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PC 128631

DATA EVALUATION RECORD

FCR 4545 Technical (β-CYFLUTHRIN)

Study Type: 83-3a; Developmental Toxicity Study with FCR 4545 in the Wistar Rat

Work Assignment No. 2-59.1 (MRID 44116501)

Prepared for

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DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study - Rat
OPPTS Number: 870.3700 OPP Guideline Number: §83-3a

DP BARCODE: D230589 SUBMISSION CODE: S512824
P.C. CODE: 128831 TOX. CHEM. NO.: 266E

TEST MATERIAL (PURITY): FCR 4545 Technical (β-Cyfluthrin, 96.5-97.3% a.i.)

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

CITATION: Astroff, A.B., (1996) A Developmental Toxicity Study with FCR 4545 Technical in the Wistar Rat. Bayer Corporation, 17745 South Metcalf, Stillwell, Kansas. Laboratory Study No. 95-612-EW, September 4, 1996. MRID 44116501. Unpublished.

SPONSOR: Bayer Corporation, Agriculture Division, Box 4913, Hawthorn Road, Kansas City, Missouri

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 44116501), FCR 4545 Technical (96.5-97.3% a.i.) was administered by gavage to 30 female Wistar rats/dose in aqueous 1% Cremophor solution at dose levels of 0, 3, 10, or 40 mg/kg/day from days 6 through 15 of gestation.

Maternal toxicity was noted at 10 mg/kg/day by reduction in mean food consumption (.10-15%, $p \leq 0.05$ or 0.01) with recovery of appetite following treatment. Mean body weights and mean body weight gains were not significantly reduced, however, mean adjusted terminal weights were significantly reduced (.14%, $p \leq 0.05$) at 10 mg/kg/day. Clinical signs of toxicity were absent. Maternal toxicity at 40 mg/kg/day included reduced survival (↓10%), mean body weight gains (↓56%, $p \leq 0.01$, Days 6-16 and .16%, $p \leq 0.01$, Days 0-20), weight gain (↓32%, $p \leq 0.01$) corrected for gravid uterine weights, and reduced mean food consumption during treatment (↓20-49%, $p \leq 0.01$). Clinical signs of toxicity included hypoactivity, locomotor incoordination, and salivation.

The maternal LOAEL is 10 mg/kg/day, based on reduced body weight gain and reduced food consumption with post-treatment recovery. The maternal NOAEL is 3 mg/kg/day.

The developmental LOAEL is 40 mg/kg/day, based on reduced fetal body weights and increased skeletal variations. The developmental NOAEL is 10 mg/kg/day.

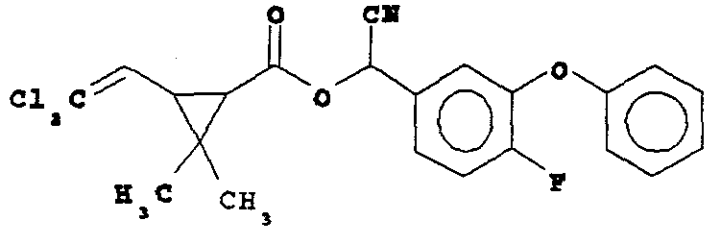
This developmental toxicity study is classified **Acceptable** and satisfies the guideline requirements for a developmental toxicity study (**§83-3a**) in rats.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: FCR 4545 Technical
   Description: Cream colored powder, stable at least 14 months
   Lot/Batch #: 3030125
   Purity: 96.5-97.3% a.i.
   CAS #: 68359-37-5
   Structure:



2. Vehicle: 1% Cremophor in municipal tap water

3. Test animals: Species: Rat
   Strain: Wistar
   Age at mating: 12-15 weeks
   Weight at mating: 179.9-271.4 g (on gestation day 0)
   Source: Harlan Sprague-Dawley, Dublin, VA
   Housing: Individually (prior to mating) in suspended stainless steel cages, then (sperm positive females) individually in plastic cages with corn cob bedding.
   Diet: Rodent Lab Chow 5001-4, ad libitum
   Water: Municipal tap water, ad libitum
   Environmental conditions:
   - Temperature: 17.8-25.6 C
   - Humidity: 40-70%
   - Air changes: Not reported
   - Photoperiod: 12 hrs dark/12 hrs light

