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PC 128831

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

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.: 43792901 Cyfluthrin: [Pilot One-Generation Reproduction Study] **This supplement includes a revised executive summary which includes changing NOELs and LOELs to NOAELs and LOAELs and reproductive to offspring effects**

STUDY TYPE: Pilot Two-generation Reproduction Study - Rat OPPTS 870.3800 (83-4).

DP BARCODE: D220788
PC CODE: 128831
MRID#: 43792901
CASE: 003677

SUBMISSION CODE: S496545
TOX CHEM NO.: 266E
CAS REG. NO.: 68359-37-5

TEST MATERIAL (PURITY): Baythroid™ (Cyfluthrin, tech., purity 95.9%-11/5/92; 96.2%-6/10/93)

SYNONYMS: Cyfluthrin, Cyano-(4-fluoro-3-phenoxyphenyl)-methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: DA Eigenberg and HE Hoss (1995) Pilot study to establish dose levels for a two-generation reproduction study in rats using technical grade cyfluthrin administered via diet. Testing Lab. Bayer Corp. Ag. Div., Toxicology, 17745 South Metcalf, Stilwell, KS 66085-9104. Lab. Report No. 92-972-SH & 107010. August 21, 1995. MRID# 43792901. Unpublished.

SPONSOR: Bayer Corp., Ag Div.

EXECUTIVE SUMMARY: In this single generation pilot study (MRID# 43792901), cyfluthrin (95.7-96.2%) was administered to 10 Sprague Dawley rats per sex per group at 0, 50, 150, 400 or 600 ppm (premating dose levels in males: 0, 3.4, 9.3, 24.2 or 38.9 mg/kg/day; females: 0, 4.1, 10.5, 27.2 or 43.9 mg/kg/day) for 28 days and through mating, gestation and lactation for females and to the end of mating for males. Only F1a litters were produced and dams and weanlings were necropsied about 28 days postpartum. Body weight, food consumption, reproduction data, observational data, necropsy data, testes and ovarian weights were collected.

The most notable effects seen in the study were hind leg splaying in lactating dams at 400 (4/10 dams) and 600 ppm (9/10 dams) and ataxia at 400 (4/10 dams), 600 ppm (9/9 dams); in addition to tremors in pups at 150 (38/112 pups, 7/10 litters), 400 (41/114 pups, 7/10 litters) and 600 ppm (18/96 pups, 4/9 litters) on day 8-17 of lactation. The ataxia and splayed hind legs in dams may be due to the higher test material consumption during week 2 and 3 of lactation (≥ 89.2 mg/kg/day), which was ≥ 228% higher than the highest premating dose levels of 27.2 mg/kg/day at 400 ppm. Therefore, the effects in dams are probably due to increased test material consumption rather than to a change in sensitivity. However, the tremors in pups occurred at lactation days 8 to 17, starting at a dietary dose level of 150 ppm (20.3 to 23.8 mg/kg/day). Pups generally begin eating the mothers diet around lactation day 14, but the amount consumed, and the time when the pups started eating the mother's diet was not reported. It would appear most

likely that the pups with tremors were dosed mostly through the mothers' milk rather than through eating the diet.

P female body weight (6% from control) and weight gain was reduced during premating and gestation (≥ 27% from control) at 600 ppm and during lactation (≥ 52% from control) at ≥ 400 ppm. Food consumption was decreased during these periods of female weight reduction, but food efficiency was also nominally reduced (15%, 9% and 30% at the 3 top dose levels), but only the value at 600 ppm were considered to be biologically significant.

Pup weights were reduced on lactation day 21 (≥ 11% from control) in the ≥ 150 ppm dose groups, at lactation day 14 (≥ 20% from control) in the ≥ 400 ppm dose groups and at lactation day 7 (26% from control) in the 600 ppm dose group.

The offspring LOAEL is 150 ppm (22.9 mg/kg/day) based on tremors in pups during lactation days 8 to 17 and pup weight decreases lactation day 21 at 150 ppm (22.9 mg/kg/day). The offspring NOAEL is 50 ppm (7.8 mg/kg/day). The parental LOAEL is 400 ppm (59.6 mg/kg/day based on decreased body weight gain during lactation and ataxia and hind leg splaying in parental females during lactation days ≥ 11 and the parental NOAEL is 150 ppm (22.9 mg/kg/day).

Classification: This study is acceptable nonguideline for a pilot 1-generation reproduction study. It is acceptable for its intended purpose to determine dose levels for a guideline study (83-4), which will be reviewed after submission.

