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

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EPA Reviewer: Pamela M. Hurley
Registration Action Branch 2 (7509C)

Pamela M Hurley . Date 2/28/2002

for EPA Secondary Reviewer: John Whalan
Registration Action Branch 2 (7509C)

Pamela M Hurley . Date 2/28/2002

DATA EVALUATION RECORD

Supplement to DER for MRID No.:44371401 Cyfluthrin: [Multigeneration Study in the Rat]
This supplement includes a revised executive summary (changing ppm to mg/kg/day and changing systemic and reproductive NOAELs to parental and offspring NOAELs)

STUDY TYPE: Multigeneration Reproduction Study - Rat
OPPTS Number: 870.3800 OPP Guideline Number: §83-4

DP BARCODE: D240006 SUBMISSION CODE: S531858
P.C. CODE: 128831 TOX. CHEM. NO.: None
TEST MATERIAL (PURITY): Cyfluthrin (technical, 95.4% a.i.)

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

CITATION: Eigenberg, D.A., (1996) Two-Generation Reproductive Study in Rats Using Technical Grade Cyfluthrin Administered Via the Diet. Bayer Corporation, Stilwell, KS. Laboratory Study number 93-672-UZ, March 8, 1996. MRID 44371401. Unpublished.

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

EXECUTIVE SUMMARY: In a 2-generation reproduction study (MRID 44371401) cyfluthrin (95.4% a.i.) was administered in the diet to 30 Sprague Dawley rats/sex/dose at dose levels of 0, 50, 125, or 400 ppm (equivalent to doses of 0, 3/4, 9/10, or 29/33 (M/F) mg/kg/day during premating and gestation and 0, 7, 19, or 59 mg/kg/day during the first two weeks of lactation). Exposure to P animals (30/sex/dose) began at 7 weeks of age and lasted for 10 weeks prior to mating to produce F_1 pups. Upon weaning, F_1 pups (30/sex/dose) selected to become parents of the F_2 generation were fed cyfluthrin in test diets at the same concentration their dam received. F_1 animals were given test diets for 11 weeks prior to mating. All animals were mated on a 1:1 ratio.

Parental toxicity of cyfluthrin was evident at 125 and 400 ppm. At 125 ppm, marginal treatment-related reductions in mean body weight (↓6-8%, $p \leq 0.05$) were observed during the premating period and terminal body weights were similarly reduced (↓6%, $p \leq 0.05$) in F_1 males. During lactation there was a treatment-related decrease in food consumption (↓9-11%, $p \leq 0.05$ or 0.01) for F_1 females at this dose. At 400 ppm, treatment-related splaying of hind limbs was observed in P and F_1 females during lactation (15/30 P females, 9/30 F_1 females vs. 0/30 in both P and F_1

controls, $p \leq 0.01$). Treatment-related reductions in body weights (↓7-14%, $p \leq 0.01$) and food consumption (↓11-22%, $p \leq 0.01$) compared to lactating controls were also noted in lactating females of both generations. Marginal treatment-related decreases in mean body weights (↓7-8%, $p \leq 0.05$ or ≤ 0.01) were observed in F_1 males during the premating period. The reduction of terminal body weights (↓6-8%, $P \leq 0.05$) in F_1 males and females was also considered treatment-related.

It is noted that for all dams (treated and controls), food consumption was markedly increased during lactation when compared to the premating and gestation periods. Although a decrease in food consumption was observed in the mid- and high-dose groups during lactation, this was in comparison to the control group. Food consumption in the treated groups was still increased in comparison to food consumption in these same groups during the premating and gestation periods. As a result, cyfluthrin intake by dams was approximately doubled during lactation compared to premating and gestation periods. Therefore, since most of the treatment-related effects of cyfluthrin in females (decreases in food consumption and body weights and splayed hind limbs) were observed during this period, they were likely associated with the increase in dose during lactation. In contrast, during the premating period most of the observed parental treatment-related changes consisted of marginal reductions in body weights.

There were no treatment-related mortalities or treatment-related effects on reproductive parameters or function. There were no treatment-related microscopic findings for any treatment group of the P generation and no treatment-related gross pathologic findings in either P or F_1 generations. **The LOAEL for parental toxicity is 125 ppm (9/10 mg/kg/day, M/F) based on reductions in body weight and food consumption. The parental NOAEL is 50 ppm (3/4 mg/kg/day, M/F).**

Offspring toxicity of cyfluthrin was manifest at 125 and 400 ppm. At 125 ppm, treatment-related coarse tremors were observed in 16% of the F_1 pups and 73% of the F_2 pups during lactation days 5-17. Treatment-related decreases (↓6-14%) in mean body weight were observed between 4-21 days in F_1 and F_2 pups. At 400 ppm, treatment-related coarse tremors were observed in F_1 and F_2 pups between days 5 and 17 of lactation. These tremors were observed in 54% of the F_1 pups and 36% of the F_2 pups. A treatment-related reduction (↓6-26%, $p \leq 0.05$ or 0.01) in mean litter weights was observed in F_1 and F_2 pups between days 0 and 21 of lactation.

The offspring LOAEL is 125 ppm (19 mg/kg/day) based on coarse tremors during lactation and decreases in mean litter weights. The offspring NOAEL is 50 ppm (7 mg/kg/day).

The reproductive study is classified **acceptable (§83-4)** and satisfies the guideline requirement for a 2-generation reproductive study in the rat.