   Acclimation period (P): ≥6 days

B. PROCEDURES AND STUDY DESIGN

1. In life dates - Start: 11/06/95 End: 12/06/95

2. Mating: Females were co-housed with a maximum of two females per male of the same strain. Day 0 of gestation was designated as the day sperm were found in a vaginal smear.

3. Animal Assignment: Mated females were randomly assigned to dose groups as indicated in Table 1.

Table 1. Animal Assignment

Test Group	Dose (mg/kg/day)	Number of Females
Control	0	30
Low (LDT)	3	30
Mid (MDT)	10	30
High (HDT)	40	30

4. Dose selection rationale: In a range-finding study, summarized but not included in the current submission, FCR 4545 was administered to rats by oral gavage, once daily from day 6 through day 15 of gestation at dosages of 0, 1, 3, 10, or 30 mg/kg/day. No mortality was observed at any dose. Clinical signs of toxicity observed in the high dose group were hypoactivity, salivation, oral stain, and locomotor incoordination. There was a 24% net decrease in body weight gain at 30 mg/kg/day and food consumption was decreased by 10-55% throughout dosing. No other compound-related maternal effects were observed. No compound-related embryotoxicity or fetal effects were observed at any dose level.

   Based on the results of this range-finding study, 40 mg/kg/day was selected as the high dose to ensure significant maternal effects at the high dose for the subsequent full developmental toxicity study in rats. Low- and mid-dose levels chosen were 3 and 10 mg/kg/day, respectively.

5. Dosage preparation and analysis

   The test article was analyzed three times for percent active ingredient over a 14 month period. Stock test substance formulations were prepared prior to the first day of dosing by mixing appropriate amounts of test substance in 1% aqueous Cremophor. The concentration of test ingredient in each stock solution was analyzed and stocks were stored under refrigeration temperatures for the duration of the study. The homogeneity and stability of FCR 4545 in 1% Cremophor was tested prior to study initiation for stock solutions stored at refrigeration temperature. Three aliquots of test concentrations at 0.08 and 20.0 mg/mL were analyzed for homogeneity. These same solutions were tested for stability for up to 35 days following preparation.

Results:

Chemical Purity Analysis: The percent active ingredient found at the three test intervals was 96.5, 97.3 and 96.9%.

Homogeneity Analysis: The mean test value for three aliquots from a 0.08 mg/mL sample of FCR 4545 in 1% aqueous Cremophor was 0.0737 mg/mL (CV=1.5%) and for a 20.0 mg/mL sample was 19.2 mg/mL (CV=3.0%).

Stability Analysis: Analysis of test solutions after 0, 7, 14, 21, 28, and 35 days of refrigerated storage, resulted in a range of 99-102% of nominal for a 0.08 mg/mL sample and 100-104% for a 20.0 mg/L sample.

Concentration Analysis: The actual concentrations for the 3, 10, and 40 mg/kg doses prepared and administered on days 6 through 15 of gestation were 2.71, 9.42, and 41.96 mg/kg, respectively (90.4-104.9% of 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.

6. Dosage administration: All doses were administered once daily by gavage, on gestation days 6 through 15, in a volume of 10 ml/kg of body weight/day. Dosing was adjusted daily, based on the most recent body weight determinations.