Dosages for the LOAEL and NOAEL were calculated from weekly mean test material consumption during lactation (Table 7) because both the large variation in consumption values (standard deviation) and the increased test material consumption during the time that the effects were noted.

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: PC Code 128831; Cyfluthrin, DER for a pilot single generation reproduction study in rats (MRID# 437929201).

Barcode: D220788. ToxChem No.: 266E.
Submission No.: S496545. PC No.: 128831.
MRID No.: 43792901. Case No.: 003677.
CAS Reg No.: 68359-37-5.

From: David G Anderson, PhD David G Anderson 12/16/96
Section 3, Toxicology Branch-1
HED (7509C)

To: George Larocca/John Hebert PM 13
Insecticide-Rodenticide Branch
RD (7505C)

Thru: Edwin Budd, Acting
Section 3 Head, Toxicology Branch-1
HED (7509C)

Attached is a DER for a pilot single generation reproduction study in rats. The results from this study may indicate the need for a developmental neurotoxicity study in rats because neurotoxic signs (tremors) were noted in pups at a lower dose levels than toxic signs were noted in the mothers. In addition, cyfluthrin causes neurotoxic signs in lactating mothers. The reference to the study and the executive summary from the study are presented below.

CITATION: DA Eigenberg and HE Hoss (1995) Pilot study to establish dose levels for a two-generation reproduction study in rats using technical grade cyfluthrin administered via diet. Testing Lab. Bayer Corp. Ag. Div., Toxicology, 17745 South Metcalf, Stilwell, KS 66085-9104. Lab. Report No. 92-972-SH & 107010. August 21, 1995. MRID# 43792901. Unpublished.

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data, necropsy data, testes and ovarian weights were collected.

The most notable effects seen in the study were hind leg splaying in lactating dams at 400 (4/10 dams)and 600 ppm (9/10 dams) and ataxia at 400 (4/10 dams), 600 ppm (9/9 dams), in addition to tremors in pups at 150 (7/10 litters), 400 (7/10 litters) and 600 ppm (4/9 litters) on day 8-17 of lactation. The ataxia and splayed hind legs in dams maybe due to the higher test material consumption during week 2 and 3 of lactation (≥ 89.2 mg/kg/day), which was ≥ 228% higher than the highest premating dose levels of 27.2 mg/kg/day at 400 ppm. Therefore, the effects in dams are probably due to increased test material consumption rather than to a change in sensitivity. However, the tremors in pups occurred at lactation days 8 to 17, starting at a dietary dose level of 150 ppm (20.3 to 23.8 mg/kg/day). Pups generally begin eating the mothers diet around lactation day 14, but the amount and when the pups started eating the mother's diet was not reported. It would appear most likely that the pups with tremors were dosed mostly through the mother milk supply rather than through eating the diet.

P female body weight (6% from control at 600 ppm) and weight gain was reduced premating and gestation (≥ 27% from control) during gestation at 600 ppm and lactation (≥ 52% from control) at ≥ 400 ppm. Food consumption was decreased during these periods of female weight reduction, but food efficiency was also nominally reduced (15%, 9% and 30% at the 3 top dose levels), but only the value at 600 ppm were considered to be biologically significant.

Pup weights were reduced on lactation day 21 (≥ 11% from control) in the ≥ 150 ppm dose groups, at lactation day 14 (≥ 20% from control) in the ≥ 400 ppm dose groups and at lactation day 7 (26% from control) in the 600 ppm dose group.

The LOEL for reproductive effects is 150 ppm (22.9 mg/kg/day) based on tremors in pups during lactation days 8 to 17 and pup weight decreases lactation day 21 at 150 ppm (22.9 mg/kg/day). The NOEL for these reproductive (pup) effects is 50 ppm (7.8 mg/kg/day). The LOEL is 400 ppm (59.6 mg/kg/day based on decreased body weight gain during lactation and ataxia and hind leg splaying in parental females during lactation days ≥ 11.; which corresponded to a NOEL = 22.9 mg/kg/day).

Classification: This study is acceptable (NG) for a pilot 1-generation reproduction study. It is acceptable for its intended purpose to determine dose levels for a guideline study (83.4), which will be reviewed after submission.

Dosages for the LOEL and NOEL were calculated from weekly mean test material consumption during lactation (Table 7) because both the large variation in consumption values (standard deviation) and the increased test material consumption during the time that the effects were noted.

EPA Reviewer: David G Anderson, PhD David G Anderson 12/16/96
Review Section 3:
Secondary Reviewer: Edwin Budd
Review Section 3:

DATA EVALUATION RECORD

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(20.3 to 23.8 mg/kg/day). Pups generally begin eating the mothers diet around lactation day 14, but the amount and when the pups started eating the mother's diet was not reported. It would appear most likely that the pups with tremors were dosed mostly through the mother milk supply rather than through eating the diet.