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

EPA Reviewer: Pamela M. Hurley
Registration Action Branch 2 (7509C)
Pamela M Hurley . Date 2/13/2001

EPA Secondary Reviewer: John Whalan
Registration Action Branch 2 (7509C)
John Whalan . Date 2-13-01

DATA EVALUATION RECORD
Supplement to DER for MRID No.:44371401 Cyfluthrin: [Multigeneration Study in the Rat]
This supplement includes a revised executive summary (changing ppm to mg/kg/day and changing systemic and reproductive NOAELs to parental and offspring NOAELs)

STUDY TYPE: Multigeneration Reproduction Study - Rat
OPPTS Number: 870.3800 OPP Guideline Number: §83-4

DP BARCODE: D240006 SUBMISSION CODE: S531858
P.C. CODE: 128831 TOX. CHEM. NO.: None
TEST MATERIAL (PURITY): Cyfluthrin (technical, 95.4% a.i.)

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

CITATION: Eigenberg, D.A., (1996) Two-Generation Reproductive Study in Rats Using Technical Grade Cyfluthrin Administered Via the Diet. Bayer Corporation, Stilwell, KS. Laboratory Study number 93-672-UZ, March 8, 1996. MRID 44371401. Unpublished.

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

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Parental toxicity of cyfluthrin was evident at 125 and 400 ppm. At 125 ppm, marginal treatment-related reductions in mean body weight (↓6-8%, $p \leq 0.05$) were observed during the premating period and terminal body weights were similarly reduced (↓6%, $p \leq 0.05$) in F_1 males. During lactation there was a treatment-related decrease in food consumption (↓9-11%, $p \leq 0.05$ or 0.01) for F_1 females at this dose. At 400 ppm, treatment-related splaying of hind limbs was observed in P and F_1 females during lactation (15/30 P females, 9/30 F_1 females vs. 0/30 in both P and F_1 controls, $p \leq 0.01$). Treatment-related reductions in body weights (↓7-14%, $p \leq 0.01$) and food

consumption (↓11-22%, p≤0.01) compared to lactating controls were also noted in lactating females of both generations. Marginal treatment-related decreases in mean body weights (↓7-8%, p≤0.05 or ≤0.01) were observed in F_1 males during the premating period. The reduction of terminal body weights (↓6-8%, P≤0.05) in F_1 males and females was also considered treatment-related.

It is noted that for all dams (treated and controls), food consumption was markedly increased during lactation when compared to the premating and gestation periods. Although a decrease in food consumption was observed in the mid- and high-dose groups during lactation, this was in comparison to the control group. Food consumption in the treated groups was still increased in comparison to food consumption in these same groups during the premating and gestation periods. As a result, cyfluthrin intake by dams was approximately doubled during lactation compared to premating and gestation periods. Therefore, since most of the treatment-related effects of cyfluthrin in females (decreases in food consumption and body weights and splayed hind limbs) were observed during this period, they were likely associated with the increase in dose during lactation. In contrast, during the premating period most of the observed parental treatment-related changes consisted of marginal reductions in body weights.

There were no treatment-related mortalities or treatment-related effects on reproductive parameters or function. There were no treatment-related microscopic findings for any treatment group of the P generation and no treatment-related gross pathologic findings in either P or F_1 generations. **The LOAEL for parental toxicity is 125 ppm (9/10 mg/kg/day, M/F) based on reductions in body weight and food consumption. The parental NOAEL is 50 ppm (3/4 mg/kg/day, M/F).**

Offspring toxicity of cyfluthrin was manifest at 125 and 400 ppm. At 125 ppm, treatment-related coarse tremors were observed in 16% of the F_1 pups and 73% of the F_2 pups during lactation days 5-17. Treatment-related decreases (↓6-14%) in mean body weight were observed between 4-21 days in F_1 and F_2 pups. At 400 ppm, treatment-related coarse tremors were observed in F_1 and F_2 pups between days 5 and 17 of lactation. These tremors were observed in 54% of the F_1 pups and 36% of the F_2 pups. A treatment-related reduction (↓6-26%, p≤0.05 or 0.01) in mean litter weights was observed in F_1 and F_2 pups between days 0 and 21 of lactation.

The offspring LOAEL is 125 ppm (9/10 mg/kg/day, M/F) based on coarse tremors and decreases in mean litter weights. The offspring NOAEL is 50 ppm (3/4 mg/kg/day, M/F).

The reproductive study is classified **acceptable (§83-4)** and satisfies the guideline requirement for a 2-generation reproductive study in the rat.

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

DATA EVALUATION RECORD

CYFLUTHRIN

Study Type: 83-4; A Two-Generation Reproductive Study in Rats Using Technical grade Cyfluthrin Administered Via the Diet.

Work Assignment No. 3-32A (MRID 44371401)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
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Prepared by

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Date: 4/16/98

Disclaimer

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

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Toxicology Branch I (7509C)

EPA Secondary Reviewer: Marion Copley, DVM, DABT
Registration Action Branch I (7509C)

Laurence D. Chitlik 3/20/

DATA EVALUATION RECORD

STUDY TYPE: Multigeneration Reproduction Study - Rat
OPPTS Number: 870.3800 OPP Guideline Number: §83-4

DP BARCODE: D240006 SUBMISSION CODE: S531858
P.C. CODE: 128831 TOX. CHEM. NO.: None
TEST MATERIAL (PURITY): Cyfluthrin (technical, 95.4% a.i.)

