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

pc 128831

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Registration Action Branch 2 (7509C)

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Registration Action Branch 2 (7509C)

DATA EVALUATION RECORD
Supplement to DER for MRID No.: 44371402 Cyfluthrin: [Supplementary Two-Generation Reproduction Study] **This supplement includes a revised executive summary (changing systemic to parental, reproductive to offspring and ppm to mg/kg/day)**

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

DP BARCODE: D240006
P.C. CODE: 128831
SUBMISSION CODE: S531858
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Cyfluthrin (technical, 95.5% a.i.)

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

CITATION: Eigenberg, D.A., (1997) A Supplementary Two-Generation Dietary Reproductive Study in Rats Using Technical Grade Cyfluthrin. Bayer Corporation, Stilwell, KS. Laboratory Study number 94-672-CK, January 30, 1997. MRID 44371402. Unpublished.

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

EXECUTIVE SUMMARY: In this "supplemental" 2-generation reproduction study (MRID 44371402) cyfluthrin (95.5% a.i.) was administered to 30 Sprague Dawley rats/sex/dose at dose levels of 0, 25, or 50 ppm in the diet (equivalent to doses of 0, 1.9 or 3.8 mg/kg/day in males; 0, 2.1, or 4.2 mg/kg/day in females during premating; and 0, 2.0 or 3.9 mg/kg/day during gestation in females). 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.

In a previously submitted 2-generation reproduction study (MRID 44371401) in which rats were dosed at 50 to 400 ppm, parental toxicity of cyfluthrin was observed at 125 and 400 ppm. At 125 ppm, treatment-related reductions in body weights and/or food consumption were observed in F_1 males during premating and in lactating F_1 females. At 400 ppm, treatment-related splaying of hind limbs and reductions in body weights and food consumption were observed in P and F_1

females during lactation. Equivocal evidence of a treatment-related decrease in pup weight was observed at 50 ppm.

The objectives of the present study were to determine the reproducibility of the effect on pup weight and to verify and/or establish a reproductive NOAEL for cyfluthrin at 50 ppm. There was no evidence of parental toxicity of cyfluthrin at 25 or 50 ppm. There were no treatment-related clinical findings or increases in mortality. There were no significant differences in body weights between the controls, treated P males, P females, F_1 males, or F_1 females during the premating interval. There were no treatment-related changes in food consumption in males or females. During gestation and lactation there were no treatment-related effects on body weights, body weight gains, or food consumption of dams.

The LOAEL for parental toxicity was not observed. The parental NOAEL is 50 ppm (3.8/4.2 mg/kg/day).

At 25 and 50 ppm, 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. The reduction in pup weights observed at 50 ppm in the previous two-generation reproductive study (MRID 44371401) could not be reproduced.

The LOAEL for offspring toxicity was not observed. The offspring NOAEL is 50 ppm (3.8/4.2 mg/kg/day).

The reproductive study in the rat is classified **acceptable nonguideline (§83-4)** and does not (by itself) satisfy the guideline requirement for a 2-generation reproductive study in rat.

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

DATA EVALUATION RECORD

CYFLUTHRIN

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

Work Assignment No. 3-32B (MRID 44371402)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by

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Disclaimer

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

Cyfluthrin **Reproduction Study (S83-4)**

EPA Reviewer: Laurence D. Chitlik, DABT
Toxicology Branch I (7509C)

Laurence D. Chitlik 3/25/00

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

DATA EVALUATION RECORD

STUDY TYPE: Multigeneration Reproduction Study - Rat
OPPTS Number: 870.3800 OPP Guideline Number: S83-4

DP BARCODE: D240006 SUBMISSION CODE: S531858
P.C. CODE: 128831 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Cyfluthrin (technical, 95.5% a.i.)

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

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EXECUTIVE SUMMARY: In this "supplemental" 2-generation reproduction study (MRID 44371402) cyfluthrin (95.5% a.i.) was administered to 30 Sprague Dawley rats/sex/dose at dose levels of 0, 25, or 50 ppm in the diet (equivalent to doses of 0, 1.9 or 3.8 mg/kg/day in males; 0, 2.1, or 4.2 mg/kg/day in females during premating; and 0, 2.0 or 3.9 mg/kg/day during gestation in females). 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.