P female body weight (6% from control at 600 ppm) and weight gain was reduced premating and gestation (≥ 27% from control) during gestation at 600 ppm and lactation (≥ 52% from control) at ≥ 400 ppm. Food consumption was decreased during these periods of female weight reduction, but food efficiency was also nominally reduced (15%, 9% and 30% at the 3 top dose levels), but only the value at 600 ppm were considered to be biologically significant.

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

I. MATERIAL AND METHODS:

A. MATERIALS

1. Test material: Baythroid™, see Figure 1
   Description: Brown viscous liquid
   Lot/Batch #: 2030025 (Res sample stock)
   Purity: 95.9% ai - 11/5/92; 96.2% ai - 6/10/93.

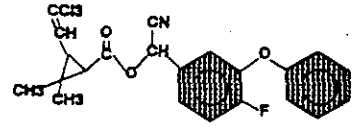

Figure 1: Baythroid™

2. Vehicle: Acetone and corn oil

3. Test animals: Sprague Dawley rats
   Age at start of dosing: 10 weeks

Weight at start of dosing;
P Males: 303-307 g
P Females: 203-209 g
Source: SASCO, St Louis, MO.
Housing: Stainless steel cages over deodized cage board, premating. Individually after gestation and lactation; changed 2-3 time per week.
Diet: Purina Rodent Chow 5001-4 Etts form, *ad libitum*
Water: Analyzed periodically for contaminants, *ad libitum*
Environmental conditions:
Temperature: 18-26°C
Humidity: 40-70%
Air changes: Not presented
Photoperiod: 12 hr light 12 hours dark
Acclimatization period: 2 weeks

B. PROCEDURES AND STUDY DESIGN

1. Mating procedure: Following 4 weeks of diet administration, 1 male was cohoused with 1 male for a maximum of 7 consecutive days. Females were checked for sperm each day and separated from males when sperm was found. There was no indication that any animals were remated.

After sperm was found, females were housed individually in solid bottomed cages through gestation and lactation.

2. Study schedule: The P parental animals were given test diets for 4 weeks before mating and F1a litters (the only litters produced) were reduced to 8 pups per litter on post natal day 4 (smaller litters were not reduced in size) and P parental females and F1a pups were sacrificed about day 28 of lactation. P parental males were sacrificed after mating.

3. Animal assignment: P animals were randomly assigned to test groups as seen in Table 1. To aid in understanding the timing of events during the study, a time line of events is presented in Table 2 and in greater detail in Table 12 in the Appendix.

4. Dose selection rationale: This is a range-finding study and were based on previous studies.

5. Dosage preparation and analysis: All analyses indicated that homogeneity, stability and concentrations were within acceptable ranges.

Test material was dissolved in acetone/corn oil and added to the feed and mixed in the diet at 1% corn oil. Storage temperature was not stated. Diet was prepared weekly. Homogeneity (triplicate samples were taken from the top, middle and bottom of the mixing bowl) was checked on the 50 and 600 ppm samples. Mean values were 99.2% of nominal, CV equals 8%. Stability on room temperature stored samples was determined for 1 week. Mean values at 50 ppm ranged from 100% to 116% and at 600 ppm from 85.6% to 108% of nominal. Concentrations determined and the mean values of nominal and CVs were, respectively: at 50 ppm (103%, CV = 11%), at 150 ppm (93%, CV = 11%), at

400 ppm (92%, CV = 5%) and at 600 ppm (100%, CV = 8%).

TABLE: 1 Animal assignment and mean analytical concentrations[a].

Test group	Dose in diet (ppm)	Analytical dose levels (ppm)	Animals/group[b]			
			P Males	P Females	F1 Males	F1 Females
Control	0	0	10	10	NA	NA
Low (LTD)	50	50.1	10	10	NA	NA
Mid (MTD1)	150	139	10	10	NA	NA
Mid (MDT2)	400	366	10	10	NA	NA
High (HDT)	600	598	10	10	NA	NA

[a] = Data extracted from submitted study report, MRID# 43792901, page 16 and 65.
NA = Not applicable
[b] = Doses were administered from start of the study to sacrifice.