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

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Parental toxicity of cyfluthrin was evident at 125 and 400 ppm. At 125 ppm, marginal treatment-related reductions in mean body weight (↓6-8%, $p \leq 0.05$) were observed during the premating period and terminal body weights were similarly reduced (↓6%, $p \leq 0.05$) in F_1 males. During lactation there was a treatment-related decrease in food consumption (↓9-11%, $p \leq 0.05$ or 0.01) for F_1 females at this dose. At 400 ppm, treatment-related splaying of hind limbs was observed in P and F_1 females during lactation (15/30 P females, 9/30 F_1 females vs. 0/30 in both P and F_1 controls, $p \leq 0.01$). Treatment-related reductions in body weights

(↓7-14%, p≤0.01) and food consumption (↓11-22%, p≤0.01) compared to lactating controls were also noted in lactating females of both generations. Marginal treatment-related decreases in mean body weights (↓7-8%, p≤0.05 or ≤0.01) were observed in F_1 males during the premating period. The reduction of terminal body weights (↓6-8%, P≤0.05) in F_1 males and females was also considered treatment-related.

For all dams (treated and controls) food consumption was markedly increased during lactation compared to the premating and gestation periods. As a result, cyfluthrin intake by dams was approximately doubled during lactation compared to premating and gestation periods. Most treatment-related effects of cyfluthrin in females were observed during this period and were probably associated with the increase in dose during lactation. During the premating period in males and females most of the observed parental treatment-related changes consisted of marginal reductions in body weights.

There were no treatment-related mortalities or treatment-related effects on reproductive parameters or function. There were no treatment-related microscopic findings for any treatment group of the P generation and no treatment-related gross pathologic findings in either P or F_1 generations. **The LOAEL for systemic toxicity is 125 ppm based on reductions in body weight and food consumption. The systemic NOAEL is 50 ppm.**

Reproductive toxicity of cyfluthrin was manifest at 125 and 400 ppm. At 125 ppm, treatment-related coarse tremors were observed in 16% of the F_1 pups and 73% of the F_2 pups during lactation days 5-17. Treatment-related decreases (↓6-14%) in mean body weight were observed between 4-21 days in F_1 and F_2 pups. At 400 ppm, treatment-related coarse tremors were observed in F_1 and F_2 pups between days 5 and 17 of lactation. These tremors were observed in 54% of the F_1 pups and 36% of the F_2 pups. A treatment-related reduction (↓6-26%, p≤0.05 or 0.01) in mean litter weights was observed in F_1 and F_2 pups between days 0 and 21 of lactation.

The LOAEL for reproductive toxicity is 125 ppm based on coarse tremors and decreases in mean litter weights. The reproductive NOAEL is 50 ppm.

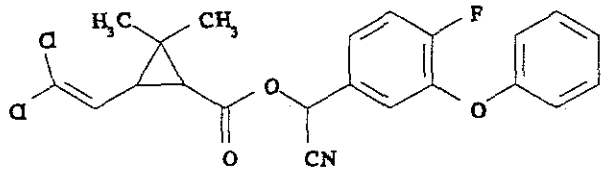
The reproductive study is classified **acceptable (§83-4)** and satisfies the guideline requirement for a 2-generation reproductive study in the rat.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Cyfluthrin
   Description: Cyfluthrin technical, brown viscous liquid
   Lot/Batch #: 2030025
   Purity: 95.4±0.8% a.i.
   CAS #: 68359-37-5
   Structure:



2. Vehicle: Corn oil and acetone

3. Test animals: Species: rat
   Strain: Sprague-Dawley
   Age at start of dosing: (P) approximately 7 weeks, (F_1) approximately 3 weeks (at weaning)
   Weight at start of dosing:
   (P) Males: 178.1-248.8 g Females: 133.6-183.6 g
   (F_1) Males: 103.2-278.6 g Females: 115.8-192.8 g
   Source: SASCO Inc., St. Louis, MO
   Housing: Stainless steel cages suspended over bedding of deotized animal cage board (DACB); During gestation and lactation phases females were housed individually in polycarbonate cages with Bed-O-Cobs bedding.
   Diet: Purina Rodent Laboratory Chow No. 5001-4 Etts form, ad libitum
   Water: Potable municipal water, ad libitum
   Environmental conditions:
   Temperature: 18-26° C
   Humidity: 40-70%
   Air changes: Not reported
   Photoperiod: 12 hrs dark/12 hrs light
   Acclimation period (P): Two weeks

B. PROCEDURES AND STUDY DESIGN

1. Mating procedure: One male and one female from the same test group were caged together for up to 21 consecutive days until an internal vaginal plug was observed or sperm was found in the daily vaginal lavage. Females which were never observed as being inseminated were placed in nesting cages at the end of the breeding period and treated as if pregnant (in case insemination occurred but was not observed). Sibling matings within the F_1 generation were avoided.

After successful mating, each pregnant female was individually placed into a plastic nesting cage.

2. Study schedule: Starting at approximately 7 weeks of age, P animals were given test diets for 10 weeks before they were mated. Upon weaning at 3 weeks of age, F_1 pups were selected to become parents of the F_2 generation and were given the same concentration test diets as their dam. F_1 animals were given test diets for 11 weeks prior to mating. Exposure of all animals to the test material in the diet was continuous throughout the study.

3. Animal assignment: Parents (P) were randomly assigned based on body weight for P rats. F_1 weanlings were randomly chosen to become parents of the F_2 generation. The dose groups to which the animals were assigned are shown in Table 1.

Table 1. Animal assignment

Test Group	Dose in Diet[a] (ppm)	Animals/group			
		P Males	P Females	F_1 Males	F_1 Females
Control	0	30	30	30	30
Low (LDT)	50	30	30	30	30
Mid (MDT)	125	30	30	30	30
High (HDT)	400	30	30	30	30

a Diets were administered from the beginning of the study until sacrifice.

