchronic neurotoxicity screening battery in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. A Flagging statement was not provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Beta-cyfluthrin
   Description: Cream-colored powder
   Lot/Batch #: 3030125
   Purity (w/w): ≥96.5% a.i.
   Stability of compound: Stable for up to 14 days at room temperature and up to 35 days frozen.
   CAS #: 68359-37-5
   Structure:



2. Vehicle: Corn oil, 1% by weight in diet

3. Test animals: Species: Rat
   Strain: Fischer 344
   Age and mean weight at the start of dosing: Approximately 8 weeks old; 194.2-194.9 g (males), 130.2-133.6 g (females)
   Source: SASCO, Inc., Madison, WI
   Housing: Individually in suspended stainless steel wire-mesh cages
   Diet: Rodent Lab Chow 5001-4 (Purina Mills), ad libitum, except during neurobehavioral assessment
   Water: Tap water, ad libitum
   Environmental conditions:
   Temperature: 17.8-25.6 °C
   Humidity: 40-70%
   Air changes: Not provided
   Photoperiod: 12 hours light/12 hours dark
   Acclimation period: At least 6 days

B. STUDY DESIGN:

1. In life dates: start: 09/11/95 end: 12/14/95

2. Animal assignment: The rats were randomly assigned (stratified by weight) to the test groups shown in Table 1.

Table 1. Study design.[a]

Test Groups	Dose (ppm)	Mean Achieved Dose (mg/kg/day) [M/F]	Number of Animals	
			Males	Females
Control	0	0/0	12	12
Low	30	2.02/2.34	12	12
Mid	125	7.99/9.40	12	12
High	400	26.81/30.83	12	12

a Data were obtained from study report, pages 19 and 26.

3. Dose selection rationale: Dose levels for the current study were chosen based on the results of two range-finding studies, a 13 week subchronic dietary toxicity study in Wistar rats and a 3 week dietary study in Fischer 344 rats, both using doses of 0, 30, 125, or 500 ppm. The NOAEL in each study was 125 ppm, while uncoordinated gait, reduced body weight, and decreased food consumption were observed at 500 ppm in both studies. Additionally, two deaths were observed at 500 ppm in the 13 week study which were possibly treatment-related. Based on the results of these range-finding studies, the doses presented in Table 1 were selected for the subsequent full neurotoxicity study.

4. Treatment preparation and analysis: All test diets were prepared weekly using corn oil and a small amount of acetone, which was allowed to evaporate, and stored at freezer conditions; no further information was provided. Homogeneity (top, middle, bottom) was determined for 20 and 1000 ppm samples. Stability was determined for 20 and 1000 ppm dose formulations after storage at room and freezer temperatures for 14 and 35 days, respectively. Concentration analyses were performed on samples collected during weeks 1, 5, 10, and 14 from each dose level.

   Results:
   Homogeneity (range as mean % of nominal): 96.4-104% with coefficients of variance of 5-8.1%

   Stability analysis: Samples, stored at room temperature for up to 14 days or frozen for up to 35 days, were 95.8-102% and 90.6-110% of day 0, respectively.

   Concentration (range as mean % of nominal): 94.1-98.1%

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

5. Statistics: All data were analyzed using analysis of variance followed by a Dunnett's test if a significant F-value was observed. In the event of unequal variances, data were analyzed using a Kruskal-Wallis ANOVA followed by the Mann-Whitney U test. Additionally, categorical FOB data were analyzed using General Linear Modeling and Categorical Modeling.

C. METHODS:

1. Observations

a. Clinical signs - All animals were observed at least twice daily for mortality and moribundity (once daily during holidays and weekends). Detailed clinical examinations were performed weekly and just prior to necropsy.

b. Functional observational battery and motor activity - All animals were subjected to functional observational battery (FOB) and motor activity measurements during weeks -1, 4, 8, and 13. The FOB assessment included the following parameters:

Home Cage Observations
Posture
Piloerection
Gait abnormalities
Involuntary motor movements (clonic/tonic)
Vocalizations
Decreased activity
Nutation
Increased reactivity

Observations During Handling
Ease of removal
Reaction to handling
Muscle tone
Palpebral closure
Pupil size/condition
Lacrimation
Salivation
Stains
Alopecia
Bite marks
Broken teeth/malocclusion
Dehydration
Emaciation
Exophthalmia
Missing toe nails

Open Field Observations
Piloerection
Respiratory abnormalities
Posture
Involuntary motor movements (clonic/tonic)
Stereotypic behavior
Bizarre behavior
Gait abnormalities
Vocalizations
Arousal
Rearing
Fecal boli
Urine pools

