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

pc 128831

EPA Reviewer: Pamela M. Hurley 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.: 44401101 Cyfluthrin: [Neurotoxicity Screening Battery - Acute] **This supplement includes a revised executive summary with a change in the NOAEL and LOAEL and an upgrade from unacceptable to acceptable**

STUDY TYPE: Acute Oral Neurotoxicity [Gavage] - rat
OPPTS Number: 870.6200 OPP Guideline Number: §81-8a

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

TEST MATERIAL (PURITY): Beta cyfluthrin (≥96.9% a.i.)

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

CITATION: Sheets, L.P. and Gilmore, R.G., (1997). An Acute Oral Neurotoxicity Screening Study with Technical Grade FCR 4545 in Fischer 344 Rats. Bayer Corporation Agriculture Division Toxicology, Stilwell, KS. Laboratory Study Number 96-412-GO. October 2, 1997. MRID 44401101. Unpublished.

SPONSOR: Bayer Corporation Agriculture Division, Kansas City, MO

EXECUTIVE SUMMARY: In this acute oral neurotoxicity study (MRID 44401101), beta cyfluthrin (≥96.9% a.i., Lot/batch # 3030125) was administered in a single dose by gavage to 12 Fischer 344 rats/sex/dose at doses of 0, 0.5, 2, or 10 mg/kg. After two 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 were evaluated during week -1 and on days 0 (approximately 2 hours post-dosing), 7, and 14. No mortalities occurred during the study. Body weights, body weight gains, brain weights, and neuropathology were unaffected by the test substance.

At 0.5 mg/kg, slight repetitive chewing was observed in the females (2/12 treated vs. 0/12 controls) during the day 0 open field observations of the FOB. This is not considered to be toxicologically significant due to a lack of a dose-response (no females were affected at 2 mg/kg) and no males exhibited this behavior at this dose level. During the reflex/physiologic observations of the FOB on day 0, lack of approach response was observed in the males (2/12 treated vs. 1/12 controls). This is also not considered to be a toxicologically significant response

because 2/12 controls had a lack of approach response during both the pretest and day 7 time intervals and no females had a lack of approach response at this time period and dose level.

At 2 mg/kg, perianal staining was observed more frequently in treated animals than in controls (22/24 treated vs. 13/24 controls). During the open field observations of the FOB on day 0, slight repetitive chewing was observed in the males (1/12). During the reflex/physiologic observations of the FOB on day 0, lack of approach response was observed in both sexes (4/24 treated vs. 1/24 controls). This is not considered to be a toxicologically significant effect because 5/24 control animals during the pretest and 3/24 animals during the day 7 time interval had a lack of approach response.

At 10 mg/kg, oral staining was observed in the males and females (19/24 vs. 0/24 controls) and urine staining was observed in the males only (4/12 treated vs. 0/12 controls). In addition, perianal staining was observed more frequently in treated animals than in controls (23/24 treated vs.13/24 controls). During the home cage observations of the FOB on day 0, slight to severe repetitive chewing was observed in the males (3/12). Slight gait incoordination was observed in the females (7/12) and moderate to severe gait incoordination was observed in both sexes (8/24). Decreased activity was observed in the males and females (9/24); these animals were also observed to be lying flattened (2/24). Writhing was observed in the high-dose males (2/12). None of the home cage observations were noted in any control animal during the study. In addition, no treatment-related observations were noted in any treated animal on days 7 and 14. During the handling observations of the FOB on day 0, slight salivation was observed in the females (2/12) and moderate to severe salivation was observed in the animals of both sexes (2/24). In addition, slight to severe clear oral stains were observed in the males and females (19/24). Moderate to severe urine stains were observed in both sexes (7/24). None of the handling observations were noted in any control animal during the study, except for urine stains on one female on day 7. In addition, no treatment-related observations were noted in any treated animal on days 7 and 14. During the open field observations of the FOB on day 0, slight repetitive chewing was observed in the males and females (4/24). In addition, moderate to severe repetitive chewing was observed in one male. Slight gait incoordination was observed in animals of both sexes (12/24). In addition, moderate to severe gait incoordination was observed in these animals (6/24). Writhing and lying flattened (posture) were observed in the males (2/12 each) and repetitive pawing motion was observed in animals of both sexes (4/24). Slight muscle fasciculations were observed in one female. None of these open field observations were noted in any control animal at any time point, nor were they observed in any treated animal on days 7 and 14. Arousal (sluggish, minimal movement) was affected in the females mainly at day 0 (6/12 vs. 0/12 controls), but also on day 14 in both sexes (9/24 treated vs. 3/12 controls). During the reflex/physiologic observations of the FOB on day 0, lack of approach response was observed in the males and females (5/24 treated vs. 1/24 controls). Lack of touch response was observed in both sexes (5/24 treated vs. 0/24 controls), and lack of tail pinch response was observed in the males only (3/12 treated vs. 0/12 controls). Righting reflex was adversely affected (slight incoordination, lands on back, or lands on side) in the males and females (13/24 treated vs. 0/24 controls). All control animals appeared normal and no treatment-related observations were noted in any treated animal on days 7 and 14. Motor activity was decreased ($p \leq 0.05$) relative to concurrent controls in the females during intervals 1, 2, and 3 (↓62-94%). Locomotor activity

was decreased ($p \leq 0.05$) relative to concurrent controls in the males during intervals 1 and 2 (↓72-95%), the females during intervals 1, 2, and 3 (↓69-94%).

**The changes in clinical signs, FOB parameters, and motor activity measurements suggest that the test substance is neurotoxic.**

**The LOAEL for this study is 10 mg/kg based on clinical signs, changes in FOB parameters and decreases in motor activity.**

**The NOAEL for this study 2 mg/kg.** The increase in number of animals with perianal staining and slight repetitive chewing in one animal at this dose level is not considered to be toxicologically significant. This decision was made on the basis of the weight of the evidence from the subchronic neurotoxicity and developmental rat studies conducted with the same test chemical in the same laboratory. In the subchronic neurotoxicity study, no perianal staining was observed at any dose level and repetitive chewing was only observed at the highest dose tested (26.81/30.83 mg/kg/day). The subchronic neurotoxicity study was a dietary study conducted with the same strain of rat (Fischer) and the developmental rat study was a gavage study conducted with Wistar rats. Neither clinical sign was observed in the developmental study up to a dose level of 40 mg/kg/day, although it is possible that repetitive chewing may have been missed because the animals were not specifically examined for that effect. In addition, a NOAEL of 2 mg/kg would be consistent with the NOAELs established in the remainder of the toxicity database for cyfluthrin and beta-cyfluthrin.

