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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 2/7/2001

EPA Secondary Reviewer: Stephen Dapson
Registration Action Branch 3 (7509C)

Stephen C. Dapson, Date 02/14/2001

DATA EVALUATION RECORD

Supplement to DER for MRID No.: 42675401 Cyfluthrin: [Developmental Toxicity Study in the Rabbit] **This supplement includes a revised executive summary, including a change in the developmental NOAEL and tables supporting the change in the NOAEL.**

STUDY TYPE: Prenatal Developmental Study - Rabbit
OPPTS Number: 870.3700 OPP Guideline Number: §83-3b

DP BARCODE: D195277
P.C. CODE: 128831

SUBMISSION CODE: S448766
TOX. CHEM. NO.: 266E

TEST MATERIAL (PURITY): Cyfluthrin Technical; Cyano(fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropanecarboxylate (96%)

SYNONYMS: FCR 1272, Baythroid™

CITATION: Becker, H., Biedermann, K. (1992) Embryotoxicity study (including teratogenicity) with FCR 1272 (Baythroid) in the rabbit. RCC, Research and Consulting Company, Ltd., Itingen, Switzerland. Lab Project Number: 309914: 103980. December 3, 1992. MRID 42675401. Unpublished.

SPONSOR: Bayer AG, Wuppertal, Germany

EXECUTIVE SUMMARY:

In a developmental study (MRID 42675401), cyfluthrin (96% a.i.) in corn oil was administered via gavage to pregnant female Chinchilla (CHbb: CH, Hybrids, SPF Quality) rabbits (25/dose) during days 6-18 of gestation at dose levels of 0, 20, 60, or 180 mg/kg/day. There were no maternal deaths or clinical signs of toxicity during the study, and no treatment-related gross pathology was observed. All groups lost weight during the dosing period. The mid- and high dose groups lost a statistically significantly greater amount of weight than the control group: a loss of 40 grams in the control group versus losses of 189 and 233 grams in the mid- and high-dose groups, respectively ($p \leq 0.01$). Nonstatistically significant increases in body weight were observed in the two highest dose groups during the post-dosing period. At 180 mg/kg/day, food

consumption was decreased during days 6-15 (↓41-48%, $p \leq 0.01$) and days 15-19 (↓27%). At 60 mg/kg/day, food consumption was decreased during days 6-19 (↓24-29%). Food consumption in the 60 and 180 mg/kg/day dose groups also increased during the post-dosing period. There were no treatment-related effects on the number of live litters, fetal weights, implantations, external, visceral or skeletal malformations and variations. Postimplantation loss (expressed as a percentage of the number of implantation sites) was significantly increased at 60 mg/kg/day ($p \leq 0.05$) and 180 mg/kg/day ($p \leq 0.01$). "Embryonic resorptions" (early resorptions, when expressed as a percentage of the number of implantation sites: 3.6, 6.3, 11.5 and 15.1for the 0, 20, 60 and 180 mg/kg/day groups, respectively, were significantly increased ($p \leq 0.01$) at 60 and 180 mg/kg/day. The total number of fetuses (also expressed as a percentage of the number of implantation sites) were significantly decreased ($p \leq 0.05$) at 60 and 180 mg/kg/day: (89.1, 89.1, 80.3 and 71.5 for the 0, 20, 60 and 180 mg/kg/day groups, respectively). Upon examination of the data, it appears that the increases in resorptions over the control group are not likely to be toxicologically significant because the number of live pups/litter are comparable across the dose groups and although the control group has slightly more, there is no indication of a dose-response across a dose range of 1 order of magnitude. In addition, the individual animal data indicate that the does with a higher number of implantation sites generally have a higher number of resorptions. This is probably because the does cannot support a higher number of fetuses and thus, some are resorbed. The highest dose group had five does with 15-19 implantation sites. They each resorbed 4-9 embryos/fetuses. The control group had two does with 15 implantation sites. These 2 does resorbed 2 and 5 embryos/fetuses, respectively. The mid-dose group had one doe with 18 implantation sites. This doe resorbed 7 embryos/fetuses.

The maternal LOAEL is 60 mg/kg/day based on decreased body weight gain and food consumption during the dosing period. The maternal NOAEL is 20 mg/kg/day.

The developmental LOAEL is greater than 180 mg/kg/day. The developmental NOAEL is 180 mg/kg/day.

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a developmental study (870.3700, §83-3) in the rabbit.