TABLE 2: Time line for study events[a]

Days dosed and on study (± 1 day)	Event
0-28	Premating dosing
29-35	Males sacrificed at end on mating, day 36-37
-	Gestation, ranged 21 to 23 days
51-57	Parturition; ranged due to days to mating and gestation length.
61-67	Lactation day 8, 9, 10; pups developed tremors at 150 ppm
65-71	Lactation day 14; other pups developed tremors at ≥ 150 ppm and 4 dams 400 ppm and 8 dams at 600 ppm developed splayed hind legs and ataxia on days 63,66,70
72-70	Lactation day 21; pups weaned
about 78	All weanlings and dams sacrificed by this day

[a] = Data extracted from the submitted report, MRID# 43792901, pages 82, 83, 85, 86, 87, 136, 140, 141, 145, 146, 147, 162, 163, 164 and 165.

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72-70	Lactation day 21; pups weaned
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C. OBSERVATIONS

1. Parental animals: Observations and the schedule for those observations are summarized from the report. Twice daily observations were conducted for morbidity, mortality and clinical signs at cage side. Once per week, animals were removed from the cage and detailed clinical observations conducted. Estrous cyclicity was conducted daily for 2 weeks prior to mating. Animals were weighed and food consumption determined weekly premating, day 0, 6, 13 and 21 during gestation and 0, 4, 7, 14 and 21 of lactation. Food consumption was determined once per week during gestation and during week 2 and 3 of lactation.

2. Litter observations: Litters were observed at birth, post natal day 1, 4, 14 and 21. Litters were sacrificed on post natal day 28. Observations included clinical signs, live and dead pups, pup weight, external alterations and sex (Table 3).

On day 4 postpartum, litters were standardized to a maximum of 8 pups/litter (4/sex/litter); excess pups were necropsied.

Dead pups were examined grossly for external and internal abnormalities and possible cause of death.

TABLE 3: F1a litters observations[a]

Observations	Day of observation at lactation					
	0	4[b]	4[c]	7	14	21
Live pups #	Y	Y	Y	Y	Y	Y
Pup wt	Y	Y	Y	Y	Y	Y
External alterations	N	N	N	N	N	N
Dead pups #	Y	Y	Y	Y	Y	Y
Sex #Male/#Female	Y	Y	Y	Y	Y	Y
Other observations	Y	Y	Y	Y	Y	Y

[a] = Data seen or could be extracted from in the submitted report, MRID# 43792901, various pages.
[b] = Before standardization
[c] = After standardization

3. Postmortem observations:

1. Parental animals: Males were sacrificed after mating and females were sacrificed about day 28 of lactation and subjected to necropsy. The following tissues were weighed and examined: testes and ovaries.

2. Offspring: The F1a litters (the only litters produced) were sacrificed about day 28 of lactation and subjected to gross necropsy.

D. DATA ANALYSIS

1. Statistical analyses: The usual statistical analyses were conducted.

2. Indexes: Viability (%) = [(#live pups/litter)/(#live pups born or base #)] X 100.

Other reproductive indexes were either not reported or showed no dose related changes.

3. Historical control data: No data was provided.

II. RESULTS:

A. PARENTAL ANIMALS and OFFSPRING

1. Observations, mortality and clinical signs:

There were no clinical signs or death occurred in P males or in P females, premating, but females showed hind splaying and ataxia during week 2 and 3 of lactation at 400 and 600 ppm (Table 4). This observation was noted on day 63 to 70 after the start of administration of the test material. This would have been from lactation day 11-19, but mostly ≥ day 14.

In addition, tremors occurred in pups as early as lactation day 8 at 150 ppm. It can be seen in Table 7 that lactating females at 400 and 600 ppm displayed splaying of the hind limbs and ataxia at higher dose levels 89.2 to 137.0 mg/kg/day than the preweanling pups displayed tremors (lactating dams consuming ≥ 20.3 to 23.8 mg/kg/day). The timing of the tremors in pups (lactation day 8-17) indicates that the pups were probably getting most of the test material via the milk supply not through the food supply although later in lactation (about day 14) the food supply was also a source of test material for the pups.

During lactation (lactation day ≥ 8 and dam dosages of ≥ 20.3 to 23.8 mg/kg/day), pups showed tremors at 150, 400 and 600 ppm and unthriftiness at 600 ppm (Table 4).