C. OBSERVATIONS

1. Maternal Observations and Evaluations - The animals were checked twice daily for mortality, moribundity, behavioral changes, and clinical signs of toxicity on Gestational Days 0-19 and once on Day 20 of gestation. Detailed clinical observations were performed at least once daily on weekends and holidays. Body weights were recorded on Gestational Days 0, 2, 4, 6 through 16, 18, and 20. Food consumption data were recorded for Gestational Days 2, 4, 6 through 16, 18, and 20. Dams were sacrificed on day 20 of gestation. Examinations at sacrifice consisted of a gross external exam followed by gross necropsies of the thoracic, abdominal, and pelvic cavities. The reproductive tract was removed and the following data were recorded:
   - -number of corpora lutea in each ovary
   - -gravid uterine weights for uteri with visible implantations
   - -numbers and sites of implantations
   - -numbers of live and dead fetuses
   - -numbers of early and late resorptions
   - -placental weights

Dams found to be not pregnant at sacrifice were not examined further. Dams found dead were subjected to gross necropsies.

2. Fetal Evaluations - Each live fetus was weighed, sexed, examined for external abnormalities, and then euthanized. For each litter, approximately one half of the fetuses were fixed in 70% alcohol, eviscerated, processed, and evaluated for skeletal development. The remaining fetuses in each litter were processed for visceral examination, then placed in Bouin's solution. Prior to cranial examination, the fetuses were transferred to 70% alcohol and heads were sectioned according to Wilson's procedure (Wilson, 1965).

D. DATA ANALYSIS

1. Statistical analyses: All data collected were subjected to routine appropriate statistical procedures. For fetal observations, statistical analyses were performed on the numerical incidence values rather than the percent incidence on both a fetal and litter basis.

2. Indices: Pre-implantation and post-implantation loss indices were calculated from cesarean section records of animals in the study.

   Pre-implantation loss indices were calculated as:
   (# corpora lutea - # implantations)/# corpora lutea x 100

   Post-implantation loss indices were calculated as:
   (# implantations - # live fetuses/# implantations x 100

3. Historical control data: Historical control data were provided to allow comparison with concurrent controls.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: Three of the 30 animals in the 40 mg/kg/day group died on Gestation Days 7-8. Treatment-related clinical signs observed for the 40 mg/kg/day treatment group were hypoactivity, locomotor incoordination, and salivation. Sporadic, dose-independent hair thinning and oral staining were observed in all groups including controls. There were no deaths or treatment-related clinical signs of toxicity in the 3 or 10 mg/kg/day groups.

2. Body Weights and Weight Gain - There was no overall significant difference in mean maternal body weights at any treatment level, compared to controls, throughout the 0 through 20-day observation period (Table 2). Statistically

significant decreases in mean maternal body weights during the Days 6-9 of treatment for 10 and 40 mg/kg/day dams ($p \leq 0.05$ and 0.01, respectively) are shown in Table 3. Significant ($p \leq 0.01$) decreases in body weight (↓55%) occurred at the 40 mg/kg/day treatment level during the dosing period (Gestational Days 6-16) and (↓17%) throughout the course of the study. In addition, body weight gains, corrected for gravid uterine weights, were reduced at the mid- and high-doses by 14% ($p \leq 0.05$) and 32% ($p \leq 0.01$), respectively. Body weight gains were comparable to the controls during the post-treatment interval (days 16-20) at all dose levels. No significant difference in mean gravid uterine weights was observed at any treatment level compared to controls. Because the reduction in mean body weight gains observed during treatment for the 40 mg/kg/day group rebounded after treatment, this effect was considered treatment-related. The reduction in body gains for the mid-dose was also considered a treatment-related effect because the reduction during the initial dosing period (↓42%, $p \leq 0.05$) also rebounded in the post-treatment period and the overall body weight gain, corrected for gravid uterine weight was reduced. No significant treatment-related decrease in mean maternal body weight gain was observed at the 3 mg/kg/day treatment level.