In a previously submitted 2-generation reproduction study (MRID 44371401) in which rats were dosed at 50 to 400 ppm, parental toxicity of cyfluthrin was observed at 125 and 400 ppm. At 125 ppm, treatment-related reductions in body weights and/or food consumption were observed in F_1 males during premating and in lactating F_1 females. At 400 ppm, treatment-related splaying of

hind limbs and reductions in body weights and food consumption were observed in P and F_1 females during lactation. Equivocal evidence of a treatment-related decrease in pup weight was observed at 50 ppm.

The objectives of the present study were to determine the reproducibility of the effect on pup weight and to verify and/or establish a reproductive NOEL for cyfluthrin at 50 ppm. There was no evidence of parental toxicity of cyfluthrin at 25 or 50 ppm. There were no treatment-related clinical findings or increases in mortality. There were no significant differences in body weights between the controls, treated P males, P females, F_1 males, or F_1 females during the premating interval. There were no treatment-related changes in food consumption in males or females. During gestation and lactation there were no treatment-related effects on body weights, body weight gains, or food consumption of dams.

The LOAEL for systemic/parental toxicity was not observed. The systemic/parental NOAEL is 50 ppm.

At 25 and 50 ppm, 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. The reduction in pup weights observed at 50 ppm in the previous two-generation reproductive study (MRID 44371401) could not be reproduced.

The LOAEL for reproductive toxicity was not observed. The reproductive NOAEL is 50 ppm.

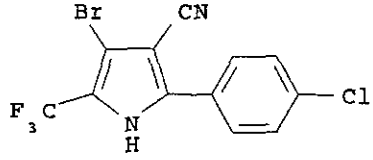
The reproductive study in the rat is classified **acceptable non-guideline (§83-4)** and does not (by itself) satisfy the guideline requirement for a 2-generation reproductive study in rat.

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: 95.5±0.8% a.i.
   CAS #: 68359-37-5



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: 167.0-211.7 g Females: 133.2-176.5 g
   (F_1) Males: 119.3-284.4 g Females: 130.5-198.6 g
   Source: SASCO Inc., Omaha, NE
   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: PMI Feeds Rodent Chow No. 5001-4 Etts form, ad libitum
   Water: Potable municipal water, ad libitum
   Environmental conditions:
   Temperature: 64-78° F
   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 not observed 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). 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. F_1 pups selected to become parents of the F_2 generation and were given the same concentration test diets as their dam upon weaning at 3 weeks of age. F_1 animals were given test diets for approximately 11 weeks prior to mating. Exposure of the animals to test material in the diet was continuous throughout the study.

3. Animal assignment: Parents (P) were randomly assigned based on body weight. F_1 pups were randomly chosen to become parents of the F_2 generation at weaning. The dose group 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)	25	30	30	30	30
High (HDT)	50	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 selected based upon results of a two-generation reproductive toxicity study in rats with cyfluthrin in the diet (MRID 44371401). In the prior reproductive study a decrease in pup weight was observed at birth and on days 4 and 7 at the low dose (50 ppm). The overall objective of the present study was to establish a NOEL for effects of cyfluthrin on pup weight. The high dose, 50 ppm, was chosen to evaluate the reproducibility of the pup body weight effect observed at this dose and the low dose, 25 ppm, was chosen in order to establish a NOEL for effects of cyfluthrin on pup weight.

5. Dosage preparation and analysis: Test feed was prepared weekly during the study. The stability of the test substance in the feed (25 and 50 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 feed

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 25 ppm diet being 97.9% of nominal, the 50 ppm diet being 99.2% of nominal, and both having coefficients of variation of 8%.

Stability Analysis: Stable in the diet for up to 28 days at approximately -20° C and for up to 14 days at ambient temperature.

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

Storage interval (days)	Storage temperature	% of day 0 concentration[b]
7, 14, 21, 28	-23° C	97.5-112
0, 1, 3, 7, 10, 14	22° C	98.1-116

a Data extracted from the study report page 87.
b Range reported is for 25 and 50 ppm diets with samples of each diet analyzed for the indicated storage interval.

Concentration Analysis: The average concentrations in the 25 and 50 ppm test levels were 24.9 and 48.7 ppm, respectively. These concentrations correspond to 99.7 and 97.4% of the nominal, respectively.