TABLE 4: Observation results on adult females during lactation[a] and pups[b]

Observation	Dose group (ppm) for P females				
# with observ. (%)	Control	50	150	400	600
Number animals observed	10	10	10	10	10
Hind limb spaying (study day 62-72, last lactation week or at weaning)	0	0	0	4 (40)	9 (90)
Ataxia	0	0	0	4 (40)	9 (90)
Food spiller	1 (10)	0	1 (10)	0	1 (10)
	Dose group for F1a pups (ppm)				
# with observ. (%)	Control	50	150	400	600
#F1a pups	86	89	112	114	96
Cannibalized/bite marks	0	4	0	0	0
Missing/moribund/sacrificed	0	0	0	0	4
Tremors (# litter/total #) (tremors-lactation day ≥ 8)	0 (0/10)	0 (0/7)	38 (7/10)	41 (7/10)	18 (4/9)
Lactation days tremors seen[c]			8 to 15	9 to 17	10 to 15
Unthrifty	0	0	0	0	8

[a] = Data extracted from submitted report, MRID# 43792901, page 30 and 31 (Sum Clinical Observ.)
[b] = Data extracted from submitted report, MRID# 43792901, page 55 (Table 11)
[c] = All tremors were seen in some pups in the litter and only 1-2 days during the lactation day 8-15 period.

2. Parental (P) body weight and food consumption: P male body weight was nominally reduced (7%, $p \geq 0.05$) at the HDT and P female premating body weight (6%, $p \leq 0.05$) and gestational body weight gain (27%, $p \leq 0.05$) were statistical significantly reduced at 600 ppm. In addition, during lactation body weight gain in females was reduced 52%, $p \leq 0.05$, at 400 ppm and 87%, $p \leq 0.05$, at 600 ppm (Table 5).

Food consumption in premating males was statistical significantly reduced (23%) at 600 ppm. Food consumption in premating females was statistical significantly reduced at 150, 400 and 600 ppm during the first week, but may not have been due to palatability; in addition an apparent reduction in relative efficiency of food utilization at 150, 400 and 600 ppm (reduced 15%, 9% and 30% of control at the latter 3 dose levels, however only the reduction at 600 ppm was considered to indicated reduced efficiency) between premating day 21 and 28 (Table 6).

TABLE 5: Parental (P) body weight and food consumption[a]

Parameter	Group (ppm)				
	Control	50	150	400	600
	P males (10)				
Mean BWt. (g), Day 28	370.5	345.3	361.2	361.2	344.0
Mean BWt. (g), Day 0	306.8	303.6	303.3	306.8	303.8
Food (g/anim/day), Day 28	23.84	20.81	22.97	22.47	21.25
Food (g/anim/day), Day 7	23.29	21.99	21.38	21.05	17.89*

Female parameters listed on the next page

Parameter	Group (ppm)				
	P females (10, premating, # anim. not given during lactation)				
Mean BWt. (g), Day 28	229.8	230.7	221.9	224.1	217.1*
Mean BWt. (g), Day 0	208.6	206.3	204.7	205.8	203.5
Wt gain	21.2	24.4	17.2	18.3	13.6
	Mean weekly female food consumption (g/animal/day)				
Relative food (g/anim/day), mean from day 21-28	16.66	16.76	15.89	15.86	15.27*
Food (g/anim/day), Day 0-7	18.21	17.86	16.11*	15.54*	13.39*
Relative food efficiency day 21-28	1.27	1.46	1.08	1.15	0.89
BWt gain during gestation/# anim (g)	131	123	118	115	96*
Food consumption during gestation at GD 14-20 (g)	162	164	149*	153	143*
BWt gain during lactation (g)	31	24	38	15*	4*
Relative food consumption during lactation at LD 14-21 (g)	495	447	479	475	405

[a] = Data was extracted form MRID# 43792901, Tables on pages 33, 34, 36, 37, 39 & 40.
* = statistically significant at $p \geq 0.05$. GD = gestational day. LD = Lactation day. BWt. = Body weight

TABLE 6: Mean body weight and weight gain in P females during gestation and lactation[a].

Level (ppm)	Mean body weight (g)										
	GW0	GW6	GW13	GW20	GWCHG	LW0	LW4	LW7	LW14	LW21	LWCHG
Control	240	254	284	362	131	274	285	293	312	305	31
50	234	255	283	358	123	277	287	294	308	302	24
150	227	251	274	346	118	269	282	293	311	307	38
400	224	248	271	339	115	267	261*	268*	276*	281*	15*
600	219	237*	256*	315*	96*	250*	238*	247*	251*	254*	4*

[a] = Data extracted from Tables in the submitted report, MRID# 43792901, page 40. * = statistically significant at $p \leq 0.05$. GW# = gestation weight on day #. GWCHG = gestation weight change day 0 to 21. LW# = lactation weight day #. LWCHG = lactation weight change LD 0 to LD 21

3. Test material intake: Test material intake was determined during the premating period, gestation period and lactation period to show the intake during lactation when the neurotoxicity signs occurred (Table 7).