The submitted study is classified as **acceptable (§81-8[a])**

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

# DATA EVALUATION RECORD

BETA CYFLUTHRIN

Study Type: §81-8a, Neurotoxicity Screening Battery in Rats

Work Assignment No. 2-01-73C (MRID 44401101)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Quality Assurance
Sharon Meyer, Ph.D.

Signature: _____
Date: _____

Disclaimer

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

**BETA CYFLUTHRIN** **Acute oral neurotoxicity (§81-8[a])**

EPA Reviewer: William Greear, M.P.H., D.A.B.T.
Registration Action Branch III/HED (7509C)

Work Assignment Manager: Marion Copley, D.V.M., D.A.B.T
Registration Action Branch I/HED (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Neurotoxicity [Gavage] - rat
OPPTS Number: 870.6200 OPP Guideline Number: §81-8a

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

TEST MATERIAL (PURITY): Beta cyfluthrin (≥96.9% a.i.)

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

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SPONSOR: Bayer Corporation Agriculture Division, Kansas City, MO

EXECUTIVE SUMMARY: In this acute oral neurotoxicity study (MRID 44401101), beta cyfluthrin (≥96.9% a.i., Lot/batch # 3030125) was administered in a single dose by gavage to 12 Fischer 344 rats/sex/dose at doses of 0, 0.5, 2, or 10 mg/kg. After two 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 were evaluated during week -1 and on days 0 (approximately 2 hours post-dosing), 7, and 14. No mortalities occurred during the study. Body weights, body weight gains, brain weights, and neuropathology were unaffected by the test substance.

At 0.5 mg/kg, slight repetitive chewing was observed in the females (2/12 treated vs. 0/12 controls) during the day 0 open field observations of the FOB. During the reflex/physiologic observations of the FOB on day 0, lack of approach response was observed in the males (2/12 treated vs. 1/12 controls).

At 2 mg/kg, perianal staining was observed more frequently in treated animals than in controls (22/24 treated vs. 13/24 controls). During the open field observations of the FOB on day 0, slight repetitive chewing was observed in the males (1/12). During the reflex/physiologic

observations of the FOB on day 0, lack of approach response was observed in both sexes (5/24 treated vs. 1/24 controls).

At 10 mg/kg, oral staining was observed in the males and females (19/24 vs. 0/24 controls) and urine staining was observed in the males only (4/12 treated vs. 0/12 controls). In addition, perianal staining was observed more frequently in treated animals than in controls (23/24 treated vs.13/24 controls). During the home cage observations of the FOB on day 0, slight to severe repetitive chewing was observed in the males (3/12). Slight gait incoordination was observed in the females (7/12) and moderate to severe gait incoordination was observed in both sexes (8/24). Decreased activity was observed in the males and females (9/24); these animals were also observed to be lying flattened (2/24). Writhing was observed in the high-dose males (2/12). None of the home cage observations were noted in any control animal during the study. In addition, no treatment-related observations were noted in any treated animal on days 7 and 14. During the handling observations of the FOB on day 0, slight salivation was observed in the females (2/12) and moderate to severe salivation was observed in the animals of both sexes (2/24). In addition, slight to severe clear oral stains were observed in the males and females (19/24). Moderate to severe urine stains were observed in both sexes (7/24). None of the handling observations were noted in any control animal during the study, except for urine stains on one female on day 7. In addition, no treatment-related observations were noted in any treated animal on days 7 and 14. During the open field observations of the FOB on day 0, slight repetitive chewing was observed in the males and females (4/24). In addition, moderate to severe repetitive chewing was observed in one male. Slight gait incoordination was observed in animals of both sexes (12/24). In addition, moderate to severe gait incoordination was observed in these animals (6/24). Writhing and lying flattened (posture) were observed in the males (2/12 each) and repetitive pawing motion was observed in animals of both sexes (4/24). Slight muscle fasciculations were observed in one female. None of these open field observations were noted in any control animal at any time point, nor were they observed in any treated animal on days 7 and 14. Arousal (sluggish, minimal movement) was affected in the females mainly at day 0 (6/12 vs. 0/12 controls), but also on day 14 in both sexes (9/24 treated vs. 3/12 controls). During the reflex/physiologic observations of the FOB on day 0, lack of approach response was observed in the males and females (5/24 treated vs. 1/24 controls). Lack of touch response was observed in both sexes (5/24 treated vs. 0/24 controls), and lack of tail pinch response was observed in the males only (3/12 treated vs. 0/12 controls). Righting reflex was adversely affected (slight incoordination, lands on back, or lands on side) in the males and females (13/24 treated vs. 0/24 controls). All control animals appeared normal and no treatment-related observations were noted in any treated animal on days 7 and 14. Motor activity was decreased ($p \leq 0.05$) relative to concurrent controls in the females during intervals 1, 2, and 3 (↓62-94%). Locomotor activity was decreased ($p \leq 0.05$) relative to concurrent controls in the males during intervals 1 and 2 (↓72-95%), the females during intervals 1, 2, and 3 (↓69-94%).

**The changes in clinical signs, FOB parameters, and motor activity measurements suggest that the test substance is neurotoxic.**

**The LOAEL for this study is 0.5 mg/kg/day based on changes in FOB parameters.**

**The NOAEL for this study was not established.**

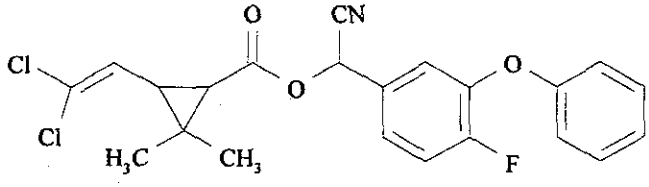
The submitted study is classified as **unacceptable/not upgradable (§81-8[a])** because a NOAEL was not established.

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: ≥96.9% a.i.
   Stability of compound: Stable in solvent vehicle up to 35 days under refrigeration.
   CAS #: 68359-37-5
   Structure:




2. Vehicle: 1% Cremophor EL in deionized water

3. Test animals: Species: Rat
   Strain: Fischer 344
   Age and weight at the start of dosing: Approximately 9 weeks old; 171.6-176.3 g (males), 136.2-139.5 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 for 16-18 hours prior to dosing and 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: 03/11/96 end: 03/29/96

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 Group | Dose (mg/kg) | Animals Assigned | |
|---|---|---|---|
| | | Male | Female |
| Control | 0 | 12 | 12 |
| Low | 0.5 | 12 | 12 |
| Mid | 2 | 12 | 12 |
| High | 10 | 12 | 12 |

a Data obtained from the study report, page 19.