Reflex/Physiological Observations
Approach response
Touch response
Auditory response
Tail pinch response
Righting reflex
Forelimb grip strength
Hindlimb grip strength
Landing foot splay
Body weight
Body temperature

Motor and locomotor activity were evaluated with a figure eight maze for nine 10-minute intervals (Columbus Instruments Universal Maze Monitoring System, Columbus OH) after completion of the FOB. Motor activity was measured as the

number of beam interruptions that occurred during the test session. Locomotor activity was measured by eliminating consecutive counts for a given beam; only one interruption of a beam was counted until the rat relocated in the maze and interrupted a different beam. In addition, habituation was evaluated as a decrease in activity during the test session.

c. Positive controls - Summaries were provided for four neurotoxicity studies performed to generate positive control data and validate the procedures and observers of the performing lab to conduct the FOB and to assess motor activity, neurotoxicity and behavioral effects. Triadimefon (200 mg/kg, i.p.) induced increased motor activity, while chlorpromazine (2 mg/kg, i.p.) caused decreased motor activity. Clinical and/or functional effects produced by acrylamide (25 or 50 mg/kg, i.p.) included ataxia, piloerection, muscle fasciculations, tremors, and urine or oral stains. In addition, acrylamide produced peripheral neuropathy and axonal degeneration in the spinal cords of treated animals. Triphenyltin (12 mg/kg, i.p.) induced increased incidences of the following: neuronal necrosis in the olfactory tract, piriform cortex, and hippocampus; chromatolysis of large neuronal soma in the pons, medulla, spinal cord, dorsal root ganglia, and gasserian ganglia; axonal or nerve fiber degeneration in the spinal cord and several peripheral nerves; and digestion chamber in dorsal root ganglia, gasserian ganglia, spinal cord, and sciatic nerve. Urine, oral, nasal, and perianal staining, ataxia, decreased touch and approach responses, repetitive chewing, muscle fasciculations, and tremors were observed following carbaryl exposure (15 or 30 mg/kg, i.p.).

2. Body weight - All animals were weighed weekly during the study.

3. Food consumption - Food consumption was measured weekly throughout the study and reported as g/animal/day.

4. Ophthalmology- Ophthalmic exams were performed during weeks -1 and 12 on all study animals. Any animals with defects noted during week -1 were sacrificed without necropsy.

5. Sacrifice and pathology - Six animals/sex/group were sacrificed by perfusion fixation and subjected to neuropathological examinations. The following control and high-dose tissues were embedded in paraffin, epoxy resin, or glycol methacrylate, sectioned, stained with hematoxylin and eosin, luxol fast blue-cresyl violet, Sevier-Munger silver, toluidine blue, or modified Lee's stains, and examined microscopically:

Central Nervous System			
Brain			
Olfactory bulbs	Cerebral cortex	Caudate putamen/globus pallidus	
Medulla oblongata	Hippocampus	Cerebellum	
Thalamus	Hypothalamus	Midbrain	
Spinal cord			
Cervical	Thoracic	Lumbar	Cauda equina
Peripheral Nervous System			
Sciatic nerve		Sural nerve	Tibial nerve
Optic nerve		Lumbar dorsal root ganglion	Lumbar spinal root
Gasserian ganglia		Cervical dorsal root ganglion	Cervical spinal root

In addition, the eyes and muscle tissue from the control and high-dose animals (6/sex) were examined microscopically. All animals that died during the study or were killed by perfusion fixation were subjected to gross necropsy. The remaining animals (up to 6 rats/sex/group) were killed by CO_2 asphyxiation and discarded.

II. RESULTS

A. Observations

1. Mortality - No animals died during the study.

2. Clinical signs - Ataxia was observed in all of the high-dose animals (24/24 treated vs. 0/24 controls) beginning on day 11 and continuing throughout most of the study. Red crusty zones on one or both ears were observed in the high-dose males and females (13/24 treated vs. 0/24 controls) and in the mid-dose males (3/12 treated vs. 0/12 controls). Repetitive chewing movements were observed in the high-dose males (2/12 vs. 0/12 controls) on day 25 only. In the high-dose females, increased reactivity (4/12), increased activity (1/12), pawing at the bottom of the cage (2/12) and red nasal staining (2/12) were observed (vs. 0/12 controls). In addition, eye opacity was observed in one high-dose female; however, it was stated that the opacity resulted from injury and was therefore considered unrelated to the test substance.