4. Dose selection rationale: Doses for this study were based upon a range finding study in rats with cyfluthrin in the diet. Details of this study were not provided with this report.

5. Dosage preparation and analysis: Diet batches were prepared weekly. Prior to the start of the study, the stability of the test substance in the diet (50 and 600 ppm diets) was evaluated for a period of 28 days frozen (approx. -23° C) and for a period of 14 days at ambient temperature (approx. 22° C). To evaluate homogeneity, three samples were taken from each of three areas of a Hobart mixing bowl (top, middle and bottom) and were analyzed. The test substance was considered homogeneously mixed in the feed if the CV of the nine samples was ≤10%. During the study, samples of treated food at each dose level were analyzed for cyfluthrin

concentration in rodent chow mixtures during weeks 1, 9, 18, 27, and 36.

Results - Homogeneity Analysis: The test substance was considered homogeneously mixed, with the coefficients of variation samples assayed from 3 layers of the mix of 4-8%.

Stability Analysis: The test substance was stable in the diet for up to 28 days at -15 to -20°C and for up to 14 days at ambient temperatures

Table 2. Stability analysis of cyfluthrin in test diets.[a]

Storage interval (days)	Storage temperature	% of day 0 concentration b
7, 14, 21, 28	-15 to -20°C	96.3-112
1, 3, 7, 10, 14	22°C	85.6-116

a Data extracted from the study report pages 93-98.
b Range reported is for 50 and 600 ppm diets with samples of each diet analyzed for the indicated storage interval.

Concentration Analysis: The average concentrations at the 50, 125 and 400 ppm test levels were 46, 122, and 403 ppm, respectively. These concentrations correspond to 93-101% of the nominal.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable. In addition, the test substance was demonstrated to be stable in the test diets as they were prepared and stored in the study.

C. OBSERVATIONS

1. Parental animals: Animals were observed for mortality, moribundity and clinical signs of toxicity twice daily. Males were weighed initially and weekly during the study. Females were weighed initially, weekly through mating, on gestational days 0, 6, 13, and 20, and on lactational days 0, 4, 7, 14, and 21. Food consumption was recorded weekly during the pre-breeding treatment periods. Food consumption by males was measured once a week during the ten-week period prior to F_1 and F_2 matings. Maternal food consumption was recorded once a week during gestation, twice a week during the first week of lactation, and once a week during weeks 2 and 3 of lactation.

2. Litter observations: According to the report, the following litter observations (X) were made (see Table 3).

Table 3. F_1/F_2 Litter observations.[a]

Observation	Time of observation (lactation day)				
	Day 0	Day 4[b]	Day 7	Day 14	Day 21
Number of live pups[c]	X	X	X	X	X
Pup weight	X	X	X	X	X
Clinical Signs[c]	X	X	X	X	X
Sex of each pup (M/F)	X	X	X	X	X

a Data extracted from the study report page 23.
b Each litter was randomly culled on day 4 .
c Litter counts and clinical observations were performed daily.

On day 4 postpartum, litters were randomly culled to standardize the litters to a maximum of 8 pups/litter with 4/sex/litter. No adjustment was made in litters of eight or fewer pups. Culled pups were terminated and subjected to a gross necropsy.

3. Postmortem observations:

1) Parental animals: Parental males were terminated after completion of the mating period. Dams were terminated after the litters were weaned or died, when day 24 of gestation was reached, or 24 days after the last day of co-housing. These animals were subjected to postmortem examinations as follows.

A complete necropsy was performed on all adult animals. Uteri from all dams were examined for implantation sites which were enumerated. The following tissues from the controls and high-dose P and F_1 animals (X) were prepared for microscopic examination. The ovaries and testes from all P and F_1 animals were weighed (XX) and weights were calculated relative to terminal body weights. Because of clinical signs of neurotoxicity, the brain, spinal cord and one sciatic nerve were collected from all F_1 adults and were placed in buffered 10% formalin. Parental animals dying during the study also underwent gross and histopathological examinations.

XX	Ovaries	X	Epididymides
X	Uterus	X	Prostate
X	Vagina	X	Seminal vesicles
X	Cervix	XX	Testes
X	Gross lesions	X	Pituitary
		X	Coagulatory gland

2) Offspring: A complete necropsy was performed on all pups, except those born to dams which died or were sacrificed due to dystocia. For pups found dead on day 0 the ability of the lungs to float in water was used to determine if the pups were stillborn. Organs from one male/female pair of pups from each dose group scheduled to be sacrificed on days 4 and 21 were preserved in buffered formalin following necropsy.

D. DATA ANALYSIS

1. Statistical analyses: All collected data were subjected to routine appropriate statistical procedures.

2. Indices:

Reproductive indices: The following reproductive indices as presented in the study report (page 24) were calculated for the P and F_1 adults:

Mating index(%) = # of inseminated females[a]/# of females paired x 100%
Fertility index(%) = # of pregnant females[b]/# of inseminated females x 100%

[a] Includes pregnant females in which insemination was not observed.
[b] Includes females which delivered or had implantation sites.