3. Dose selection rationale - Dose levels for the current study were chosen based on the results of a range-finding study using doses of 0.01, 0.05, 0.1, 0.2, 0.5, 2, 5, 10, 25, and 50 mg/kg. The NOAEL for clinical signs in both sexes was 0.5 mg/kg, while the 5 and 10 mg/kg doses produced clear evidence of toxicity and the 25 mg/kg dose produced 80-100% mortality. Clinical signs were generally apparent within 1-3 hours of treatment. The time of peak neurobehavioral effects was estimated to be approximately 2-3 hours after treatment. Based on the results of this range finding study, the doses presented in Table 1 were selected for the subsequent full neurotoxicity study.

4. Treatment preparation and dosing - The test substance was weighed and diluted with the appropriate volume of deionized water containing 1% Cremophor EL. No information was provided regarding frequency of preparation. Dose formulations were stored under refrigeration.

   Prior to treatment, homogeneity was confirmed in triplicate using the 0.05, 0.08, and 20 mg/mL dose formulations. It was stated that the 0.001 mg/mL dose was determined to be homogeneous by visual examination. The dose preparations were determined to be stable for up to 35 days under refrigeration.

   Results - Homogeneity analysis (as mean % of nominal): 92.1-97.8% with a coefficient of variation of 1.5-2.3%.

   Stability analysis: Samples stored under refrigeration for up to 35 days were 100-103% of day 0.

   Concentration analysis (range as % of nominal): 101-106%

   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. Additionally, categorical FOB data were analyzed using General Linear Modeling and Categorical Modeling.

C. METHODS

1. Observations

A. Clinical signs - All animals were examined daily for mortality and clinical signs of toxicity.

B. Functional observational battery and motor activity - All animals were subjected to functional observational battery (FOB) and motor activity measurements one week prior to treatment and on days 0 (approximately 2 hours post-dosing), 7, and 14. The FOB assessment included the following parameters:

Home Cage Observations
Posture
Piloerection
Gait abnormalities
Involuntary motor movements (clonic/tonic)
Vocalizations
Arousal

Observations During Handling
Ease of removal from cage
Reaction to being handled
Muscle tone
Palpebral closure
Pupil size/condition
Lacrimation
Salivation
Stains
Alopecia
Bite marks
Broken teeth/malocclusion
Dehydration
Emaciation
Exophthalmia

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

Reflex/Physiological Observations
Approach response
Touch response
Auditory response
Tail pinch response
Righting reflex
Frontlimb grip strength
Hindlimb grip strength
Landing footsplay
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 as a component of the FOB during week -1 and on days 0 (approximately 2 hours post-dosing), 7, and 14.

3. Food consumption - No information was provided regarding food consumption.

4. 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 (GMA), sectioned, stained with hematoxylin and eosin, luxol fast blue/cresyl violet, Sevier-Munger, 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 | | Dorsal root ganglion | Lumbar spinal root |
| Gasserian ganglia | | 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 - Selected clinical signs are presented in Table 2. Oral staining was observed in the high-dose males and females (10/12 and 9/12, respectively vs. 0/24 controls) and urine staining was observed in the high-dose males only (4/12 treated vs. 0/12 controls). In addition, perianal staining was observed more frequently than controls at the mid- and high-doses (males-11/12 and 12/12 treated, respectively vs. 8/12 controls; females-11/12 each treated vs. 5/12 controls). No other treatment-related clinical signs were observed.

Table 2. Selected clinical signs in rats treated with beta-cyfluthrin once by gavage (number of affected animals).[a]

| Observation | Dose (mg/kg) | | | |
|---|---|---|---|---|
| | 0 | 0.5 | 2 | 10 |
| Males | | | | |
| Oral stain | 0 | 0 | 0 | 10 |
| Urine stain | 0 | 0 | 0 | 4 |
| Perianal stain | 8 | 8 | 11 | 12 |
| Females | | | | |
| Oral stain | 0 | 0 | 0 | 9 |
| Perianal stain | 5 | 6 | 11 | 11 |

a Data obtained from the study report, Table 1 page 34; n=12.

B. Body weights and body weight gains: Body weights and overall (0-14) body weight gains were comparable between treated and control animals at all dose levels throughout the study (Table 3).

Table 3. Body weights (g) and overall (days 0-14) body weight gains in rats treated with beta-cyfluthrin once by gavage (mean± standard deviation).[a]

| Day | Dose (mg/kg) | | | |
|---|---|---|---|---|
| | 0 | 0.5 | 2 | 10 |
| Males | | | | |
| Pretreatment | 165±11 | 165±9 | 165±11 | 168±10 |
| 0 | 167±11 | 167±10 | 166±12 | 169±9 |
| 7 | 204±15 | 205±15 | 201±15 | 208±11 |
| 14 | 223±16 | 226±16 | 221±16 | 231±13 |
| Overall body weight gain (0-14)[b] | 56 | 59 | 55 | 62 |
| Females | | | | |
| Pretreatment | 137±5 | 137±7 | 136±8 | 136±6 |
| 0 | 129±6 | 129±7 | 129±8 | 129±6 |
| 7 | 153±5 | 154±8 | 153±9 | 154±7 |
| 14 | 164±6 | 165±9 | 164±9 | 164±6 |
| Overall body weight gain (0-14)[b] | 35 | 36 | 35 | 35 |

a Data obtained from the study report, Table 2, page 35; n=12.
b Calculated by reviewers

C. Functional observational battery:

1. Home cage observations: Selected home cage observations ($p \leq 0.05$ or not statistically significant) on day 0 are presented in Table 4a. Slight and moderate to severe repetitive chewing was observed in the high-dose males (2/12 and 1/12, respectively). Slight gait incoordination was observed in the high-dose females (7/12) and moderate to severe gait incoordination was observed in the high-dose males and females (6/12 and 2/12, respectively). Decreased activity was observed in the high-dose males and females (7/12 and 2/12, respectively); these animals were also observed to be lying flattened (1/12 each). Writhing was observed in the high-dose males (2/12). None of the home cage observations were noted in any control animal during the study. In addition, no treatment-related observations were noted in any treated animal at the days 7 and 14 time points.