TABLE 7: Test material consumption in premating males and females and in females at various periods during gestation and lactation[a]

Dose group	50 ppm	150 ppm	400 ppm	600 ppm	Dose group	50 ppm	150 ppm	400 ppm	600 ppm
	Mean test material consumption by males premating					Mean test material consumption by females premating			
Days 0-28	3.4	9.3	24.2	38.9	Day 0-28	4.1	10.5	27.2	43.9
Days	Test material consumption (mg/kg/day) during gestation in P females				Days	Test material consumption (mg/kg/day) during lactation in P females			
0-6	4.0	10.7	27.9	46.3	0-4	4.8	16.7	36.4	55.8
6-13	3.9	10.2	27.6	45.8	4-7	6.9	20.3	51.2	90.4
13-20	3.8	9.5	26.2	42.8	7-14	8.5	23.8	61.5	100.5
					14-21	10.8	30.8	89.2	137.0
Mean	3.9	10.1	27.2	45.0	Mean	7.8	22.9	59.6	95.9
SD	0.1	0.6	0.9	1.9	SD	2.5	6.0	22.3	33.4

[a] = Data extracted from submitted report, MRID# 43792901, page 23, 117 and 118.

4. Reproductive function:

a. Estrous cycle length and periodicity: Estrous cyclicity was determined 2 weeks prior to mating and reported as mean number of cycles seen for the P females. No dose related effects on the number of cycles or the average length of estrous cycles were seen in P females. The results in P females indicated that in control, 50, 150, 400 and the 600 ppm dose groups, 2 cycles with a mean of 4.3 days, 2 cycles with a mean of 4.0 days, 3 cycles with a mean of 4.1 days, 2 cycles with a mean 4.3 days and 2 cycles with a mean of 4.3 days, respectively, were seen.

b. Sperm measures: No sperm parameters were determined.

c. Sexual maturation (F1a): Sexual maturation parameters were not studied.

5. Reproductive performance: No effects were noted on reproductive performance. Results for the parental animals are summarized from the report in Table 8.

TABLE 8: Reproductive performance[a]

Observation	Control	50 ppm	150 ppm	400 ppm	600 ppm
		Males			
Mean precoital interval (days)	3	2	4	3	2
Number mated	9	10	10	10	10
Number sperm positive	9	9	10	10	10
Fertility not determined	3	2	0	0	1
Intercurrent deaths	0	0	0	0	0
		Females			
Number mated	9	10	10	10	10
Number fertile (probable)	7	8	10	10	9
Fertility not determined	3	2	0	0	1
Intercurrent deaths	0	0	0	0	0
Medium gestation days	22	22	22	22	22
Number litters	7	8	10	10	9
Number litters with implantation sites	7	8	10	10	9
Mean implantation sites	13	13	13	12	11

[a] = Data extracted from submitted report, MRID# 43792901, Tables on pages 131, 132, 133, 134, 135, 137, 138, 139, 140, 141, 143, 144, 145, 146, 147, 149, 150, 151, 152, 153.

5. Parental postmortem results

a) Organ weights: The report noted no dose related effects on testes weights or ovarian weights. Absolute ovarian weights at 600 ppm were 75% of control weights and were statistically significantly reduced, but the relative ovarian weights were not (Table 9).

TABLE 9: Testes and ovarian weights in P males and female[a]

Parameter	Groups (ppm)				
	0	50	150	400	600
	P males day 36 (10 animals per group)				
Body weight (g)	379.2	360.1	359.9	369.3	355.6
SD	26.9	33.5	31.6	21.9	30.4
Testes weight (g)	3.601	3.500	3.689	3.552	3.524
SD	0.342	0.358	0.342	0.386	0.473
Test/Body weight	0.956	0.980	1.030	0.963	0.994
SD	0.129	0.144	0.110	0.098	0.136
	P female day 49 (10 animals per group)				
Body weight (g)	281.8	282.8	293.1	269.7	249.4
SD	24.5	18.9	13.9	21.8	14.1
Ovarian weight (g)	0.121	0.126	0.115	0.106	0.091*
SD	0.018	0.017	0.017	0.012	0.014
Ovarian weight/body weight	0.043	0.045	0.039	0.039	0.037
SD	0.007	0.008	0.006	0.005	0.005

[a] = Data extracted from submitted report, MRID# 43792901, tables on pages 234, 235, 236, 236, 237, 238, 239, 240, 241, 242 & 243. SD = Standard deviation. * = Statistically significant.

b) Pathology

1) Macroscopic examination: The report noted no dose relate effects

2) Microscopic examination: No effects were reported from microscope examination if conducted.

1. Viability and clinical signs: The following findings were reported.

No dose related effects were seen on viability (Table 10). Mean litter size and viability results from pups during lactation are summarized from the report in Table 10. The only clinical signs seen were

tremors and are reported under Observations.