Offspring viability indices: The following viability indices as presented in the study report (page 24) were calculated for the F_1 and F_2 litters:
Gestation index(%) = # of females with live pups/# of pregnant females x 100%
Birth index(%) = total # of pups born per litter/total number of implantation sites/dam x 100%
Live birth index(%) = # of live pups born per litter/total number of pups/litter x 100%
Viability index(%) = # of live pups per litter on day 4 preculling/# of live pups born per litter x 100%
Lactation Index(%) = # of live pups per litter on day 21/# of live pups per litter on day 4 postculling x 100%

3. Historical control data: Historical control data for pup body weight values were provided.

II. RESULTS

A. PARENTAL ANIMALS

1. Mortality and clinical signs: No treatment-related clinical findings or increases in mortality were noted in males. For the P and F_1 females there was a compound-related increase in splayed hind limbs in the high-dose groups during lactation (15/30 high-dose P females, 9/30 high-dose F_1 females; 0/30 in P or F_1 controls, $p \leq 0.01$). This finding was attributed to the higher cyfluthrin intake associated with the increase in food consumption, which occurs in all lactating rats to compensate for the increased metabolic needs during lactation. In treated animals this increase resulted in an approximate doubling of cyfluthrin intake during lactation (to 7, 19 and 59 mg/kg/day in low-, mid-, and high-dose animals) compared to the premating and gestation phases (Table 5). No treatment-related increases in mortality were observed. One mid-dose group P female died on day 99 due to aspiration pneumonia and another was sacrificed with a broken palate on day 44. One F_1 male was sacrificed *in extremis* on day 48.

2. Body weight and food consumption: Compound-related reductions in body weights were observed in the F_1 mid- and high-dose group males. Mean body weights of mid-dose F_1 males were decreased (↓6-8%, $p \leq 0.05$) during weeks 3-6, 8, 10-13 and those of high-dose F_1 males were decreased (↓7-8%, $p \leq 0.05$ or 0.01) during weeks 1 and 4-14. Although, there were no significant differences in body weights between treated P males and females and their respective controls, reduced mean weight gains were observed during premating in the mid- (↓12%) and high-dose P males (↓16%) and in the high-dose P females (↓15%). A smaller reduction in mean weight gain during premating was also observed in high-dose F_1 males and females (↓5-8%).

   There was no compound-related effect on food consumption for males or females although sporadic significant differences in food consumption were noted in P and F_1 generation animals. Decreased food consumption was observed in the first week for high-dose P males (↓14%, $p \leq 0.01$) and P females (↓5%, $p \leq 0.05$). Increased food consumption was noted in the mid-dose F_1 females in 7 of the 10 premating weeks (↑6-12%, $p \leq 0.05$ or 0.01) and sporadically in other treated animals (↑3-8%, $p \leq 0.05$ or 0.01). These premating alterations in food consumption were not considered treatment-related because they either lacked dose-dependence or were transient in nature.

Selected data for body weights, body weight gains and food consumption during the premating period are summarized in Tables 4a and 4b.

Table 4a. Mean body weights (g), gains (g), and food consumption (g/kg/day) - P generation pre-mating.[a]

Observation/Study Days	Dose Group (ppm)			
	0	50	125	400
P Generation Males - Pre-mating				
Mean body weight/Week 1	220.6	215.0	219.2	222.6
Mean body weight/Week 4	307.0	297.1	294.4	293.7
Mean body weight/Week 11	392.2	379.3	370.5	367.1
Mean weight gain/Week 1-11[b]	171.6	164.3	151.3	144.5
Mean food consumption/Days 0-7	106.2	105.6	103.9	91.6**
Mean food consumption/Days 21-28	73.2	74.8	73.9	70.8
Mean food consumption/Days 63-70	58.7	58.4	62.5**	60.4
P Generation Females - Pre-mating				
Mean body weight/Week 1	155.9	153.2	156.0	156.1
Mean body weight/Week 4	192.5	191.2	190.2	187.7
Mean body weight/Week 11	231.5	231.6	228.5	220.6
Mean weight gain/Weeks 1-11[b]	75.6	78.4	72.5	64.5
Mean food consumption/Days 0-7	100.3	101.4	97.8	95.3**
Mean food consumption/Days 21-28	83.4	86.4	84.2	85.3
Mean food consumption/Days 63-70	70.5	70.7	72.8	73.1

a Data extracted from the study report pages 45-46 and 50-51.
b Calculated by the reviewer from the mean body weight data presented in the study report on pages 45-46.
* Statistically different from control, p\0.05.
** Statistically different from control, p\0.01.

Table 4b. Mean body weights (g), gains (g), and food consumption (g/kg/day) - F_1 generation pre-mating.[a]

Observation/Study Day	Dose Group (ppm)			
	0	50	125	400
F_1 Generation Males - Pre-mating				
Mean body weight/Week 1	225.9	228.3	207.7	209.4*
Mean body weight/Week 4	319.3	323.5	294.8*	297.7*
Mean body weight/Week 11	409.4	417.4	382.8*	379.5*
Mean weight gain/Week 1-11[b]	183.5	189.1	175.1	170.1
Mean food consumption/Days 0-7	102.8	104.0	108.5	105.3
Mean food consumption/Days 21-28	71.2	71.1	73.8	74.9
Mean food consumption/Days 63-70	59.0	59.6	61.8*	63.2**
F_1 Generation Females - Pre-mating				
Mean body weight/Week 1	156.0	157.7	147.5	149.8
Mean body weight/Week 4	192.7	198.4	190.1	188.0
Mean weight gain/Week 11	234.3	240.6	231.9	224.3
Mean weight gain/Week 1-11[b]	78.3	82.9	84.4	74.5
Mean food consumption/Days 0-7	99.4	102.6	111.5*	101.8
Mean food consumption/Days 21-28	82.4	82.0	85.4	85.5
Mean food consumption/Days 63-70	72.0	72.3	77.0**	76.3**

a Data extracted from the study report pages 47-48 and 52-53.
b Calculated by the reviewer from the mean body weight data presented in the study report on pages 47-48.
* Statistically different from control, p\0.05.
** Statistically different from control, p\0.01.