Table 2. Selected clinical signs in rats treated with beta-cyfluthrin for 3 months (number of affected animals).[a]

Observation	Dose (ppm)			
	0	30	125	400
Males				
Ataxia	0	0	0	12
Repetitive chewing movements	0	0	0	2
Red crusty zone, one or both ears	0	0	3	7
Females				
Ataxia	0	0	0	12
Pawing at bottom of cage	0	0	0	2
Increased reactivity	0	0	0	4
Increased activity	0	0	0	1
Red nasal stain	0	0	0	2
Red crusty zone, one or both ears	0	0	0	6

a Data obtained from the study report, Table 1 page 35; n=12.

B. Body weights and body weight gains: Selected body weight and overall body weight gain data are presented in Table 3. Body weights were decreased ($p \leq 0.05$) in the high-dose males (↓14-21%) and females (↓13-19%) throughout the study. In the mid-dose females, body weights were decreased slightly from day 35 until the end of the study (↓6-9%, $p \leq 0.05$). Overall (day 0-91) body weight gains (calculated by reviewers) were decreased in the high-dose animals (↓31-39%).

Table 3. Selected body weights (g) and overall (days 0-91) body weight gains in rats treated with beta-cyfluthrin for 3 months (mean± standard deviation).[a]

Day	Dose (ppm)			
	0	30	125	400
Males				
0	194.2±8.4	194.5±7.4	194.9±10.2	194.8±9.2
14	246.9±11.3	247.3±6.3	242.5±14.3	204.5*±10.7 (↓17)
28	275.0±14.8	279.7±6.8	267.1±25.8	217.6*±20.0 (↓21)
56	318.2 ±21.2	322.6±10.0	314.2±21.7	266.0*±17.6 (↓16)
91	358.4±23.8	363.7±11.3	353.9±23.4	308.4*±17.8 (↓14)
Overall body weight gain (0-91)[b]	164.2	169.2	159	113.6 (↓31)
Females				
0	133.6±5.3	130.2±3.8	130.5±5.6	130.6±6.6
14	156.1±5.7	153.6±5.5	151.1±6.3	136.2*±7.4 (↓13)
28	174.4±6.0	169.5±6.6	165.4±7.1	141.2*±16.0 (↓19)
56	188.2±8.0	184.9±8.5	176.2*±9.3 (↓6)	158.4*±11.5 (↓16)
91	206.0±9.2	203.0±8.4	188.0*±11.4 (↓9)	175.1*±11.2 (↓15)
Overall body weight gain (0-91)[b]	72.4	72.8	57.5	44.5 (↓39)

a Data obtained from the study report, Table 2, pages 36-37; n=12. Percent difference from controls is listed parenthetically.
b Calculated by reviewers
* Statistically significant at $p \leq 0.05$

C. Food consumption: Selected food consumption data are presented in Table 4. Food consumption was decreased ($p \leq 0.05$) in the high-dose males and females throughout most of the study (↓6-42 and 10-38%, respectively); however, the magnitude of decreased food consumption appeared to lessen over time. At the mid-dose, decreased ($p \leq 0.05$) food consumption was observed in the males on day 7 only (↓7%) and sporadically in the females (↓6-12%) throughout the study. In addition, slight decreases (↓5-7%, $p \leq 0.05$) were observed in the low-dose females at 4/13 time points.

Table 4. Selected food consumption (g/rat/day) in rats treated with beta-cyfluthrin for 3 months (mean ± standard deviation).[a]

Day	Dose (ppm)			
	0	30	125	400
Males				
7	20.36±1.09	20.21±1.04	18.85*±1.08 (↓7)	11.91*±0.68 (↓42)
28	20.49±1.15	21.37±1.11	20.01±1.60	16.63*±1.47 (↓19)
49	19.67±1.20	19.90±0.99	19.40±1.44	18.43*±0.64 (↓6)
63	19.02±1.26	19.38±0.73	18.48±1.29	18.15±1.03
91	19.66±1.18	19.75±0.91	19.15±1.17	18.25*±0.95 (↓7)
Females				
7	14.35±0.39	13.84±0.77	13.41*± 0.78 (↓7)	8.87*±0.82 (↓38)
28	14.91±0.60	14.17*±0.52 (↓5)	13.95*±0.77 (↓6)	11.99*±0.92 (↓20)
49	13.90±1.08	13.64±0.86	13.22±1.20	12.48*±0.75 (↓10)
63	14.71±1.19	13.61*±0.70 (↓7)	12.97*±1.17 (↓12)	12.08*±0.71 (↓18)
91	12.85±0.69	13.12±0.55	12.30±0.67	12.38±0.61

a Data obtained from the study report, Table 3, pages 38-39; n=12. Percent difference from controls is listed parenthetically.