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. Additionally, 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 (once daily on weekends and holidays). Males were weighed initially and weekly during the study. Females were weighed initially, weekly prior to 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. 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 3 and 4 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
Number of viable pups	X	X	X	X	X
Sex of each pup (M/F)	X	X	X	X	X

a Data extracted from the study report page 21.
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: Adult 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.

All adult animals were necropsied. For females, the uterus was examined for implantation sites and the number of sites was recorded. The following tissues from the controls and high-dose P and F_1 animals (X) were fixed either in buffered 10% formalin or in Bouins's fluid and examined microscopically. Terminal body weights and gonad weights (XX) were determined in all P and F_1 animals. To determine the relative weights of gonads, gonad weights were divided by terminal body weights.

XX	Ovaries	X	Epididymides
X	Uterus	X	Prostate
X	Vagina	X	Seminal vesicles
X	Cervix	XX	Testes
X	Gross lesions	X	Pituitary
X	Coagulating 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.

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 22) 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 22) 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 per dam x 100%
Live birth index(%) = # of live pups born per litter/total number of pups per 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 not provided.

II. RESULTS

A. PARENTAL ANIMALS

1. Mortality and clinical signs: No treatment-related clinical findings or increases in mortality were noted. One high-dose P male was sacrificed on day 56 due to a fractured nose. Two P females (one low-dose and one high-dose) died due to dystocia on days 97 and 98. A F_1 female was sacrificed in extremis on day 42.

2. Body weight and food consumption: There were no treatment-related effects on body weights or food consumption. There were no significant differences in body weights between treated P males, P females, F_1 males or F_1 females and their respective controls.

   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. Increased food consumption was noted in the low and high-dose P females during week 3 (↑7-9%, $p<0.01$) and in F_1 males during week 9 (↑4%, $p<0.05$). These premating alterations in food consumption were not considered treatment-related because they were transitory.

   Selected data for body weights, 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/animal/day) - P generation pre-mating.[a]

Observation/Study Days			
	0	25	50
P Generation males- Pre-mating			
Mean body weight/Week 1	242.4	244.7	244.4
Mean body weight/Week 4	320.8	322.3	323.2
Mean body weight/Week 11	404.4	405.6	406.2
Mean weight gain/Days 0-77b	212.3	213.2	213.5
Mean food consumption/Days 0-7	119.0	119.7	119.9
Mean food consumption/Days 21-28	76.4	74.2	75.6
Mean food consumption/Days 63-70	57.8	58.6	59.9
P Generation females- Pre-mating			
Mean body weight/Week 1	172.6	173.7	174.3
Mean body weight/Week 4	209.8	209.9	206.2
Mean body weight/Week 10	241.5	241.6	239.2
Mean weight gain/Days 0-70b	89.4	87.5	87.3
Mean food consumption/Days 0-7	111.6	108.8	111.1
Mean food consumption/Days 21-28	85.8	85.0	86.8
Mean food consumption/Days 63-70	70.3	69.5	71.9

a Data extracted from the study report pages 38-39 and 43-44.
b Calculated by the reviewer from the mean data presented in the study report.

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

Observation/Study Day	Dose Group (ppm)		
	0	25	50
F_1 Generation Males - Pre-mating			
Mean body weight/Week 1	274.8	271.0	264.5
Mean body weight/Week 4	338.0	332.7	330.5
Mean body weight/Week 11	397.7	391.4	391.5
Mean weight gain/Days 0-77b	162.3	155.6	168.2
Mean food consumption/Days 0-7	109.4	107.4	114.9
Mean food consumption/Days 21-28	75.9	76.0	78.4
Mean food consumption/Days 63-70	61.8	62.7	63.6
F_1 Generation Females - Pre-mating			
Mean body weight/Week 1	181.9	184.9	177.2
Mean body weight/Week 4	215.6	219.5	211.8
Mean weight gain/Week 11	245.2	245.3	240.3
Mean weight gain/Days 0-70b	76.0	74.4	77.2
Mean food consumption/Days 0-7	112.3	109.6	112.9
Mean food consumption/Days 21-28	89.7	89.1	88.0
Mean food consumption/Days 63-70	76.0	74.7	75.1

a Data extracted from the study report pages 40-41 and 45-46.
b Calculated by the reviewer from the mean data presented in the study report.