TABLE 10: Mean litter size and viability[a]

Observation	Dose group (ppm)				
	0	50	150	400	600
		F1a generation			
# litters	7	8	10	10	9
Total # pups born	86	89	112	114	96
Mean litter size	12.3	11.1	11.2	11.4	10.7
Day 0	12	10	11	11	11
Day 4a	12	10	11	11	10
Day 4b	8	7	8	8	8
Day 7	8	7	8	8	8
Day 14	8	6	8	8	8
Day 21	8	6	8	8	8
Number live pups					
Day 0	86	77	112	113	95
Day 4a	86	76	112	113	94
Day 4b	55	53	80	80	71
Day 7	55	52	80	80	71
Day 14	55	51	80	80	70
Day 21	55	51	80	80	70
Dead at birth	0	12	0	1	1
Number deaths					
Day 0-4	0	1	0	1	0
Day 4-21	0	1	0	0	1
Survival indices					
Viability index day 21	98	92	100	100	99
Lactation index	NC	NC	NC	NC	NC
Sex ratio %Male/%Female	47/53	52/44	55/45	41/59	48/52

[a] = Data extracted from the submitted report, MRID# 43792901, pages 57, 167, 168, 169, 170, 171, 173, 174, 175, 176, 177, 178, 179, 180, 181 and 182.
NC = Not calculated

The report stated that the clinical observations during lactation included in a previous section on parental and offspring observations, mortality and clinical signs. The results of these observations are as follows. Tremors were noted in pups starting from lactation day 8 through 17 at 150, 400 and 600 ppm (Table 4 and 12).

2. Body weight: Offspring body weights were reduced 26% by day 7 at 600 ppm, ≥ 20% by day 14 at 400 and 600 ppm and ≥ 11% by day 21 at 150, 400

and 600 ppm, respectively. Selected mean pup body weight data are presented in Table 11.

TABLE 11: Mean liter weight[a]

Day of Lactation	Group (ppm)				
	0	50	150	400	600
	F1a pups weights(g)				
Day 0	6.9	6.7	6.7	6.6	6.3
Day 4[b]	NC	NC	NC	NC	NC
Day 4[c]	10.0	10.5	10.3	9.7	8.5
Day 7	15.5	16.0	15.2	13.5	11.7*
Day 14	30.3	30.5	27.3	24.1*	21.1*
Day 21	47.9	48.5	42.4*	37.5*	32.6*

[a] = Data extracted from the submitted report, MRID# 43792901, page 63.
NC = Not calculated

3. Offspring postmortem results:

a) Organ weights: No organs from offspring were weighed.

b) Pathology:

1) Macroscopic examination: No dose related pathology was reported.

2) Microscopic examination: No dose related pathology was reported.

III. DISCUSSION:

A. INVESTIGATORS' CONCLUSIONS: Parental females at 400 and 600 ppm developed compound related hind leg splaying during the second and third weeks of lactation and compound related lower body weights and/or body weight gains during the premating and gestation periods . Pups developed compound related tremors and lower body weights at 150, 400 and 600 ppm. The investigator's concluded the NOEL for the study was 50 ppm with a LOEL of 150 ppm based on tremors and reduced pup weight.

The reduction in food consumption, premating females at 150, 400 and 600 ppm during the first week of the study and in males at 600 ppm were not considered to be biologically insignificant.

B. REVIEWER'S DISCUSSION: No clinical signs or death occurred in males or in females, premating, but females showed hind leg splaying and ataxia during

week 2 and 3 of lactation at 400 and 600 ppm (Table 4). This observation was noted mostly on day 63 to 70 after the start of administration of the test material. This would have been approximately the last 2 weeks of lactation, about lactation day 10 to 19, i.e., at maximal food and test material consumption by the dams occurred. The report attributed this to the increased test material consumption during the lactation period. This may be true since females dosed at 400 ppm during lactation consumed more test material than premating females at 600 ppm; 109% more between lactation day 4-7, 131% more between lactation day 7-14 and higher later in lactation (lactation day 14-21). However, no data was supplied on the proportion of test material consumption by pups/adult females during various periods during lactation and pup test material consumption is minimal during the day 7-14 of lactation. In addition, tremors occurred in pups as early as lactation day 8 at 150 ppm. It can be seen in Table 7 that lactating females displayed splaying of the hind limbs and ataxia at higher dose levels (400 and 600 ppm) (89.2 to 137.0 mg/kg/day) than the preweanling pups displayed tremors (lactating dams consuming ≥ 23.8 mg/kg/day). The timing of the tremors in most pups (lactation day 7-14) indicates that the pups were probably getting the test material via the milk supply not through food supply although later in lactation (after day 14) the food supply was also a source of test material for the pups.