* Statistically significant at $p \leq 0.05$

D. Functional observational battery:

1. Home cage observations: Selected home cage observations are presented in Table 5a. Slight gait incoordination was observed in the high-dose males at weeks 4 (4/12) and 8 (1/12) and in the high-dose females at weeks 4 (4/12) and 13 (1/12). Moderate to severe gait incoordination (1/12) and increased reactivity (3/12) were observed in the high-dose females at week 4 only. None of these home cage observations were noted in any control animal at any time point.

Table 5a. Selected home cage observations noted during the FOB in rats treated with beta-cyfluthrin for 3 months (number of affected animals).[a]

Observation	Dose (ppm)							
	Males				Females			
	0	30	125	400	0	30	125	400
Pretest								
Gait abnormalities not observed	12	12	12	12	12	12	12	12
Week 4								
Gait incoordination slight	0	0	0	4*	0	0	0	4*
moderate/severe					0	0	0	1*
Increased reactivity	0	0	0	0	0	0	0	3*
Week 8								
Gait incoordination slight	0	0	0	1	0	0	0	0
Week 13								
Gait incoordination slight	0	0	0	0	0	0	0	1

a Data obtained from the study report, Tables 5-7 pages 41-74; n=12.
* Statistically different from controls at $p \leq 0.05$.

2. Handling observations: No adverse treatment-related effects were observed in any treated group during the handling observations.

3. Open field observations: Selected open field observations are presented in Table 5b. Slight repetitive chewing was observed in the high-dose males and females at weeks 4 (2/12 and 7/12, respectively) and 8 (2/12 and 5/12, respectively). Slight gait incoordination was observed in the high-dose males at weeks 4 (6/12) and 8 (5/12) and in the high-dose females at weeks 4 (10/12), 8 (5/12), and 13 (1/12). In addition, moderate to severe gait incoordination was observed in the high-dose females (1/12) and males (5/12) at week 4. None of these open field observations were noted in any control animal at any time point.

Table 5b. Selected open field observations noted during the FOB in rats treated with beta-cyfluthrin for 3 months (number of affected animals).[a]

Observation	Dose (ppm)							
	Males				Females			
	0	30	125	400	0	30	125	400
Pretest								
Gait abnormalities not observed	12	12	12	12	12	12	12	12
Bizarre behavior not observed	12	12	12	12	12	12	12	12
Week 4								
Repetitive chewing slight	0	0	0	2	0	0	0	7*
Gait incoordination slight	0	0	0	6*	0	0	0	10*
moderate/severe	0	0	0	5*	0	0	0	1*
Week 8								
Repetitive chewing slight	0	0	0	2	0	0	0	5*
Gait incoordination slight	0	0	0	5*	0	0	0	5*
Week 13								
Gait incoordination slight	0	0	0	0	0	0	0	1

a Data obtained from the study report, Tables 5-7 pages 41-74; n=12.
* Statistically different from controls at $p \leq 0.05$.

4. Reflex/physiologic observations: Selected reflex and physiological observations are presented in Table 5c. Righting response was adversely affected (slight incoordination or lands on back) in the high-dose females at weeks 4 (5/12 treated vs. 0/12 controls) and 13 (6/12 treated vs. 1/12 controls) and in the high-dose males at week 4 only (1/12 treated vs. 0/12 controls). Body weight was decreased in the high-dose males and females at all time points relative to concurrent controls (↓14-21%, $p \leq 0.05$). In addition, forelimb grip strength was decreased ($p \leq 0.05$) in the high-dose males at weeks 4 (↓19%) and 8 (↓21%) and in the high-dose females at weeks 4 (↓19%), 8 (↓12%), and 13 (↓14%). Hindlimb

grip strength was decreased ($p \leq 0.05$) in the high-dose males at weeks 4 (↓26%) and 13 (↓20%) and in the high-dose females at weeks 4 (↓18%) and 8 (↓17%).