Table 2. Group mean maternal body weights (g)[a]

Interval	Dose in mg/kg/day (# of Dams)			
	0 (27)	3 (24)	10 (21)	40 (20-26)
Pre-treatment: Day 0	218	219	226	225
Treatment: Day 6	238	237	243	242
Treatment: Day 9	245	242	247	233
Treatment: Day 12	256	254	258	243
Post-treatment: Day 16	276	273	278	260
Post-treatment: Day 20[b]	318 (263) **56**	317 (259) **58**	324 (264) **60**	309 (256) **53**

a Data extracted from study report Table 5 and Appendix IV, pages 37 and 116-123.
b Terminal body weights corrected for gravid uterine weights are shown parenthetically and gravid uterine weights are shown in bold.
* $p \leq 0.05$, ** $p \leq 0.01$

Table 3. Group mean maternal body weight gain (g)[a]

Interval	Dose in mg/kg/day (# of Dams)			
	0 (27)	3 (24)	10 (21)	40 (23-26)
Pre-treatment: Days 0-6	20.2	18.3	17.5	17.4
Treatment: Days 6-9	6.5	4.8	3.8*	-9.8**
Treatment: Days 9-12	11.5	12.6	10.4	9.2
Treatment: Days 12-16	20.3	18.9	20.4	17.4
Post-treatment: Days 16-20	42.0	43.4	45.8	49.3
Overall treatment: Days 6-16	38.4	36.3	34.8	17.2**
Overall pre-treatment through post-treatment: Days 0-20[b]	100.6 (44.8)	98.0 (40.1)	98.2 (38.5)*	83.6** (30.5)**

a Data extracted from study report Tables 2 and 5, pages 31 and 37.
b Data in parenthesis corrected for gravid uterine weights (net wt. change from day zero.
* $p \leq 0.05$, ** $p \leq 0.01$

3. Food Consumption - Food consumption data are presented in Table 4. During treatment (Days 6-16), mean food consumption for the 10 and 40 mg/kg/day groups was significantly lower than controls (high dose ↓20-49%, $p \leq 0.01$; mid-dose ↓10-15%, $p \leq 0.05$ or 0.01). Food consumption was not reduced during the post-treatment interval (Days 16-20) at any dose level. Because of the magnitude of the reductions and their persistence throughout treatment, with a rebound afterward, the significant differences for the 10 and 40 mg/kg/day groups were considered treatment-related. The statistically significant reduction in food consumption for the low dose was not considered treatment-related, because one finding occurred prior to dosing and it did not persist throughout treatment.Food consumption data are presented in Table 4.

Table 4. Mean maternal food consumption (g/kg/day)[a]

Interval	Dose in mg/kg/day (# of Dams)			
	0 (27)	3 (24)	10 (21)	40 (23-26)
Pre-treatment: Days 0-6	87.3	81.9*	81.0*	85.7
Treatment: Days 6-9	87.6	79.4*	77.8*	44.6**
Treatment: Days 9-12	89.8	83.3	76.1**	67.7**
Treatment: Days 12-16	82.6	83.2	74.1*	65.8**
Post-treatment: Days 16-20	80.2	84.4	82.2	91.4

a Data extracted from study report Table 3, page 33.
* $p \leq 0.05$, ** $p \leq 0.01$

4. Gross Pathology - There was no treatment-related gross pathologic finding at necropsy. The cause of death and the gestational status, of the 3 dams (40 mg/kg/day) found dead on Days 7-8, were not reported.

5. Cesarean Section Data - There were no significant differences in percent live fetuses, litter size, sex ratio, early or late resorptions, implantations/dam, Implantation losses (pre- or post-treatment), corpora lutea/dam, or number of dead fetuses for any treated group. At the high dose, a statistically significant treatment-related reduction (↓8-9%, $p \leq 0.01$) in the mean body weights of male and female fetuses was noted. Cesarean section observations are summarized in Table 5.