During gestation, body weights of high-dose P dams were reduced (↓5-6%) and significantly reduced on gestation day 20 (↓7%, p≤0.05). The reduction in body weight gain of high-dose P females during days 0-20 of gestation (↓13%, p≤0.01) was considered treatment-related. Body weights and body weight gains of F_1 females during gestation were comparable to controls. Other than a transient decrease in food consumption in mid-dose F_1 females during gestation days 0-6 (↓6%, p≤0.05,) food consumption was comparable to the respective controls during gestation.

During lactation, mean maternal body weights were significantly decreased (p≤0.01) between day 4 and day 21 in high-dose P females (↓7-14%) and in high-dose F_1 females (↓9-11%) relative to the lactating controls. These decreases in body weights were considered treatment-related and were associated with a significant (p≤0.01) reduction in food consumption compared to lactating controls between day 0 and 14 of lactation in the P dams (↓17-22%) and throughout lactation in the F_1 dams (↓11-22%). F_1 dams treated at 125 ppm cyfluthrin also had a treatment-related reduction in food consumption (↓9-11%, p≤0.05 or 0.01) compared to lactating controls between lactational days 7 and 21.

There were significant ($p \leq 0.05$) treatment-related decreases in terminal body weights of the mid- and high-dose F_1 males (↓6% and ↓8%, respectively) and the high-dose F_1 females (↓8%) compared to the respective controls.

3. Test Substance Intake: Based on food consumption and body weight, the daily test substance doses expressed as mean daily mg test substance/kg body weight during the pre-mating period (11 weeks), gestation and lactation are presented in Table 5. Due to the high metabolic requirements of lactation, food consumption also increased causing an approximate doubling of compound intake.

Table 5. Test substance intake (mean mg/kg body weight/day).[a]

	Male			Female		
	50 ppm	125 ppm	400 ppm	50 ppm	125 ppm	400 ppm
Premating	3	9	29	4	10	33
Gestation				4	10	33
Lactation				7	19	59

a Date extracted from study report page 28.

4. Reproductive function:

a. Estrous cycle length and periodicity: There was no compound-related effect on estrous cycling. The number of cycles in a three-week period was comparable in all treatment groups to the respective controls. The significant ($p \leq 0.05$) increase (↑21%) in estrous cycle length of the P low-dose group was considered an incidental finding due to a lack of dose-dependence.
b. Sperm measures: Insemination length, a daily cumulative percentage of inseminated females, was similar in control, and treated P and F_1 females.
c. Sexual maturation (F_1): No observations were made pertaining to the sexual maturation rates of the F_1 or F_2 litters.

5. Reproductive performance: Reproductive performance results are presented in Table 6. There were no treatment-related effects noted in the reproductive performance of the P or F_1 adults. Mating, fertility, gestation, and birth indices were not affected by treatment. No treatment-related changes in gestation interval or number of litters was observed.

Table 6. Reproductive performance[a]

Observation	Dose Group (ppm)			
	0	50	125	400
P Generation - Litter F_1				
Mating Index(%)	100.0	100.0	100.0	100.0
Fertility Index(%)	100.0	93.3	89.7	96.7
Gestation Index(%)	100.0	96.4	100.0	100.0
Birth Index(%)	95.8	89.3	94.7	89.0
Median Gestation Interval (Days)	22.0	21.9	22.0	22.0
Number of Litters	30	27	26	29
F_1 Generation - Litter F_2				
Mating Index(%)	100.0	100.0	100.0	100.0
Fertility Index(%)	83.3	90.0	90.0	86.7
Gestation Index(%)	100.0	100.0	100.0	96.2
Birth Index(%)	92.0	90.7	92.1	88.3
Median Gestation Interval (Days)	22.3	22.0	22.1	22.0
Number of Litters	25	27	27	25

a Data extracted from the study report pages 72-75.

5. Parental postmortem results

a) Organ weights: Minor reductions in absolute weights of testes and ovaries were observed at necropsy. The mean absolute ovary weight was reduced in the high-dose P generation females (↓11%, $p \leq 0.05$) compared to controls. The mean absolute testes weight at necropsy in high-dose F_1 generation males was also decreased (↓10%, $p \leq 0.05$) compared to controls. These changes were not considered treatment-related because, when standardized on the basis of terminal body weight, these differences were not significant.

b) Pathology

1) Macroscopic examination: There were no treatment-related macroscopic findings for any treatment group of the P or F_1 parental generations.

2) Microscopic examination: There were no treatment-related microscopic findings for any treatment group of the P parental generation.

B. OFFSPRING

1. Viability and clinical signs: Treatment-related coarse tremors were observed in F_1 and F_2 pups of the mid- and high-dose groups. No tremors were observed in the control or low-dose groups. In 16% (4/25) of the mid-dose F_1 litters these tremors were observed during lactation days 7-14. In 54% (15/28) of the high-dose F_1 litters these tremors were observed during lactation days 5-17. In 73% (19/26) of the F_2 mid-dose litters these tremors were observed between lactation days 7-12 and days 15-16. In 36% (9/25) of the high-dose F_2 litters these tremors were observed between days 7-13. Although these findings were described as "statistically significant for all but the F_1 mid-dose group" the statistical test used and p values were not reported.