Table 4a. Selected home cage observations noted during the FOB in rats treated with beta-cyfluthrin once by gavage (number of affected animals).[a]

| Observation | Dose (mg/kg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| | 0 | 0.5 | 2 | 10 | 0 | 0.5 | 2 | 10 |
| **Pretest** | | | | | | | | |
| Gait abnormalities not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Posture | | | | | | | | |
| Standing normally | 4 | 1 | 3 | 1 | 3 | 2 | 5 | 6 |
| Rearing | 3 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| Sitting/lying normally | 5 | 11 | 8 | 11 | 9 | 9 | 7 | 6 |
| **Day 0** | | | | | | | | |
| Repetitive chewing | | | | | | | | |
| slight | 0 | 0 | 0 | 2* | 0 | 0 | 0 | 0 |
| moderate/severe | 0 | 0 | 0 | 1* | 0 | 0 | 0 | 0 |
| Gait incoordination | | | | | | | | |
| slight | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7* |
| moderate/severe | 0 | 0 | 0 | 6* | 0 | 0 | 0 | 2* |
| Decreased activity | 0 | 0 | 0 | 7* | 0 | 0 | 0 | 2 |
| Writhing | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Posture | | | | | | | | |
| Lying flattened | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| **Day 7** | | | | | | | | |
| Gait abnormalities not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Posture | | | | | | | | |
| Standing normally | 3 | 5 | 4 | 3 | 5 | 3 | 3 | 3 |
| Rearing | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 |
| Sitting/lying normally | 8 | 7 | 8 | 8 | 6 | 9 | 8 | 8 |
| **Day 14** | | | | | | | | |
| Gait abnormalities not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Posture | | | | | | | | |
| | 5 | 3 | 6 | 4 | 6 | 5 | 5 | 3 |
| | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 |
| | 7 | 8 | 5 | 8 | 6 | 6 | 6 | 8 |

a Data obtained from the study report, Tables 3-5 pages 36-71; n=12.
* Statistically different from controls at $p \leq 0.05$.

2. Handling observations: Selected handling observations ($p \leq 0.05$ or not statistically significant) on day 0 are presented in Table 4b. Slight salivation was observed in the high-dose females (2/12) and moderate to severe salivation was observed in the high-dose animals of both sexes (1/12 each). In addition, slight to severe clear oral stains were observed in the high-dose males (10/12) and females (9/12). Moderate to severe urine stains were observed in the high-dose males (5/12) and females (2/12). None of the handling observations were noted in any control animal during the study, except for urine stains on one female on day 7. In addition, no treatment-related observations were noted in any treated animal at the days 7 and 14 time points.

Table 4b. Selected handling observations noted during the FOB in rats treated with beta-cyfluthrin once by gavage (number of affected animals).[a]

| Observation | Dose (mg/kg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| | 0 | 0.5 | 2 | 10 | 0 | 0.5 | 2 | 10 |
| **Pretest** | | | | | | | | |
| Salivation | | | | | | | | |
| not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Stains | | | | | | | | |
| not observed | 12 | 11 | 12 | 12 | 12 | 12 | 12 | 12 |
| yellow urine | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Day 0** | | | | | | | | |
| Clear salivation | | | | | | | | |
| slight | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2* |
| moderate/severe | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1* |
| Stains | | | | | | | | |
| clear oral (slight) | 0 | 0 | 1 | 7* | 0 | 0 | 0 | 6* |
| clear oral (moderate/severe) | 0 | 0 | 0 | 3* | 0 | 0 | 0 | 3* |
| yellow urine (moderate/severe) | 0 | 0 | 0 | 5* | 0 | 0 | 0 | 2 |
| **Day 7** | | | | | | | | |
| Salivation | | | | | | | | |
| not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Stains | | | | | | | | |
| not observed | 12 | 12 | 12 | 12 | 11 | 12 | 12 | 11 |
| yellow urine | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| **Day 14** | | | | | | | | |
| Salivation | | | | | | | | |
| not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Stains | | | | | | | | |
| not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |

a Data obtained from the study report, Tables 3-5 pages 36-71; n=12.
* Statistically different from controls at $p \leq 0.05$.

3. Open field observations: Selected open field observations ($p \leq 0.05$ or not statistically significant) on day 0 are presented in Table 4c. Slight repetitive chewing was observed in the mid- and high-dose males (1/12 and 2/12, respectively) and low- and high-dose

females (2/12 each). In addition, moderate to severe repetitive chewing was observed in one high-dose male. Slight gait incoordination was observed in the high-dose males (4/12) and females (8/12). In addition, moderate to severe gait incoordination was observed in these animals (4/12 and 2/12, respectively). Writhing and lying flattened (posture) were observed in the high-dose males (2/12 each) and repetitive pawing motion was observed in the high-dose animals of both sexes (2/12 each). Slight muscle fasciculations were observed in one high-dose female. None of these open field observations were noted in any control animal at any time point, nor were they observed in any treated animal at the days 7 and 14 time points. Arousal (sluggish, minimal movement) was affected in the high-dose females mainly at day 0 (6/12 vs. 0/12 controls), but also on day 14 in the high-dose males (7/12 treated vs. 3/12 controls) and females (2/12 treated vs. 0/12 controls). No other treatment-related open field observations were noted.

Table 4c. Selected open field observations noted during the FOB in rats treated with beta-cyfluthrin once by gavage (number of affected animals).[a]

| Observation | Dose (mg/kg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| | 0 | 0.5 | 2 | 10 | 0 | 0.5 | 2 | 10 |
| **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 |
| Posture | | | | | | | | |
| standing normally | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Involuntary movements (clonic/tonic) | | | | | | | | |
| not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Arousal | | | | | | | | |
| normal | 12 | 11 | 11 | 11 | 12 | 11 | 12 | 12 |
| sluggish, some exploratory movement | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 |
| **Day 0** | | | | | | | | |
| Repetitive chewing | | | | | | | | |
| slight | 0 | 0 | 1 | 2 | 0 | 2 | 0 | 2 |
| moderate/severe | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Gait incoordination | | | | | | | | |
| slight | 0 | 0 | 0 | 4* | 0 | 0 | 0 | 8* |
| moderate/severe | 0 | 0 | 0 | 4* | 0 | 0 | 0 | 2* |
| Posture | | | | | | | | |
| lying flattened | 0 | 0 | 0 | 2* | 0 | 0 | 0 | 0 |
| Writhing | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Repetitive pawing motion | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 2 |
| Arousal | | | | | | | | |
| Sluggish, some exploratory movement | 5 | 3 | 6 | 6 | 5 | 5 | 5 | 3 |
| Sluggish, minimal movement | 6 | 4 | 4 | 5 | 0 | 1 | 3 | 6 |
| Muscle fasciculations | | | | | | | | |
| slight | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |



*(Table continues)*

**BETA CYFLUTHRIN** **Acute oral neurotoxicity (§81-8[a])**

| Observation | Dose (mg/kg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| | 0 | 0.5 | 2 | 10 | 0 | 0.5 | 2 | 10 |
| **Day 7** | | | | | | | | |
| Gait abnormalities | | | | | | | | |
| not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Bizarre behavior | | | | | | | | |
| not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Posture | | | | | | | | |
| standing normally | 12 | 12 | 11 | 12 | 12 | 12 | 12 | 12 |
| sitting or lying normally | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Involuntary movements (clonic/tonic) | | | | | | | | |
| not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Arousal | | | | | | | | |
| normal | 0 | 4 | 0 | 1 | 8 | 5 | 7 | 8 |
| sluggish, some exploratory movement | 8 | 6 | 5 | 6 | 4 | 7 | 5 | 4 |
| sluggish, minimal movement | 4 | 2 | 7 | 5 | 0 | 0 | 0 | 0 |
| **Day 14** | | | | | | | | |
| Gait abnormalities | | | | | | | | |
| not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Bizarre behavior | | | | | | | | |
| not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Posture | | | | | | | | |
| standing normally | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Involuntary movements (clonic/tonic) | | | | | | | | |
| not observed | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Arousal | | | | | | | | |
| normal | 2 | 6 | 2 | 1 | 9 | 10 | 8 | 8 |
| sluggish, some exploratory movement | 7 | 3 | 4 | 4 | 3 | 1 | 3 | 2 |
| sluggish, minimal movement | 3 | 3 | 6 | 7 | 0 | 1 | 1 | 2 |

a Data obtained from the study report, Tables 3-5 pages 36-71; n=12.
* Statistically different from controls at $p \leq 0.05$.

4. Reflex/physiologic observations: Selected reflex and physiological observations ($p \leq 0.05$ or not statistically significant) on day 0 are presented in Table 4d. Lack of approach response was observed in the low-, mid-, and high-dose males (2/12, 3/12, and 4/12 treated, respectively vs. 1/12 controls) and in the mid- and high-dose females (1/12 each vs. 0/12 controls). Lack of touch response was observed in the high-dose males (4/12 treated vs. 0/12 controls) and females (1/12 treated vs. 0/12 controls), and lack of tail pinch response was observed in the high-dose males only (3/12 treated vs. 0/12 controls). Righting reflex was adversely affected (slight incoordination, lands on back, or lands on side) in the high-dose males (5/12 treated vs. 0/12 controls) and females (8/12 treated vs. 0/12 controls). All control animals appeared normal and no treatment-related observations were noted in any treated animal at the days 7 and 14 time points.

Table 4d. Selected reflex/physiologic observations noted during the FOB in rats treated with beta-cyfluthrin once by gavage (number of affected animals).[a]

| Observation | Dose (mg/kg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| | 0 | 0.5 | 2 | 10 | 0 | 0.5 | 2 | 10 |
| **Pretest** | | | | | | | | |
| Approach response | | | | | | | | |
| no reaction | 2 | 1 | 2 | 0 | 3 | 2 | 0 | 3 |
| slight reaction | 10 | 11 | 10 | 12 | 9 | 10 | 12 | 9 |
| Touch response | | | | | | | | |
| slight reaction | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Tail pinch response | | | | | | | | |
| no reaction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| slight reaction | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 11 |
| Righting reflex | | | | | | | | |
| normal | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| **Day 0** | | | | | | | | |
| Approach response | | | | | | | | |
| no reaction | 1 | 2 | 3 | 4 | 0 | 0 | 1 | 1 |
| slight reaction | 11 | 10 | 9 | 8 | 12 | 12 | 11 | 11 |
| Touch response | | | | | | | | |
| no reaction | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 1 |
| slight reaction | 12 | 12 | 12 | 8 | 12 | 12 | 12 | 11 |
| Tail pinch response | | | | | | | | |
| no reaction | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| slight reaction | 12 | 12 | 12 | 9 | 12 | 12 | 12 | 12 |
| Righting reflex | | | | | | | | |
| slight incoordination | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 7* |
| lands on side | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| lands on back | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1* |
| **Day 7** | | | | | | | | |
| Approach response | | | | | | | | |
| no reaction | 2 | 1 | 2 | 1 | 1 | 2 | 1 | 1 |
| slight reaction | 10 | 11 | 10 | 11 | 11 | 10 | 11 | 11 |
| Touch response | | | | | | | | |
| slight reaction | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Tail pinch response | | | | | | | | |
| slight reaction | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |



*(Table continues)*

| Observation | Dose (mg/kg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| | 0 | 0.5 | 2 | 10 | 0 | 0.5 | 2 | 10 |
| Righting reflex | | | | | | | | |
| normal | 12 | 12 | 12 | 12 | 11 | 12 | 12 | 12 |
| slightly uncoordinated | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Day 14 | | | | | | | | |
| Approach response | | | | | | | | |
| no reaction | 2 | 1 | 1 | 3 | 0 | 1 | 0 | 1 |
| slight reaction | 10 | 11 | 11 | 9 | 12 | 11 | 12 | 11 |
| Touch response | | | | | | | | |
| slight reaction | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Tail pinch response | | | | | | | | |
| slight reaction | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Righting reflex | | | | | | | | |
| normal | 11 | 12 | 11 | 11 | 12 | 12 | 12 | 12 |
| slightly uncoordinated | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |

a Data obtained from the study report, Tables 3-5 pages 36-71; n=12.
* Statistically different from controls at $p \leq 0.05$.

E. Motor activity: Interval motor and locomotor activity data are presented in Appendix A. On day 0, motor activity was decreased ($p \leq 0.05$) relative to concurrent controls in the high-dose females during intervals 1, 2, and 3 (↓62-94%) and in the mid-dose females during interval 3 only (↓62%). Day 0 locomotor activity was decreased ($p \leq 0.05$) relative to concurrent controls in the high-dose males during intervals 1 and 2 (↓72-95%), the high-dose females during intervals 1, 2, and 3 (↓69-94%), and the mid-dose females during interval 3 only (↓65%). The decreases observed in the mid-dose females were isolated occurrences and therefore considered unrelated to treatment. No treatment-related differences from concurrent controls were observed in mean motor or locomotor activities (Table 5).