There were no treatment-related effects on body weights, body weight gains or food consumption of dams during the gestation and lactation periods. In low-dose P females on day 20 of gestation incidental increases in body weight (↑6%, $p<0.05$) and body weight gain (↑12.5%, $p<0.05$) were observed. During lactation an incidental increase in body weight was noted in low-dose P females on day 7 (↑4%, $p<0.05$). Food consumption was increased (↑9-22%, $p<0.01$) in low-dose P females between days 0-4 and days 7-14 of lactation while food consumption of high-dose females was increased 15% ($p<0.05$) on days 0-4. However, none of the above alterations were of toxicological significance or treatment-related.

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, gestation and lactation are presented in Table 5. Due to the high metabolic requirements of lactation, food consumption increases causing an approximate doubling of compound intake.

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

	Male		Female	
	25 ppm	50 ppm	25 ppm	50 ppm
Premating	1.9	3.8	2.1	4.2
Gestation			2.0	3.9
Lactation			4.4	8.6

a Data extracted from study report page 26.

4. Reproductive function:

   a. Estrous cycle length and periodicity: A reduction in the number of estrous cycles in low- and high-dose P females was noted during the three-week observation period compared to the respective controls (4 cycles, control; 3 cycles, 25 ppm group; 3 cycles 50 ppm group, $p<0.05$). This finding was considered incidental because it was not observed in the F_1 generation and no effect on estrous cycling was observed in the previous two-generation study (MRID 44371401).
   b. Sperm measures: Insemination length, a daily cumulative percentage of inseminated females, was similar in control, 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	25	50
P Generation - Litter F_1			
Mating Index(%)	100.0	100.0	100.0
Fertility Index(%)	90.0	96.7	100.0
Gestation Index(%)	100.0	96.6	96.7
Birth Index(%)	86.9	87.7	91.5
Median Gestation Interval (Days)	22.1	22.2	22.4
Number of Litters	27	28	29
F_1 Generation - Litter F_2			
Mating Index(%)	100.0	100.0	96.7
Fertility Index(%)	93.3	96.7	96.6
Gestation Index(%)	100.0	100.0	96.4
Birth Index(%)	88.2	89.4	90.4
Median Gestation Interval (Days)	22.3	22.4	22.4
Number of Litters	28	29	27

a Data extracted from the study report pages 65 through 68.

5. Parental postmortem results

a) Organ weights: Although the absolute and relative testes weights in the 50 ppm F_1 generation male group were decreased at necropsy compared to controls (↓6-8%, $p<0.05$), this reduction was not considered treatment related. Reductions in testes weights were not observed in the P males of the present study or in F_1 or P males treated with 50 or 125 ppm cyfluthrin in the previous two-generation reproductive study (MRID 44371401). One of the high-dose F_1 males with reduced testicular weight exhibited unilateral testicular atrophy which was not considered a treatment-related finding. When this animal was considered an outlier and excluded from statistical analysis, absolute testes weights remained significantly decreased but relative testes weights were not significantly different than controls.

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: Mean litter size and survival indices of F_1 and F_2 pups are summarized in Tables 7a and 7b. There were no treatment-related differences in the number of live pups, the mean litter size or the stillbirth, live birth, viability and lactation indices. There were not treatment-related clinical signs in the pups.

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

Observation	Dose Group (ppm)		
	0	25	50
F_1 Generation			
Mean litter size			
Day 0[b]	10.9	12.3	12.8
Day 4[b]	10.9	12.1	12.5
Day 4[c]	7.6	7.9	7.9
Day 7	7.6	7.9	7.9
Day 14	7.6	7.8	7.9
Day 21	7.6	7.8	7.9
Number live pups[d]			
Day 0[b]	293	343	371
Day 4[b]	292	339	361
Day 4[c]	207	220	229
Day 7	207	220	229
Day 14	207	219	227
Day 21	207	218	227
Number deaths[d]			
Days 0-4	1	4	10
Days 4-21	0	2	2
Survival indices (%)			
Stillbirth	1.3	2.3	1.6
Live Birth	98.7	98.0	98.4
Viability (Day 4)	98.8	98.9	97.4
Lactation (Day 21)	99.5	98.7	99.1

a Data extracted from the study report pages 65-66.
b Before standardization (culling)
c After standardization (culling)
d Values calculated by the reviewer from study report pages 202 through 204.