Table 5. Cesarean section observations[a]

Observation	Dose (mg/kg/day)			
	0	3	10	40
# Animals Assigned (Mated)	30	30	30	30
# Animals Pregnant Pregnancy Rate (%)	27 (90)	24 (80)	21 (70)	26 (87)
# Nonpregnant	3	6	9	4
Maternal Wastage # Died # Died Pregnant # Died Nonpregnant # Aborted # Premature Delivery	 0 0 0 0 0	 0 0 0 0 0	 0 0 0 0 0	 3 3 0 0 0
Total # Corpora Lutea Corpora Lutea/Dam	377 14.0	321 13.4	282 13.4	320 13.9
Total # Implantations Implantations/Dam	311 11.5	290 12.1	257 12.2	284 12.3
Total # Litters	27	24	21	23
Total # Live Fetuses Live Fetuses/Dam	290 10.7	273 11.4	243 11.6	255 11.1
Total # Dead Fetuses Dead Fetuses/Dam	0 0	0 0	0 0	2 0.1
Total # Resorptions Early Late Resorptions/Dam Early Late Litters with Total Resorptions	21 19 2 0.8 0.7 0.1 0	17 16 1 0.7 0.7 0 0	14 14 0 0.7 0.7 0 0	27 26 1 1.2 1.1 0.1 0
Mean Fetal Weight (g) Males Females	3.5 3.6 3.4	3.5 3.6 3.4	3.5 3.6 3.4	3.2** 3.3** 3.1**
Sex Ratio (% Male)	50	41	50	50
Pre-implantation Loss (%)	17.9	10.1	11.2	11.5
Post-implantation Loss (%)	6.9	6.7	6.2	9.8

a Data extracted from study report Tables 6 and 7, pages 39, 40, and 42.
* $p \leq 0.05$, ** $p \leq 0.01$

B. DEVELOPMENTAL TOXICITY

1. External Examination - There were no treatment-related malformations or variations observed upon external examination at any dose level. One fetus from the control group exhibited omphalocele and curly tail and one fetus in the 10 mg/kg/day group exhibited domed head (Table 6a). No external fetal malformations were observed in the 3 and 40 mg/kg/day treatment group.

Table 6a. External examinations[a]

Observations	Dose (mg/kg/day)			
	0	3	10	40
#Fetuses(#litters) examined	290 (27)	273 (24)	243 (21)	255 (23)
#Fetuses(#litters) affected	1 (1)	0 (0)	1 (1)	0 (0)
Domed head[b]	0 (0)	0 (0)	0.4 (4.8	0 (0)
Omphalocele[b]	0.3 (3.7)	0 (0)	0 (0)	0 (0)
Curly tail[b]	0.3 (3.7)	0 (0)	0 (0)	0 (0)

a Data extracted from study report Table 9, page 46 and 47
b %Fetuses (%litters)
* $p \leq 0.05$, ** $p \leq 0.01$

2. Visceral Examination - There was no statistically significant increased fetal or litter incidence of visceral malformations observed at any treatment level (Table 6b). Individual fetal malformations observed were two control group fetuses with kidney hypoplasia, one 10 mg/kg/day fetus with anophthalmia, and one 40 mg/kg/day fetus with a cleft palate and anophthalmia.

There were no statistically significant fetal or litter incidences of visceral variations observed at any treatment level. Individual variations observed, which were independent of dose and within the range of historical controls, included left-sided umbilical artery, reduced heart size, hydroureter, dilated renal pelvis, and mottled kidney.

Table 6b. Visceral examinations[a]

Observations	Dose (mg/kg/day)			
	0	3	10	40
#Fetuses (#litters) examined	138 (27)	128 (24)	116 (20)	122 (23)
#Fetuses (#litters) with malformations	2 (1)	0 (0)	1 (1)	1 (1)
#Fetuses (#litters) with variations	17 (10)	8 (7)	13 (11)	15 (11)
Left-sided umbilical artery[b] (V)[c]	8.0 (25.9)	5.5 (25.0)	7.8 (35.0)	8.2 (39.1)
Reduced heart size (V)	1.4 (3.7)	1.6 (8.3)	0 (0)	0.8 (4.3)
Mottled spleen (V)	0.7 (3.7)	0 (0)	0 (0)	0 (0)
Hydroureter (V)	2.2 (7.4)	0 (0)	2.6 (15.0)	3.3 (13.0)
Dilated pelvis (V) (kidney)	0 (0)	0 (0)	0 (0)	1.6 (4.3)
Mottled kidney (V)	0 (0)	0 (0)	0.9 (5.0)	0.8 (4.3)
Anophthalmia (M)[d]	0 (0)	0 (0)	0.9 (5.0)	0.8 (4.3)
Cleft palate (M)	0 (0)	0 (0)	0 (0)	0.8 (4.3)
Kidney hypoplasia (M)	1.4 (3.7)	0 (0)	0 (0)	0 (0)