   Mean litter size and survival indices of F_1 and F_2 pups are summarized in Tables 7a and 7b. There were no observed treatment-related differences in the number of live pups, the mean litter size or the stillbirth, live birth, viability and lactation indices.

Table 7a. Mean litter size and viability.[a]

Observation	Dose Group (ppm)			
	0	50	125	400
F_1 Generation				
Mean litter size				
Day 0[b]	12.7	12.2	12.3[d]	11.0[d]
Day 4[b]	12.6	12.0	12.4[d]	11.3[d]
Day 4[c]	8.0	8.0	8.0	7.8
Day 7	7.9	7.9	8.0	7.6
Day 14	7.9	7.9	8.0	7.6
Day 21	7.9	7.9	8.0	7.6
Number live pups[e]				
Day 0[b]	380	330	322	319
Day 4[b]	377	324	310	315
Day 4[c]	240	215	200	217
Day 7	238	214	200	214
Day 14	238	213	200	214
Day 21	237	213	200	213
Number deaths[e]				
Days 0-4	3	6	12	4
Days 4-21	3	2	0	4
Survival indices (%)				
Stillbirth	0.8	0.9	0.9	0.3
Live Birth	99.2	99.1	99.1	97.5
Viability (Day 4)	99.3	98.3	96.2	95.7
Lactation (Day 21)	98.8	99.1	100.0	97.8

a Data extracted from the study report pages 73-75.
b Before standardization (culling)
c After standardization (culling)
d Number of litters was reduced by one from previous interval
e Values calculated by the reviewer from study report pages 253-260.

Table 7b. Mean litter size and viability.[a]

Observation	Dose Group (ppm)			
	0	50	125	400
F_2 Generation				
Mean litter size				
Day 0[b]	11.8	12.5	12.1	10.8
Day 4[c]	11.6	12.1	11.9	10.6
Day 4	8.0	8.0	7.9	7.4
Day 7	8.0	8.0	7.8	7.4
Day 14	8.0	7.9	7.4[d]	7.4
Day 21	8.0	7.9	7.6	7.3
Number live pups[e]				
Day 0[b]	297	339	325	271
Day 4[c]	292	326	320	263
Day 4	200	215	212	186
Day 7	200	215	210	186
Day 14	200	213	199	186
Day 21	200	205	198	184
Number deaths[e]				
Days 0-4	5	13	5	8
Days 7-21	0	10	14	2
Survival indices				
Stillbirth	0.0	0.6	1.5	1.1
Live birth	99.6	99.4	98.5	99.1
Viability (Day 4)	98.3	96.6	98.4	95.9
Lactation (Day 21)	100.0	95.4	93.5	99.0

a Data extracted from the study report pages 73-75.
b Before standardization (culling)
c After standardization (culling)
d Number of litters was reduced by one from previous interval
e Values calculated by the reviewer from study report pages 261-268.

2. Body weight: There was a treatment-related decrease in F_1 and F_2 pup body weights relative to the respective controls in the mid- and high-dose groups (Table 8). F_1 offspring mean litter weights were reduced in the 400 ppm group on lactational days 4-21 (↓9-20%, p≤0.05 or 0.01) and in the 125 ppm group on lactational days 7 and 14 (↓6-7%, p≤0.05). Mean litter weights of the high-dose F_2 offspring were reduced (↓6-26%, p≤0.01) between lactational days 0-21. Mean litter weights of the mid-dose F_2 offspring were reduced (↓8-14%, p≤0.01) between lactation days 7-21.

Although mean litter weights of the low-dose F_2 offspring were also reduced (↓5-10%, p≤0.05) between lactation days 0-7, this reduction was not considered a treatment-related change because the reduction did not increase in mid-dose litters, it was not observed in the F_1 pups and the weights fell within the range of historical controls. The reduced birthweights of the low and high-dose F_2 pups (↓5-6%, p≤0.05 or 0.01) relative to the F_2 controls were also not

considered treatment-related because the reduction did not increase in mid-dose litters, it was not observed in the F_1 pups or in other reproductive studies at the same doses, and the weights fell within the range of historical controls.

Table 8. Mean litter weights (g).[a]

Day of lactation	Dose Group (ppm) 0	50	125	400
F_1 Generation				
Day 0[b]	6.6	6.6	6.4	6.6
Day 4[b]	10.1	10.2	9.7	9.2*
Day 4[c]	10.0	10.3	9.7	9.2*
Day 7	16.2	16.4	15.0*	13.7**
Day 14	31.4	31.5	29.5*	25.2**
Day 21	49.0	50.1	46.1	39.4**
F_2 Generation				
Day 0[b]	6.7	6.4*	6.4	6.3**
Day 4[b]	10.3	9.3*	9.5	8.2**
Day 4[c]	10.3	9.3*	9.5	8.2**
Day 7	16.1	14.7*	14.4**	12.0**
Day 14	30.3	28.8	25.8**	23.0**
Day 21	45.4	42.8	39.0**	33.6**

a Data extracted from study report pages 72 and 74.
b Before standardization (culling)
c After standardization (culling)
* Statistically different from control, p\0.05
** Statistically different from control, p\0.01

3. Offspring postmortem results:

a) Organ weights: A significant decrease in the absolute testes weights (↓10%, p≤0.05) was observed in the high-dose F_1 males. However, this decrease was not considered treatment-related because a corresponding decrease in terminal body weights (↓8%, p≤0.05) of F_1 males caused relative testes weights to be similar to controls.

b) Pathology

1) Macroscopic examination: There were no treatment-related macroscopic findings in either the F_1 or F_2 pups at any dose level. The incidence of gross lesions were comparable in the controls and treated pups with the exception of an increased incidence of subcutaneous hemorrhage in the F_1 high-dose pups culled on day 4 (6/98 treated; 0/137 controls, p≤0.05). This lesion which was found in only 1/26 F_1 high-dose litters and in no other treatment group or controls was considered

an incidental finding.