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

Observation	Dose Group (ppm)		
	0	25	50
F_2 Generation			
Mean litter size			
Day 0[b]	11.3[e]	11.1	12.0
Day 4[b]	11.4[e]	11.3	11.8
Day 4[c]	8.0	7.7	8.0
Day 7	8.0	7.7	8.0
Day 14	8.0	7.6	8.0
Day 21	8.0	7.6	8.0
Number live pups[d]			
Day 0[b]	316	322	324
Day 4[b]	309	314	318
Day 4[c]	215	215	215
Day 7	215	215	215
Day 14	215	214	215
Day 21	215	214	215
Number deaths[d]			
Days 0-4	7	6	6
Days 7-21	0	1	0
Survival indices			
Stillbirth	0.9	1.5	2.7
Live birth	99.1	98.5	97.3
Viability (Day 4)	95.0	94.4	98.4
Lactation (Day 21)	100.0	99.6	100.0

a Data extracted from the study report pages 67-68.
b Before standardization (culling)
c After standardization (culling)
d Values calculated by the reviewer from study report pages 208-210.
e Number of litters was reduced by one from previous interval

2. Body weight: There were no significant differences between mean litter body weights of treated animals and controls (Table 8).

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

Day of lactation	Dose Group (ppm)		
	0	25	50
F_1 Generation			
Day 0[b]	6.8	6.7	6.6
Day 4[b]	10.2	10.2	10.0
Day 4[c]	10.2	10.1	10.0
Day 7	15.5	15.8	15.7
Day 14	29.2	30.9	30.8
Day 21	47.9	48.1	49.7
F_2 Generation			
Day 0[b]	6.6	6.9	6.9
Day 4[b]	9.9	10.6	10.3
Day 4[c]	9.8	10.6	10.3
Day 7	15.3	16.4	16.0
Day 14	29.4	30.6	30.6
Day 21	48.4	49.2	50.3

a Data extracted from study report pages 65 and 67.
b Before standardization (culling)
c After standardization (culling)

3. Offspring postmortem results:

a) Organ weights: Organ weights of control and treated pups were comparable indicating no treatment-related effects on absolute or relative organ weights.

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.

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 or clinical signs of toxicity observed in the adults. There were no treatment-related effects on body weight or food consumption during the premating period, during gestation or lactation. There were no treatment-related effects on adult reproductive parameters or pup parameters. There were no treatment-related gross or histopathologic findings. No reproductive, parental or gestational toxicity was observed in this study. The pup body

weight effect observed in the prior two-generational reproductive study was not reproducible and not attributable to cyfluthrin treatment. The NOEL for this study was 50 ppm.

B. REVIEWER'S DISCUSSION: Over the course of a 2-generation reproduction study, cyfluthrin was administered continuously to Sprague Dawley rats at dose levels of 0, 25 or 50 ppm in the diet to achieve doses of 0, 1.9 and 3.8 mg/kg/day in males and 0, 2.1 and 4.2 mg/kg/day in females during premating, and 0, 2.0 and 3.9 mg/kg/day in females during gestation. 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 approximately -20° C 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 not observed at 25 and 50 ppm.

At 25 and 50 ppm there were no treatment-related changes in body weight, body weight gain, or food consumption during the premating period, during gestation or during lactation. There were no treatment-related clinical signs, 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.

The LOAEL for systemic/parental toxicity was not achieved in this study. The systemic/parental NOAEL was 50 ppm.

2. Reproductive Toxicity. No evidence of reproductive toxicity of cyfluthrin was observed at 25 or 50 ppm.

No differences in mean litter weights, litter sizes or pup survival indices were observed between treated animals and controls. There were no clinical signs or gross findings in treated animals.

The LOAEL for reproductive toxicity was not achieved in this study. The reproductive NOAEL is 50 ppm.

C. STUDY DEFICIENCIES: As a non-guideline study, no significant deficiencies were identified. However, only two dose levels were used in this study and no toxicity was identified at either dose in parents or offspring. In order to actually attempt to replicate/refute findings in a previous study, comparable levels of toxicity should have been identified (at a minimum) at the highest level tested. This would have confirmed the validity and utility of the replicate test.

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