During lactation (lactation day ≥ 8 and dam dosages of ≥ 23.8 mg/kg/day), pups showed tremors at 150, 400 and 600 ppm and unthriftiness at 600 ppm (Table 4).

Cyfluthrin may fit the preselected criteria of neurotoxicity and for requiring a neurotoxicity developmental study to determine the NOEL for neurotoxicity. These effects, especially on pups suggest that cyfluthrin may have a lower NOEL. In addition, the dose level at which neurotoxicity developed in pups was comparable, but lower than dose level at which maternal toxicity developed.

Dosages for the LOEL and NOEL were calculated from weekly mean test material consumption during lactation (Table 7) because both the large variation in consumption values (standard deviation) and the increased test material consumption during the time that the effects were noted. The means from the overall lactation period were considered to be more reliable and conservative than the weekly means during lactation.

The LOEL for reproductive effects is 150 ppm (22.9 mg/kg/day) based on tremors in pups during lactation days 8 to 17 and pup weight decreases lactation day 21 at 150 ppm (22.9 mg/kg/day). The NOEL for these reproductive (pup) effects is 50 ppm (7.8 mg/kg/day). The LOEL is 400 ppm (59.6 mg/kg/day based on decreased body weight gain during lactation and ataxia and hind leg splaying in parental females during lactation days ≥ 11.; which corresponded to a NOEL = 22.9 mg/kg/day).

C. STUDY DEFICIENCIES: The study was a pilot study and as such it has many of the deficiencies expected of a pilot study. Although this pilot study was successful for its designed purpose and in many other respects, it was

inadequate in number of animals, observations, necropsy, behavioral parameters and pathology and other endpoints to determine a probable NOEL.

APPENDIX: Table 12 of individual animals observation data on lactating dams and offspring.

TABLE 12: Individual animal data on splaying and ataxia[a] and pup tremors[b]

A#	IDs	GDs	LD0	SplD	LD of Spl	PPD[c]	SacD
				150 ppm			
2101	7	22	57	0	-	9-9	78
2102	4	23	55	0	-	8-11	76
2103	4	22	54	0	-	0	75
2104	4	22	54	0	-	15-15	75
2105	4	22	54	0	-	15-15	75
2106	4	22	54	0	-	9-14	75
2107	2	22	52	0	-	11-11	73
2108	3	21	52	0	-	0	73
2109	2	21	51	0	-	0	72
2110	2	21	51	0	-	12-14	72
Mean	4	22	53.4	0	-		-
A#	IDs	GDs	LD0	SplD	LD of Spl	PPD[c]	SacD
				400 ppm			
3101	7	21	56	0	-	9-16	78
3102	-	-	?	-	-	12-16	73
3103	3	22	53	0	-	10-14	74
3104	1	22	51	0	-		72
3105	2	22	52	66,70	14,18	12-12	73
3106	3	22	53	0	-	0	74
3107	2	21	51	0	-	12-17	72
3108	1	22	51	70	19	12-15	72
3109	1	22	51	70	19	13-15	72
3110	4	22	54	66,70	12,18	12-12	75
Mean	3	22	52.4				

A#	IDs	GDs	LD0	SplD	LD of Spl	PPD[c]	SacD
				600 ppm			
4101	2	22	52	63,70	11,18	13-14	73
4102	1	22	51	63,70	12,19	0	72
4103	3	22	53	70	17	12-12	74
4104	4	22	54	66,70	12,16	10-15	75
4105	1	22	51	63,70	12,19	0	72
4106	4	23	55	66,70	11,15	10-14	76
4107	2	21	51	63,70	12,19	0	72
4108	1	22	51	66,70	15,19	0	72
4109	2	-	?	0	?	0	55
4110	2	22	52	70		unthrifty	73
Mean	2	22	52.2				

[a] = Data extracted from submitted report, MRID# 43792901, pages 82, 83, 85, 86 and 87.
[b] = Data extracted from submitted report, MRID# 43792901, pages 162, 163 and 164.
[c] = Ranges of days for tremors in litter, but pups in litter showed tremors on different lactation days and showed tremors ranging from 1 to 2 days in individual pups.
A# = Animals number. IDs = Days to insemination. GDs = Days of gestation. LD0 = Days on study at lactation day 0. SplD = Days on study to observation of hind leg splaying and ataxia. LD of Spl = Lactation day corresponding to SplD. PPD = Postpartum day when pup tremors were seen. SacD = Days to sacrifice.

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