a Data extracted from the study report Tables 10 and 11, pages 49, 51-54.
b % Fetuses (%litters)
c V=variations
d M=malformations

3. Skeletal Examination - Fetal skeletal malformations are summarized in Table 6c. No treatment-related, statistically significant malformation was observed for any treatment group. Among controls, individual skeletal findings included one fetus each with the following: fused and missing thoracic arches, missing lumbar arches, missing lumbar centra, missing sacral arches, missing sacral centra, malpositioned ilium and missing ribs. Observations for the 3 mg/kg/day group included extra thoracic arches, extra thoracic centra, and missing lumbar arches or lumbar centra. At 10 mg/kg/day, extra thoracic arches or centra were observed. No malformation was observed for the 40 mg/kg/day treatment group.

Table 6c. Skeletal examinations for malformations[a]

Observations	Dose (mg/kg/day)			
	0	3	10	40
#Fetuses (#litters) examined	152 (27)	145 (24)	127 (21)	133 (23)
Total #fetuses (#litters) with malformations	1 (1)	4 (3)	3 (3)	1 (1)
Premaxilla:[b] shortened	0 (0)	0 (0)	0 (0)	0.8 (4.3)
Thoracic arches: fused missing extra	0.7 (3.7) 0.7 (3.7) 0 (0)	0 (0) 0 (0) 2.8 (12.5)	0 (0) 0 (0) 2.4 (14.3)	0 (0) 0 (0) 0 (0)
Thoracic centra: extra	0 (0)	2.8 (12.5)	2.4 (14.3)	0 (0)
Lumbar arches: missing	0.7 (3.7)	1.4 (8.3)	0 (0)	0 (0)
Lumbar centra: missing	0.7 (3.7)	1.4 (8.3)	0 (0)	0 (0)
Sacral arches: missing	0.7 (3.7)	0 (0)	0 (0)	0 (0)
Sacral centra: missing	0.7 (3.7)	0 (0)	0 (0)	0 (0)
Ilium: malpositioned	0.7 (3.7)	0 (0)	0 (0)	0 (0)
Ribs: missing	0.7 (3.7)	0 (0)	0 (0)	0 (0)

a Data extracted from study report Tables 12 and 13, pages 56, 58-78
b %fetuses (%litters)

Significantly increased fetal skeletal variations were observed for the 10 and 40 mg/kg/day treatment groups as compared to controls. At 10 mg/kg/day, significant fetal increases in incompletely ossified parietal bones (↑133%, $p \leq 0.01$), enlarged sagittal sutures (↑111%, $p \leq 0.05$), enlarged posterior fontanels (↑125%, $p \leq 0.05$), and increased fetal (↑240%, $p \leq 0.01$) and litter (↑373%, $p \leq 0.01$) incidences of wavy/curved ribs were observed. These findings were not increased at the high dose and, therefore, were not dose-dependent or treatment-related. At 40 mg/kg/day, statistically significant increases in fetal skeletal variations were observed for fetuses but not litters: incompletely ossified frontal skull bones (↑28%, $p \leq 0.05$), enlarged anterior fontanels (↑23%, $p \leq 0.05$), incompletely ossified segment 2 sternebrae (↑50%, $p \leq 0.05$), unossified segment 5 sternebrae (↑190%, $p \leq 0.01$), incompletely ossified sacral arches (↑49%, $p \leq 0.01$), unossified caudal arches (↑56%, $p \leq 0.05$), incompletely ossified metacarpals (↑54%, $p \leq 0.05$), and unossified xiphoid processes (↑450%, $p \leq 0.01$). In addition, there was a significant decrease (↓50%, $p \leq 0.05$) in incidence of fetal ossified centers of ribs for the 40 mg/kg/day group as compared to controls. The retardation in fetal skeletal