Table 5c. Selected reflex/physiologic observations noted during the FOB in rats treated with beta-cyfluthrin for 3 months (number of affected animals).[a]

Observation	Dose (ppm)							
	Males				Females			
	0	30	125	400	0	30	125	400
Pretest								
Righting response (# animals) normal	12	12	12	12	12	12	12	12
Body weight (g)	170	170	170	170	128	127	126	127
Forelimb grip strength (kg)	0.48	0.46	0.50	0.49	0.47	0.47	0.47	0.51
Hindlimb grip strength (kg)	0.24	0.22	0.24	0.23	0.21	0.21	0.20	0.22
Week 4								
Righting response (# animals) slight incoordination	0	2	0	1	0	0	0	4
lands on back	0	0	0	0	0	0	0	1
Body weight (g)	263	267	254	207* (↓21)	167	162	159	140* (↓16)
Forelimb grip strength (kg)	0.91	0.85	0.89	0.74* (↓19)	0.78	0.79	0.77	0.63* (↓19)
Hindlimb grip strength (kg)	0.35	0.35	0.32	0.26* (↓26)	0.28	0.30	0.27	0.23* (↓18)
Week 8								
Body weight (g)	313	319	310	265* (↓15)	189	183	173* (↓8)	160* (↓15)
Forelimb grip strength (kg)	1.07	1.08	1.08	0.85* (↓21)	0.89	0.93	0.93	0.78* (↓12)
Hindlimb grip strength (kg)	0.41	0.45	0.42	0.36	0.35	0.35	0.36	0.29* (↓17)
Week 13								
Righting response (# animals) slight incoordination	2	3	2	0	1	1	2	6
Body weight (g)	352	349	345	303* (↓14)	200	197	184* (↓8)	170* (↓15)
Forelimb grip strength (kg)	1.16	1.16	1.24	1.06	1.00	1.00	1.03	0.86* (↓14)
Hindlimb grip strength (kg)	0.50	0.44	0.43	0.40* (↓20)	0.37	0.41	0.35	0.34

a Data obtained from the study report, Tables 5-7 pages 41-74; n=12. Percent difference from controls is listed parenthetically.

* Significantly different from controls at $p \leq 0.05$.

E. Motor activity: No treatment-related differences from concurrent controls were observed in mean motor or locomotor activities (Table 6). During week 4, mean motor activity was increased ($p \leq 0.05$) in the mid- (↑63%) and high- (↑47%) dose males; however these increases were not dose-dependent and considered not to be treatment-related. Interval motor and locomotor activity data were comparable between the treated and control groups at all time points. All groups showed normal habituation during motor activity testing.

Table 6. Mean motor and locomotor activity (counts) in rats treated with beta-cyfluthrin for 3 months (mean ± standard deviation).[a]

Treatment interval (weeks)		Dose (ppm)			
		0	30	125	400
Males					
Pretest	Motor activity	527±206	666±246	623±143	550±178
	Locomotor activity	190±68	223±93	212±62	205±73
4	Motor activity	463±145	612±194	753*±194 (↑63)	682*±188 (↑47)
	Locomotor activity	171±64	215±73	267±79	216±94
8	Motor activity	558±224	612±239	613±281	661±128
	Locomotor activity	225±103	254±114	244±129	242±63
13	Motor activity	463±155	488±211	565±118	665±248
	Locomotor activity	195±73	216±116	243±72	266±128
Females					
Pretest	Motor activity	927±269	858±352	873±214	805±247
	Locomotor activity	342±108	304±135	320±100	296±121
4	Motor activity	943±342	997±295	1032±253	957±318
	Locomotor activity	323±125	344±134	357±102	294±116
8	Motor activity	863±262	771±200	954±353	946±246
	Locomotor activity	320±122	252±69	318±124	318±103
13	Motor activity	1103±399	926±336	1003±248	1078±192
	Locomotor activity	387±164	313±124	332±85	363±85

a Data obtained from the study report Tables 8-9, pages 75-78; n=12. Percent difference from controls is listed parenthetically.

* Statistically significant at $p \leq 0.05$

F. Pathology:

1. Neuropathology: No treatment-related gross or microscopic neuropathological changes were observed in any treated group (see Attachment).

2. Brain weights: No treatment-related differences were observed in the brain weights of any treated group compared to concurrent controls. Relative (to body) brain weights were increased ($p \leq 0.05$) in the high-dose males (↑20%) and females (↑17%) and in the mid-dose females (↑12%). These increases were due to decreased terminal body weights in these animals (↓9-14%, $p \leq 0.05$) and considered unrelated to treatment.

III. DISCUSSION

A. Investigator's conclusions - Oral administration of beta-cyfluthrin for 3 months produced clinical signs and decreased food consumption, body weight, and body weight gains. In addition, transient neurobehavioral effects, consistent with those associated with Type II pyrethroids, were evidenced in the FOB. The systemic NOAEL for this study was 30 ppm; however, no evidence of neuropathy was observed at any tested dose.