Table 5. Mean motor and locomotor activity (counts) in rats treated with beta-cyfluthrin once by gavage (mean ± standard deviation).[a]

| Treatment interval (days) | | Dose (mg/kg) | | | |
|---|---|---|---|---|---|
| | | 0 | 0.5 | 2 | 10 |
| Males | | | | | |
| Pretest | Motor activity | 591±201 | 606±154 | 529±213 | 580±166 |
| | Locomotor activity | 226±70 | 233±47 | 201±73 | 230±60 |
| 0 | Motor activity | 253±63 | 215±96 | 226±77 | 86±56 |
| | Locomotor activity | 90±21 | 72±23 | 79±28 | 21±14 |
| 7 | Motor activity | 654±188 | 569±130 | 637±137 | 553±134 |
| | Locomotor activity | 225±71 | 200±34 | 221±50 | 183±51 |
| 14 | Motor activity | 612±161 | 576±113 | 608±102 | 620±192 |
| | Locomotor activity | 221±64 | 205±51 | 219±54 | 206±69 |
| Females | | | | | |
| Pretest | Motor activity | 808±244 | 868±359 | 953±266 | 848±237 |
| | Locomotor activity | 285±87 | 314±156 | 345±106 | 287±92 |
| 0 | Motor activity | 523±258 | 448±341 | 354±184 | 146±107 |
| | Locomotor activity | 149±80 | 130±85 | 96±51 | 36±27 |
| 7 | Motor activity | 809±279 | 867±346 | 790±265 | 797±197 |
| | Locomotor activity | 278±96 | 283±133 | 279±96 | 264±69 |
| 14 | Motor activity | 918±288 | 935±246 | 982±371 | 911±193 |
| | Locomotor activity | 305±97 | 304±93 | 365±169 | 312±70 |

a Data obtained from the study report Tables 6-7, pages 72-75; n=12.

F. Pathology:

1. Neuropathology - No treatment-related gross or microscopic neuropathological changes were observed in any treated group.

2. Brain weights: Brain weights were comparable between treated and control animals.

## III. DISCUSSION

A. Investigator's conclusions - Oral administration of beta-cyfluthrin once via gavage produced clinical signs of toxicity, changes in FOB parameters, and decreased motor activity. The NOAEL for this study was 0.5 mg/kg.

B. Reviewer's discussion/conclusions - In this acute oral neurotoxicity study, beta cyfluthrin (≥96.9% a.i., Lot/batch # 3030125) was administered in a single dose by gavage to 12 Fischer 344 rats/sex/dose at doses of 0, 0.5, 2, or 10 mg/kg. After two 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 were evaluated during week -1 and on days 0 (approximately 2 hours post-dosing), 7, and 14. 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.

No mortalities occurred during the study. Body weights, body weight gains, brain weights, and neuropathology were unaffected by the test substance.

Oral staining was observed in the high-dose males and females (10/12 and 9/12, respectively vs. 0/24 controls) and urine staining was observed in the high-dose males only (4/12 treated vs. 0/12 controls). In addition, perianal staining was observed more frequently than controls at the mid- and high-doses (males-11/12 and 12/12 treated, respectively vs. 8/12 controls; females-11/12 each treated vs. 5/12 controls). No other treatment-related clinical signs were observed.

During the home cage observations ($p \leq 0.05$ or not statistically significant) of the FOB on day 0, slight and moderate to severe repetitive chewing was observed in the high-dose males (2/12 and 1/12, respectively). Slight gait incoordination was observed in the high-dose females (7/12) and moderate to severe gait incoordination was observed in the high-dose males and females (6/12 and 2/12, respectively). Decreased activity was observed in the high-dose males and females (7/12 and 2/12, respectively); these animals were also observed to be lying flattened (1/12 each). Writhing was observed in the high-dose males (2/12). None of the home cage observations were noted in any control animal during the study. In addition, no treatment-related observations were noted in any treated animal at the days 7 and 14 time points. During the handling observations ($p \leq 0.05$ or not statistically significant) of the FOB on day 0, slight salivation was observed in the high-dose females (2/12) and moderate to severe salivation was observed in the high-dose animals of both sexes (1/12 each). In addition, slight to severe clear oral stains were observed in the high-dose males (10/12) and females (9/12). Moderate to severe urine stains were observed in the high-dose males (5/12) and females (2/12). None of the handling observations were noted in any control animal during the study, except for urine stains on one female on day 7. In addition, no treatment-related observations were noted in any treated animal at the days 7 and 14 time points. During the open field observations ($p \leq 0.05$ or not statistically significant) of the FOB on day 0, slight repetitive chewing was observed in the mid- and high-dose males (1/12 and 2/12, respectively) and low- and high-dose females (2/12 each). In addition, moderate to

severe repetitive chewing was observed in one high-dose male. Slight gait incoordination was observed in the high-dose males (4/12) and females (8/12). In addition, moderate to severe gait incoordination was observed in these animals (4/12 and 2/12, respectively). Writhing and lying flattened (posture) were observed in the high-dose males (2/12 each) and repetitive pawing motion was observed in the high-dose animals of both sexes (2/12 each). Slight muscle fasciculations were observed in one high-dose female. None of these open field observations were noted in any control animal at any time point, nor were they observed in any treated animal at the days 7 and 14 time points. Arousal (sluggish, minimal movement) was affected in the high-dose females mainly at day 0 (6/12 vs. 0/12 controls), but also on day 14 in the high-dose males (7/12 treated vs. 3/12 controls) and females (2/12 treated vs. 0/12 controls). During the reflex/physiologic observations ($p \leq 0.05$ or not statistically significant) of the FOB on day 0, lack of approach response was observed in the low-, mid-, and high-dose males (2/12, 3/12, and 4/12 treated, respectively vs. 1/12 controls) and in the mid- and high-dose females (1/12 each vs. 0/12 controls). Lack of touch response was observed in the high-dose males (4/12 treated vs. 0/12 controls) and females (1/12 treated vs. 0/12 controls), and lack of tail pinch response was observed in the high-dose males only (3/12 treated vs. 0/12 controls). Righting reflex was adversely affected (slight incoordination, lands on back, or lands on side) in the high-dose males (5/12 treated vs. 0/12 controls) and females (8/12 treated vs. 0/12 controls). All control animals appeared normal and no treatment-related observations were noted in any treated animal at the days 7 and 14 time points.