ossification (growth retardation) correlates with the decreases in fetal body weights (gravid uterine weights) observed for the high-dose group. Fetal skeletal variations are summarized in Table 6d.

Table 6d. Skeletal examinations for variations[a]

Observations	Dose (mg/kg/day)			
	0	3	10	40
#Fetuses (#litters) examined	152 (27)	145 (24)	127 (21)	133 (23)
Total #fetuses (#litters) with variations	151 (27)	145 (24)	125 (21)	133 (23)
Skull bones-incompletely ossified:[b]				
Frontal	57 (96)	50 (83)	58 (95)	73*(100)
Parietal	12 (44)	8 (42)	28**(71)	12 (44)
Interparietal	24 (56)	19 (62)	35 (76)	14 (44)
Supraoccipital	20 (63)	17 (50)	28 (67)	29 (87)
Sutures:				
Sagittal-enlarged	9 (33)	3 (17)	19*(52)	8 (39)
Fontanels:				
Anterior-enlarged	60 (100)	50 (88)	61 (95)	74*(100)
Posterior-enlarged	8 (33)	5 (25)	18* (52)	8 (44)
Ribs:				
wavy/curved	5 (11)	6 (25)	17**(52)**	5 (17)
ossified center	28 (67)	29 (79)	28 (76)	14*(52)
rudimentary	7 (26)	11 (42)	13 (43)	4 (22)
Thoracic centra:				
inc. ossified	5 (30)	23 (12)	8 (43)	9 (44)
Sacral arches:				
inc. ossified	59 (93)	56 (88)	61 (95)	88**(100)
Caudal arches:				
inc. ossified	38 (93)	41 (100)	46 (95)	38 (91)
unossified	41 (78)	44 (83)	40 (76)	64*(100)
Caudal centra:				
unossified	0 (0)	0 (0)	1 (5)	2 (9)
Metacarpals:				
inc. ossified	26 (63)	19 (62)	30 (67)	40*(91)
unossified	1 (7)	0 (0)	4 (14)	5 (22)
Xiphoid processes:				
inc. ossified	78 (96)	77 (100)	76 (100)	81 (100)
unossified	2 (11)	1 (8)	4 (19)	11**(35)
Manubria:				
inc. ossified	14 (44)	14 (42)	16 (48)	22 (56)
Sternebrae:				
seg. 2-inc. ossified	13 (48)	12 (38)	19 (52)	26*(61)
-unossified	1 (7)	1 (4)	1 (5)	2 (13)
seg. 3-inc. ossified	6 (33)	8 (33)	9 (38)	12 (52)
seg. 4-inc. ossified	26 (78)	15 (58)	23 (52)	29 (87)
seg. 5-inc. ossified	74 (100)	72 (100)	62 (100)	68 (100)
-unossified	10 (41)	5 (29)	16 (43)	29**(74)

a Data extracted from study report Tables 12 and 13, pages 56, 58-78
b %fetuses (%litters)
* $p \leq 0.05$, ** $p \leq 0.01$