B. Reviewer's discussion/conclusions - In this subchronic neurotoxicity study (MRID 44296001), beta-cyfluthrin was administered continuously in the diet for 90 days to 12 Fischer 344 rats/sex/dose at doses of 0, 30, 125, or 400 ppm (equivalent to [M/F] 0/0, 2.02/2.34, 7.99/9.40, and 26.81/30.83 mg/kg/day). After 13 weeks, six animals/sex/group were perfused for neurohistological examination and animals from the control and high-dose groups were examined microscopically. Functional observational battery (FOB) and motor activity measurements were conducted during weeks -1, 4, 8, and 13. The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable. Furthermore, the results confirmed the stability of the test substance in the vehicle for a period of 14 days at room temperature.

No treatment-related findings were observed in the 30 ppm group. No mortalities occurred during the study. Handling observations of the FOB, motor activity, brain weights, and neuropathology were unaffected by the test substance.

Ataxia was observed in all of the high-dose animals (24/24 treated vs. 0/24 controls) beginning on day 11 and continuing throughout most of the study. Red crusty zones on one or both ears were observed in the high-dose males and females (13/24 treated vs. 0/24 controls) and in the mid-dose males (3/12 treated vs. 0/12 controls). Repetitive chewing movements were observed in the high-dose males (2/12 vs. 0/12 controls) on day 25 only. In the high-dose females, increased reactivity (4/12), increased activity (1/12), pawing at the bottom of the cage (2/12) and red nasal staining (2/12) were observed (vs. 0/12 controls).

Food consumption was decreased ($p \leq 0.05$) in the high-dose males and females throughout most of the study (↓6-42 and 10-38%, respectively); however, the magnitude of decreased food consumption appeared to lessen over time. At the mid-dose, decreased ($p \leq 0.05$) food consumption was observed in the males on day 7 only (↓7%) and sporadically in the females (↓6-12%) throughout the study. In addition, slight decreases (↓5-7%, $p \leq 0.05$) were observed in the low-dose females at 4/13 time points. Body weights were decreased ($p \leq 0.05$) in the high-dose males (↓14-21%) and females (↓13-19%) throughout the study. In the mid-dose females, body weights were decreased slightly from day 35 until the end of the study (↓6-9%, $p \leq 0.05$). Overall (day 0-91) body weight gains (calculated by reviewers) were decreased in the high-dose animals (↓31-39%). Decreases in food consumption and body weights at the mid- and low-doses were minor and sporadic and considered unrelated to treatment; it is likely that the decreases observed in body weights, body weight gains, and food consumption at the high-dose were due to unpalatability of the test substance and not a toxicological effect.

During the home cage observations of the FOB, slight gait incoordination was observed in the high-dose males at weeks 4 (4/12) and 8 (1/12) and in the high-dose females at weeks 4 (4/12) and 13 (1/12). Moderate to severe gait incoordination (1/12) and increased reactivity (3/12) were observed in the high-dose females at week 4 only. None of these home cage observations were noted in any control animal at any time point. During the open field observations of the FOB, slight repetitive chewing was observed in the high-dose males and females at weeks 4 (2/12 and 7/12, respectively) and 8 (2/12 and 5/12, respectively). Slight gait incoordination was observed in the high-dose males at weeks 4 (6/12) and 8 (5/12) and in the high-dose females at weeks 4 (10/12), 8 (5/12), and 13 (1/12). In addition, moderate to severe gait incoordination was observed in the high-dose females at week 4 only (1/12). None of these open field observations were noted in any control animal at any time point. During the reflex and physiological observations of the FOB, righting response was adversely affected (slight incoordination or lands on back) in the high-dose females at weeks 4 (5/12 treated vs. 0/12 controls) and 13 (6/12 treated vs. 1/12 controls) and in the high-dose males at week 4 only (1/12 treated vs. 0/12 controls). Body weight was decreased in the high-dose males and females at all time points relative to concurrent controls (↓14-21%, $p \leq 0.05$). In addition, forelimb grip strength was decreased ($p \leq 0.05$) in the high-dose males at weeks 4 (↓19%) and 8 (↓21%) and in the high-dose females at weeks 4 (↓19%), 8 (↓12%), and 13 (↓14%). Hindlimb grip strength was decreased ($p \leq 0.05$) in the high-dose males at weeks 4 (↓26%) and 13 (↓20%) and in the high-dose females at weeks 4 (↓18%) and 8 (↓17%).