Motor activity was decreased ($p \leq 0.05$) relative to concurrent controls in the high-dose females during intervals 1, 2, and 3 (↓62-94%). Locomotor activity was decreased ($p \leq 0.05$) relative to concurrent controls in the high-dose males during intervals 1 and 2 (↓72-95%), the high-dose females during intervals 1, 2, and 3 (↓69-94%).

**The changes in FOB parameters suggest that the test substance is neurotoxic at 0.5 mg/kg/day.**

**The LOAEL for this study is 0.5 mg/kg/day based on changes in FOB parameters.**

**The NOAEL for this study was not established.**

The submitted study is classified as **unacceptable/not upgradable (§81-8[a])** because a NOAEL was not established.

C. Study deficiencies

- None noted

Appendix A

BAYER CORPORATION - TOXICOLOGY

Table 8
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Motor Activity for Male Rats, pretreatment
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 217±44 | 186±68 | 91±73 | 42±43 | 25±30 | 9±22 | 11±28 | 6±19 | 4±11 |
| 0.5 mg/kg | 245±61 | 175±57 | 80±49 | 59±58 | 19±23 | 12±31 | 2±6 | 7±25 | 8±21 |
| 2 mg/kg | 217±55 | 142±71 | 68±54 | 44±47 | 14±27 | 14±27 | 2±5 | 8±19 | 20±56 |
| 10 mg/kg | 211±42 | 174±60 | 110±50 | 39±38 | 14±27 | 12±29 | 3±9 | 9±20 | 9±23 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 11MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 8
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Motor Activity for Male Rats, Day 0
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 170±39 | 62±42 | 8±13 | 3±8 | 1±1 | 4±10 | 2±5 | 3±8 | 0±1 |
| 0.5 mg/kg | 143±43 | 51±49 | 8±15 | 2±3 | 1±2 | 1±3 | 9±25 | 0±0 | 0±1 |
| 2 mg/kg | 156±64 | 54±29 | 2±5 | 1±3 | 1±2 | 1±3 | 2±4 | 0±1 | 10±32 |
| 10 mg/kg | 59±39* | 4±7* | 1±3 | 3±6 | 1±2 | 7±9 | 4±6 | 3±7 | 5±9 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 11MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 8
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Motor Activity for Male Rats, Day 7
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 256±44 | 201±71 | 99±65 | 45±45 | 22±30 | 6±14 | 4±7 | 14±26 | 7±17 |
| 0.5 mg/kg | 270±50 | 169±60 | 93±47 | 25±22 | 4±7 | 5±15 | 1±2 | 3±10 | 0±0 |
| 2 mg/kg | 264±40 | 195±48 | 94±62 | 27±33 | 20±42 | 5±11 | 0±1 | 9±23 | 22±53 |
| 10 mg/kg | 241±43 | 166±36 | 74±53 | 29±33 | 21±44 | 6±10 | 10±23 | 4±12 | 1±3 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 11MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 8
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Motor Activity for Male Rats, Day 14
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 289±42 | 175±48 | 72±62 | 48±49 | 17±21 | 1±2 | 0±0 | 2±5 | 8±14 |
| 0.5 mg/kg | 282±62 | 151±35 | 74±58 | 32±37 | 8±15 | 7±23 | 3±6 | 1±2 | 18±57 |
| 2 mg/kg | 288±41 | 173±39 | 84±43 | 50±42 | 6±12 | 0±1 | 0±0 | 2±6 | 4±13 |
| 10 mg/kg | 276±38 | 174±52 | 87±57 | 33±46 | 20±33 | 15±31 | 5±8 | 12±37 | 1±1 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 11MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 8
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Motor Activity for Female Rats, Pretreatment
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 284±51 | 215±52 | 155±67 | 90±75 | 52±70 | 13±20 | 0±0 | 0±0 | 0±0 |
| 0.5 mg/kg | 264±64 | 207±80 | 181±90 | 94±86 | 74±70 | 35±58 | 11±34 | 2±4 | 2±4 |
| 2 mg/kg | 281±34 | 240±42 | 194±50 | 114±78 | 49±65 | 40±63 | 26±56 | 3±12 | 6±16 |
| 10 mg/kg | 308±32 | 225±39 | 156±48 | 74±58 | 36±49 | 25±46 | 15±38 | 2±4 | 8±27 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 13MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 8
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Motor Activity for Female Rats, Day 0
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 213±68 | 123±78 | 87±56 | 42±50 | 31±39 | 13±25 | 4±7 | 5±16 | 6±10 |
| 0.5 mg/kg | 193±48 | 102±83 | 48±59 | 30±52 | 23±52 | 10±24 | 16±34 | 20±35 | 5±15 |
| 2 mg/kg | 189±79 | 100±66 | 33±49* | 19±37 | 3±4 | 1±2 | 3±7 | 1±3 | 4±9 |
| 10 mg/kg | 82±38* | 7±12* | 8±26* | 5±12 | 2±4 | 16±28 | 9±22 | 7±15 | 11±26 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 13MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 8
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Motor Activity for Female Rats, Day 7
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 277±54 | 205±62 | 138±63 | 103±87 | 50±62 | 23±42 | 1±5 | 6±19 | 6±18 |
| 0.5 mg/kg | 239±66 | 171±74 | 146±81 | 115±51 | 54±64 | 60±62 | 34±56 | 22±40 | 25±47 |
| 2 mg/kg | 247±48 | 196±55 | 147±49 | 70±65 | 52±67 | 25±54 | 25±40 | 15±27 | 14±37 |
| 10 mg/kg | 251±48 | 203±48 | 139±61 | 73±46 | 50±55 | 33±43 | 32±46 | 8±18 | 7±12 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 13MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 8
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Motor Activity for Female Rats, Day 14
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 288±29 | 222±51 | 147±64 | 121±78 | 50±61 | 37±57 | 6±16 | 19±48 | 29±49 |
| 0.5 mg/kg | 303±50 | 227±57 | 165±85 | 120±63 | 64±60 | 28±45 | 15±33 | 8±24 | 5±13 |
| 2 mg/kg | 262±60 | 221±38 | 173±73 | 118±80 | 74±69 | 56±64 | 34±59 | 28±49 | 16±32 |
| 10 mg/kg | 282±32 | 222±37 | 155±53 | 81±58 | 56±51 | 56±54 | 29±49 | 21±60 | 8±16 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 13MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 9
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Locomotor Activity for Male Rats, Pretreatment
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 103±17 | 69±30 | 30±26 | 12±14 | 7±11 | 2±6 | 1±3 | 3±7 | 0±1 |
| 0.5 mg/kg | 112±25 | 58±17 | 27±19 | 21±26 | 7±8 | 6±17 | 0±0 | 2±8 | 2±5 |
| 2 mg/kg | 98±20 | 48±26 | 23±18 | 14±15 | 4±6 | 4±9 | 1±3 | 2±5 | 8±22 |
| 10 mg/kg | 103±13 | 61±19 | 38±19 | 12±13 | 6±12 | 4±10 | 1±3 | 4±9 | 2±6 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 11MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 9
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Locomotor Activity for Male Rats, Day 0
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 65±14 | 20±11 | 3±4 | 1±3 | 0±0 | 1±2 | 0±0 | 0±0 | 0±1 |
| 0.5 mg/kg | 53±13 | 17±15 | 2±3 | 0±1 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 |
| 2 mg/kg | 58±21 | 17±10 | 0±0 | 0±0 | 0±0 | 0±0 | 0±1 | 0±0 | 4±14 |
| 10 mg/kg | 18±12* | 1±2* | 1±1 | 1±2 | 0±0 | 1±1 | 0±0 | 0±0 | 0±1 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 11MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 9
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Locomotor Activity for Male Rats, Day 7
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 101±20 | 69±30 | 30±22 | 13±13 | 5±9 | 2±6 | 0±0 | 4±10 | 0±1 |
| 0.5 mg/kg | 107±18 | 58±22 | 24±15 | 8±9 | 1±2 | 1±3 | 0±0 | 0±0 | 0±0 |
| 2 mg/kg | 103±21 | 67±22 | 26±19 | 7±8 | 5±14 | 1±3 | 0±0 | 3±8 | 8±21 |
| 10 mg/kg | 93±13 | 50±15 | 23±18 | 9±10 | 4±12 | 2±4 | 2±8 | 0±0 | 0±1 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 11MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 9
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Locomotor Activity for Male Rats, Day 14
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 117±23 | 61±24 | 22±21 | 16±17 | 5±8 | 0±0 | 0±0 | 0±1 | 1±3 |
| 0.5 mg/kg | 113±25 | 52±15 | 25±24 | 11±14 | 2±4 | 3±9 | 0±0 | 0±0 | 0±0 |
| 2 mg/kg | 117±16 | 56±16 | 28±21 | 16±15 | 1±2 | 0±0 | 0±0 | 1±3 | 1±5 |
| 10 mg/kg | 101±16 | 58±20 | 24±18 | 9±13 | 4±12 | 5±15 | 1±3 | 3±12 | 0±0 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 11MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 9
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Locomotor Activity for Female Rats, Pretreatment
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 110±17 | 69±12 | 50±24 | 32±28 | 21±33 | 4±7 | 0±0 | 0±0 | 0±0 |
| 0.5 mg/kg | 106±28 | 74±36 | 66±42 | 34±38 | 23±23 | 8±18 | 4±12 | 0±0 | 1±2 |
| 2 mg/kg | 115±18 | 84±21 | 68±17 | 39±31 | 15±20 | 10±17 | 10±22 | 2±5 | 2±6 |
| 10 mg/kg | 115±13 | 71±16 | 50±20 | 22±20 | 13±19 | 8±14 | 5±12 | 0±1 | 3±12 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 13MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 9
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Locomotor Activity for Female Rats, Day 0
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 67±23 | 34±23 | 23±21 | 11±18 | 8±11 | 3±6 | 1±2 | 1±4 | 1±2 |
| 0.5 mg/kg | 63±16 | 30±23 | 13±15 | 7±12 | 6±14 | 2±8 | 3±7 | 6±9 | 1±3 |
| 2 mg/kg | 59±22 | 25±20 | 8±13* | 3±5 | 0±0 | 0±0 | 0±0 | 0±0 | 1±4 |
| 10 mg/kg | 21±12* | 2±5* | 2±7* | 0±0 | 0±0 | 4±7 | 2±5 | 1±4 | 4±8 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 13MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 9
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Locomotor Activity for Female Rats, Day 7
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 98±18 | 72±30 | 47±28 | 36±33 | 16±20 | 4±10 | 0±1 | 2±6 | 2±8 |
| 0.5 mg/kg | 87±29 | 52±25 | 44±26 | 38±23 | 19±26 | 22±23 | 10±18 | 6±12 | 5±13 |
| 2 mg/kg | 97±23 | 65±20 | 51±20 | 24±24 | 18±22 | 9±17 | 8±14 | 3±8 | 6±18 |
| 10 mg/kg | 94±19 | 69±17 | 43±18 | 23±15 | 15±20 | 10±13 | 10±14 | 1±2 | 0±1 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 13MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