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS

The study author concluded that FCR 4545 Technical (96.5-97.3% a.i.) is not a primary developmental toxicant, when administered orally, based on the observation of developmental effects only at a dose level that produced maternal lethality. The maternal NOEL was reported to be 3 mg/kg/day and the maternal LOEL was 10 mg/kg/day based on reduced body weight gain and reduced food consumption with post-treatment recovery. Clinical signs of toxicity at the high-dose included hypoactivity, locomotor incoordination, and salivation. There was no reported embryotoxicity at any dose level. Reduced fetal weight and increased skeletal variations were observed in the 40 mg/kg/day test group and the developmental NOEL was reported as 10 mg/kg/day.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY: Following oral administration of FCR 4545 Technical (96.5-97.3% a.i) at 10 mg/kg/day, to pregnant rats on Days 6-16 of gestation, a reduction in body weight gain was noted on Gestational Days 6-9 (↓42%, $p \leq 0.05$) as well as an overall reduction in body weight gain (↓14%, $p \leq 0.05$), corrected for gravid uterine weight. Maternal food consumption during the treatment period (Gestational Days 6-16) was significantly reduced (↓10-15%, $p \leq 0.05$ or $p \leq 0.01$) with a rebound during the Day 16-20 post-treatment period. No clinical signs of toxicity were observed at 10 mg/kg/day.

At 40 mg/kg/day, maternal toxicity was demonstrated by 3 deaths and overall reduction in mean body weight gains during treatment (↓56%, $p \leq 0.01$) and overall during Gestational Days 0-20 (↓16%, $p \leq 0.01$). Food consumption was also reduced (↓20-49%, $p \leq 0.01$) for the high-dose group during treatment (Gestational Days 6-16), but rebounded (↑14%) during the post-treatment period (Gestational Days 16-20). The decrease in overall mean weight gain, corrected for gravid uterine weights, was ↓32% ($p \leq 0.01$). Clinical signs of toxicity included hypoactivity, locomotor incoordination, and salivation.

No biologically significant maternal toxicity was noted at 3 mg/kg/day.

Maternal NOAEL = 3 mg/kg/day
Maternal LOAEL = 10 mg/kg/day

The reviewer agrees with the study author's assessment of maternal toxicity.

2. DEVELOPMENTAL TOXICITY: Developmental effects characterized as significant decreases in fetal weights (both sexes, $p \leq 0.01$), and significant ($p \leq 0.05$ or 0.01) increases in skeletal variations, indicative of retarded growth, were noted for the 40 mg/kg/day treatment group.

   a. Deaths/Resorptions: The mean percent of early resorptions, number of dead fetuses, and mean post-implantation losses were higher for the 40 mg/kg/day group compared with those of the controls. Although these differences were not statistically significant, they are indicative of a treatment-related increase in fetolethality.

   b. Altered Growth: Fetal body weights of both sexes were significantly lower ($p \leq 0.01$) in the 40 mg/kg/day group compared with those of the controls.

   c. Developmental Variations: Fetal skeletal variations that were significantly increased ($p \leq 0.05$ or 0.01) in the 40 mg/kg/day group were enlarged anterior fontanels and incompletely or unossified bones (frontal skull bones, metacarpals, caudal arches, sacral arches, sternebrae, and xiphoid processes). In addition, the fetal incidence of ossified centers of ribs were decreased in the high-dose group. In most cases the litter incidences of these findings were comparable to controls. The retardation in fetal skeletal ossification correlates with the observed decreases in fetal body weights observed at 40 mg/kg/day.

   d. Malformations: There was no treatment-related malformation at any dose level.

   The reviewer agrees with the study author's assessment of developmental toxicity. Based on the above discussion, the developmental toxicity of FCR 4545 Technical is:

   Developmental NOAEL = 10 mg/kg/day
   Developmental LOAEL = 40 mg/kg/day

C. STUDY DEFICIENCIES: The cause of death, gestational status, and necropsy results were not reported the for the 3 dams, in the 40 mg/kg/day group, found dead on Gestational Days 7-8. This deficiency would not be expected to affect the study results.

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Chemical:	**Cyfluthrin**
PC Code:	**128831**
HED File Code	**13000 Tox Reviews**
Memo Date:	**03/16/2000 12:00:00 AM**
File ID:	**DPD230589**
Accession Number:	***412-04-0046***

HED Records Reference Center
03/25/2004