Evidence, including clinical signs and changes in FOB parameters, suggests that the test substance is neurotoxic at 400 ppm (equivalent to 26.81 mg/kg/day in males and 30.83 mg/kg/day in females).

The LOAEL for this study was 400 ppm (equivalent to 26.81 mg/kg/day in males and 30.83 mg/kg/day in females) based on clinical signs, changes in FOB parameters, and possibly decreased body weights, body weight gains, and food consumption.

The NOAEL for this study is 125 ppm (equivalent to 7.99 mg/kg/day in males and 9.40 mg/kg/day in females).

The submitted study is classified as **acceptable/guideline (§82-7[a])** and satisfies the requirements for a subchronic neurotoxicity screening battery in rats.

C. Study deficiencies

- None noted

ATTACHMENT-Neuropathology (Microscopic)

THE FOLLOWING ATTACHMENT IS NOT AVAILABLE ELECTRONICALLY. SEE THE FILE COPY.

BAYER Agriculture Division - Toxicology

Date: 16SEP1996
Time: 13:42:01

Table MP 1-SUM
MICROPATHOLOGY INCIDENCE AND AVERAGE GRADE SUMMARY
SUBCHRONIC NEUROTOXICITY STUDY WITH
TECHNICAL GRADE BAY FCR 4545 (CYFLUTHRIN) IN FISCHER 344 RATS
Study Number 95-472-FG

ORGAN and LESION		Males Level (PPM) 0	30	125	400	Females Level (PPM) 0	30	125	400
BRAIN, LEVEL 1	# Tissues Examined	6			6	6			6
No Abnormality Detected		6	-	-	6	6	-	-	6
BRAIN, LEVEL 2	# Tissues Examined	6			6	6			6
No Abnormality Detected		6	-	-	6	6	-	-	6
BRAIN, LEVEL 3	# Tissues Examined	6			6	6			6
No Abnormality Detected		6	-	-	6	6	-	-	6
BRAIN, LEVEL 4	# Tissues Examined	6			6	6			6
No Abnormality Detected		5	-	-	4	6	-	-	5
Degeneration, Nerve Fiber		1	-	-	2	-	-	-	1
		(3.0)			(2.0)				(2.0)
BRAIN, LEVEL 5	# Tissues Examined	6			6	6			6
No Abnormality Detected		5	-	-	4	6	-	-	5
Degeneration, Nerve Fiber		1	-	-	2	-	-	-	1
		(3.0)			(2.5)				(3.0)
BRAIN, LEVEL 6	# Tissues Examined	6			6	6			6
No Abnormality Detected		4	-	-	5	6	-	-	5
Axonal Swelling		1	-	-	-	-	-	-	-
		(1.0)							
Degeneration, Nerve Fiber		1	-	-	1	-	-	-	1
		(1.0)			(1.0)				(1.0)
BRAIN, LEVEL 7	# Tissues Examined	6			6	6			6
No Abnormality Detected		1	-	-	-	1	-	-	1

() = Average severity of animals with lesion: 1 (minimal) to 5 (severe).
Blank severity field = neoplasm or lesion which is not graded.
* = Significantly different from control (p<=0.05).
- = No incidence.
ER = At least one ungraded lesion.

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Study Number 95-472-FG

ORGAN and LESION		Males Level (PPM) 0	30	125	400	Females Level (PPM) 0	30	125	400
BRAIN, LEVEL 7 (continued)									
Axonal Swelling		2	-	-	1	1	-	-	-
		(1.0)			(1.0)	(1.0)			
Degeneration, Nerve Fiber		5	-	-	6	5	-	-	5
		(1.0)			(1.0)	(1.0)			(1.0)
BRAIN, LEVEL 8	# Tissues Examined	6			6	6			6
No Abnormality Detected		5	-	-	6	5	-	-	5
Axonal Swelling		1	-	-	-	1	-	-	1
		(1.0)				(1.0)			(1.0)
EYES	# Tissues Examined	6			6	6			6
No Abnormality Detected		-	-	-	3	-	-	-	1
Degeneration,Retinal		1	-	-	2	-	-	-	1
		(3.0)			(2.5)				(5.0)
Synechia		-	-	-	1	-	-	-	-
					(2.0)				
Cataract		-	-	-	-	-	-	-	1
									(4.0)
Mineralization, Cornea		6	-	-	3	6	-	-	5
		(1.0)			(1.3)	(1.2)			(1.0)
GANGLION, DORSAL ROOT	# Tissues Examined	6			6	6			6
No Abnormality Detected		6	-	-	6	6	-	-	6
GANGLION, GASSERIAN	# Tissues Examined	6			6	6			6
No Abnormality Detected		6	-	-	6	6	-	-	6