BAYER CORPORATION - TOXICOLOGY

Table 9
TECHNICAL GRADE CYFLUTHRIN
Summary Interval Locomotor Activity for Female Rats, Day 14
Study Number 96-412-GO

| Group | Interval 1 | Interval 2 | Interval 3 | Interval 4 | Interval 5 | Interval 6 | Interval 7 | Interval 8 | Interval 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg | 105±14 | 72±25 | 48±27 | 41±31 | 17±21 | 11±16 | 1±2 | 3±6 | 8±16 |
| 0.5 mg/kg | 117±27 | 72±23 | 49±27 | 40±30 | 17±18 | 5±9 | 1±5 | 2±8 | 1±4 |
| 2 mg/kg | 109±37 | 81±21 | 62±29 | 43±33 | 30±30 | 20±24 | 12±22 | 5±10 | 4±10 |
| 10 mg/kg | 110±11 | 74±18 | 51±17 | 26±25 | 16±17 | 20±20 | 8±15 | 6±18 | 2±5 |

* Significantly different from control ($p \leq 0.05$, ANOVA)
Mean ± S.D. for 1:30:00 (hh:mm:ss) Test Session, in 10 - Minute Intervals
Nominal Day 0 = 13MAR96
Number of Rats/Group: 12/0 mg/kg 12/0.5 mg/kg 12/2 mg/kg 12/10 mg/kg

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# R058542

| | |
|---|---|
| **Chemical:** | **Cyfluthrin** |
| **PC Code:** | **128831** |
| **HED File Code** | **13000 Tox Reviews** |
| **Memo Date:** | **02/27/2001 12:00:00 AM** |
| **File ID:** | **DPD243160** |
| **Accession Number:** | **412-04-0046** |

**HED Records Reference Center**
**03/25/2004**