2) Microscopic examination: Histopathology was not performed on any of the tissues collected from the F_1 or F_2 pups for any dose level.

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS: The study author concluded that there were no treatment-related mortalities. In females there was a treatment-related splaying of the hind limbs in the high-dose P and F_1 females during lactation. There were no treatment-related clinical signs for adult males. There was no treatment-related effect on body weight for P and F_1 females (premating) or P males. Treatment-related reductions of body weights were observed in the F_1 mid- and high-dose males, in the P high-dose females during gestation, and in P and F_1 high-dose females during lactation. There was a treatment-related decrease in food consumption during lactation in the F_1 mid-dose females and the P and F_1 high-dose females. There were no treatment-related effects on adult reproductive parameters.

Treatment-related coarse tremors were observed in the mid- and high-dose pups between lactation days 5-17. Treatment-related decreases in the terminal body weight of the high-dose F_1 females and mid- and high-dose F_1 males were observed. There were no treatment-related gross lesions in pups or adults and no microscopic lesions in the adults.

The reproductive toxicity NOEL for cyfluthrin was 400 ppm. The neonatal NOEL was 50 ppm based on coarse tremors in pups in the 125 and 400 ppm groups. The parental NOEL was 50 ppm based on body weight reduction and splaying of the hind limbs in the high-dose females during lactation; decreased body weights of the mid- and high-dose F_1 males and decreased terminal body weights of the high-dose F_1 females, mid- and high-dose F_1 males.

B. REVIEWER'S DISCUSSION: Over the course of a 2-generation reproduction study, cyfluthrin was administered continuously in the diet to Sprague Dawley rats at dose levels of 0, 50, 125 or 400 ppm to achieve doses of 0, 3, 9, and 29 mg/kg/day in males and 0, 4, 10, and 33 mg/kg/day in females during premating. Beginning at 7 weeks of age P animals (30/sex/group) were fed cyfluthrin in the diet for 10 weeks prior to mating to produce F_1 litters. F_1 pups were randomly chosen to become parents of the F_2 generation at weaning. They were fed the same dose of cyfluthrin as their dam received for 11 weeks prior to mating.

The test substance was found to be stable in the diet for up to 28 days frozen at -15 to -20° C conditions and for up to 14 days at ambient temperatures. The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

1. Parental Toxicity. Parental toxicity of cyfluthrin was observed at 125 and 400 ppm.

At 400 ppm, treatment-related splaying of hind limbs was observed in P and F_1 females during lactation (15/30 high-dose P females, 9/30 high-dose F_1 females vs. 0/30 in both P and F_1 controls, $p \leq 0.01$). This splaying was accompanied by treatment-related reductions in mean body weights of P and F_1 females (↓7-14%, $p \leq 0.01$) and reductions of food consumption in P and F_1 females (↓11-22%, $p \leq 0.05$ or 0.01) during lactation. For all dams cyfluthrin intake was nearly doubled during lactation compared to premating and gestation periods. Most treatment-related effects were observed during this period and were probably associated with the increase in dose during lactation. During gestation treatment-related decreases in body weight (↓7%, $p \leq 0.05$) and body weight gain (↓13%, $p \leq 0.01$) were observed in P dams. Treatment-related decreases in terminal body weight were observed in both F_1 males and females (↓6-8%, $p \leq 0.05$) with similar decreases in premating mean body weights (↓7-8%, $p \leq 0.05$) observed in mid- and high-dose F_1 males.

At 125 ppm, treatment-related reductions in mean (↓6%, $p \leq 0.05$) and terminal (↓6%, $p \leq 0.05$) body weights were observed in F_1 males. During lactation there was a treatment-related decrease in food consumption (↓9-11%, $p \leq 0.05$ or 0.01) for F_1 dams at this dose.

There were no treatment-related mortalities or treatment-related effects on reproductive parameters or function. There were no treatment-related microscopic findings for any treatment group of the P generation and no treatment-related pathology findings in either P or F_1 generations.

2. Reproductive Toxicity. Reproductive toxicity of cyfluthrin was evident at 125 and 400 ppm.

At 400 ppm, treatment-related coarse tremors were observed in F_1 and F_2 pups between days 5 and 17 of lactation. These tremors were observed in 54% of the F_1 pups and 36% of the F_2 pups. A treatment-related reduction (↓6-26%) in mean litter weights was observed in F_1 and F_2 pups between days 0 and 21 of lactation.

At 125 ppm, treatment-related course tremors were observed in 16% of the F_1 pups and 73% of the F_2 pups during lactation days 5-17. Treatment-related decreases (↓6-14%) in mean litter weight were observed between 4-21 days in F_1 and F_2 pups.

The LOAEL for systemic toxicity is 125 ppm based on reductions in body weights and food consumption. The systemic NOAEL is 50 ppm.

The LOAEL for reproductive toxicity is 125 ppm based on coarse tremors and decreases in mean litter weights. The reproductive NOAEL is 50 ppm.

C. STUDY DEFICIENCIES: There were no deficiencies with the submitted 2-generation reproduction study in the rat.

13544

R058498

Chemical:	**Cyfluthrin**
PC Code:	**128831**
HED File Code	**13000 Tox Reviews**
Memo Date:	**02/28/2002 12:00:00 AM**
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