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MUSCLE,GASTROCNEMIUS	# Tissues Examined	6			6	6			6
No Abnormality Detected		6	-	-	6	6	-	-	6
NERVE, SURAL, LEFT	# Tissues Examined	6			6	6			6
No Abnormality Detected		6	-	-	6	6	-	-	6
NERVE, SURAL, RIGHT	# Tissues Examined	6			6	6			6
No Abnormality Detected		6	-	-	6	6	-	-	6
NERVE,SCIATIC,LEFT	# Tissues Examined	6			6	6			6
No Abnormality Detected		6	-	-	6	6	-	-	6
NERVE,SCIATIC,RIGHT	# Tissues Examined	6			6	6			6
No Abnormality Detected		6	-	-	6	6	-	-	6
NERVE,TIBIAL,LEFT	# Tissues Examined	6			6	6			6
No Abnormality Detected		6	-	-	6	6	-	-	6
NERVE,TIBIAL,RIGHT	# Tissues Examined	6			6	6			6
No Abnormality Detected		6	-	-	6	6	-	-	6
OPTIC NERVES	# Tissues Examined	6			6	6			6
No Abnormality Detected		5	-	-	4	6	-	-	5
Degeneration, Nerve Fiber		1	-	-	2	-	-	-	1
		(4.0)			(3.0)				(3.0)
SPINAL CORD, CAUDA EQUINA	# Tissues Examined	6			6	6			6
No Abnormality Detected		2	-	-	2	2	-	-	1
Axonal Swelling		3	-	-	4	4	-	-	5
		(1.0)			(1.0)	(1.0)			(1.0)

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Study Number 95-472-FG

ORGAN and LESION		Males Level (PPM) 0	30	125	400	Females Level (PPM) 0	30	125	400
SPINAL CORD, CAUDA EQUINA (continued)									
Degeneration, Nerve Fiber		2	-	-	-	1	-	-	1
		(1.0)				(1.0)			(1.0)
SPINAL CORD,CERVICAL	# Tissues Examined	6			6	6			6
No Abnormality Detected		1	-	-	1	1	-	-	4
Axonal Swelling		2	-	-	2	2	-	-	1
		(1.0)			(1.0)	(1.0)			(1.0)
Degeneration, Nerve Fiber		4	-	-	5	3	-	-	1
		(1.0)			(1.0)	(1.0)			(1.0)
SPINAL CORD,LUMBAR	# Tissues Examined	6			6	6			6
No Abnormality Detected		2	-	-	2	2	-	-	2
Cyst		-	-	-	-	-	-	-	2
Axonal Swelling		4	-	-	3	2	-	-	2
		(1.0)			(1.0)	(1.0)			(1.0)
Degeneration, Nerve Fiber		2	-	-	1	2	-	-	2
		(1.0)			(1.0)	(1.0)			(1.0)
SPINAL CORD,THORACIC	# Tissues Examined	6			6	6			6
No Abnormality Detected		1	-	-	2	4	-	-	3
Axonal Swelling		4	-	-	3	1	-	-	-
		(1.0)			(1.0)	(1.0)			
Degeneration, Nerve Fiber		4	-	-	2	2	-	-	3
		(1.0)			(1.0)	(1.0)			(1.0)

() = Average severity of animals with lesion: 1 (minimal) to 5 (severe).
Blank severity field = neoplasm or lesion which is not graded.
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BAYER Agriculture Division - Toxicology

Date: 16SEP1996
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BAYER CORPORATION
95-472-FG

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ORGAN and LESION		Males Level (PPM) 0	30	125	400	Females Level (PPM) 0	30	125	400
SPINAL NERVE ROOTS	# Tissues Examined	6			6	6			6
No Abnormality Detected		5	-	-	6	6	-	-	5
Degeneration, Nerve Fiber		1 (1.0)	-	-	-	-	-	-	1 (1.0)

() = Average severity of animals with lesion: 1 (minimal) to 5 (severe).
Blank severity field = neoplasm or lesion which is not graded.
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R058538

Chemical:	**Cyfluthrin**
PC Code:	**128831**
HED File Code	**13000 Tox Reviews**
Memo Date:	**08/19/2000 12:00:00 AM**
File ID:	**DPD243160**
Accession Number:	**412-04-0046**

HED Records Reference Center
03/25/2004