RCC PROJECT 309914
FCR 1272

103980

CAE-DAM - 1
27-OCT-92

REPRODUCTION DATA
GROUP 1 (0 MG/KG)

FEMALE	CORP. LUTEA	IMPL.	-EMBRYONIC DEATHS- TOTAL	EMBR. STAGE	FETAL STAGE	FETUSES TOTAL	LIVE MALE	LIVE FEM.	DEAD MALE	DEAD FEM.	MALF. MALE	MALF. FEM.
1	14	14	1	0	1	13	7	6	0	0	0	0
2	12	11	3	3	0	8	4	4	0	0	0	0
3	13	13	2	1	1	11	7	4	0	0	0	0
4	15	15	2	1	1	13	11	2	0	0	0	0
5	11	11	3	1	2	8	4	4	0	0	0	0
6	10	10	1	0	1	9	4	5	0	0	0	0
7	14	14	1	0	1	13	5	8	0	0	0	0
8	12	10	0	0	0	10	5	5	0	0	0	0
9	11	11	0	0	0	11	4	7	0	0	0	0
10	14	14	0	0	0	14	8	6	0	0	0	1
11	14	14	1	0	1	13	6	7	0	0	1	0
12	10	8	0	0	0	8	2	6	0	0	0	0
13	11	11	0	0	0	11	6	5	0	0	0	0
14	17	15	5	0	5	10	5	5	0	0	0	0
15	14	14	1	0	1	13	6	7	0	0	1	0
16	9	8	1	1	0	7	2	5	0	0	0	1
TOTAL	201	193	21	7	14	172	86	86	0	0	2	2
MEAN	12.6	12.1	1.3	0.4	0.9	10.8	5.4	5.4			0.1	0.1
ST.DEV.	2.2	2.6	1.6	0.8	1.3	2.3	2.2	1.5			0.3	0.3

(#) Resorptions

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CAE-DAM - 2
27-OCT-92

REPRODUCTION DATA
GROUP 2 (20 MG/KG)

FEMALE	CORP. LUTEA	IMPL.	-EMBRYONIC DEATHS-- TOTAL	EMBR. STAGE	FETAL STAGE	FETUSES TOTAL	LIVE MALE	LIVE FEM.	DEAD MALE	DEAD FEM.	MALF. MALE	MALF. FEM.
17	9	9	1	0	1	8	5	3	0	0	0	1
18 <NP>												
19	12	12	0	0	0	12	10	2	0	0	0	0
20	14	13	1	0	1	12	8	4	0	0	0	0
21	11	6	0	0	0	6	2	4	0	0	0	0
22	11	7	2	1	1	5	3	2	0	0	0	0
23	12	12	3	2	1	9	6	3	0	0	0	0
24	10	8	0	0	0	8	6	2	0	0	0	0
25	4	4	3	3	0	1	0	1	0	0	0	0
26	13	13	0	0	0	13	7	6	0	0	0	0
27	12	11	2	2	0	9	5	4	0	0	0	0
28 <NP>												
29 <NP>												
30	12	12	2	0	2	10	6	4	0	0	0	0
31	12	12	0	0	0	12	7	5	0	0	0	0
32	9	9	0	0	0	9	6	5	0	0	0	0
TOTAL	141	128	16	8	6	114	71	43	0	0	0	1
MEAN	10.8	9.8	1.1	0.6	0.5	8.8	5.5	3.3				0.1
ST.DEV.	2.5	2.9	1.2	1.0	0.7	3.3	2.6	1.4				0.3

(A) Non-pregnant
(B) Resorptions

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FCR 1[illegible]

103980

CAE-DAM - 3
27-OCT-92

REPRODUCTION DATA
GROUP 3 (60 MG/KG)

FEMALE	CORP. LUTEA	IMPL.	-EMBRYONIC DEATHS- TOTAL	EMBR. STAGE	FETAL STAGE	FETUSES TOTAL	LIVE MALE	LIVE FEM.	DEAD MALE	DEAD FEM.	MALF. MALE	MALF. FEM.
33	12	12	0	0	0	12	7	5	0	0	0	0
34	15	15	1	0	1	12	7	5	0	0	0	1
35	10	10	3	0	3	7	6	1	0	0	0	0
36	10	10	0	0	0	10	6	4	0	0	0	0
37	13	13	4	1	3	9	5	4	0	0	1	0
38	8	8	1	1	0	7	4	3	0	0	0	0
39	12	12	3	1	2	9	4	5	0	0	0	0
40	13	11	1	0	1	10	5	5	0	0	0	0
41	10	8	2	2	0	6	1	5	0	0	0	0
42	13	13	2	2	0	11	4	7	0	0	0	1
43	13	13	5	5	0	8	4	4	0	0	0	0
→ 44	20	18	7	3	4	11	8	3	0	0	0	0
45	11	8	4	4	0	4	2	2	0	0	0	0
46	13	13	1	1	0	12	6	6	0	0	0	0
47	11	11	0	0	0	11	8	3	0	0	0	0
48	10	10	2	1	1	8	3	5	0	0	0	0
TOTAL	194	185	36	21	15	147	80	67	0	0	1	2
MEAN	12.1	11.4	2.3	1.3	0.9	9.2	5.0	4.2			0.1	0.1
ST.DEV.	2.7	2.6	2.0	1.5	1.3	2.4	2.0	1.5			0.3	0.3

(A) Non-pregnant
(B) Resorptions

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CAE-DAM - 4
27-OCT-92

REPRODUCTION DATA
GROUP 4 (180 MG/KG)

FEMALE	CORP. LUTEA	IMPL	-EMBRYONIC DEATHS- TOTAL	EMBR. STAGE	FETAL STAGE	FETUSES TOTAL	LIVE MALE	LIVE FEM.	DEAD MALE	DEAD FEM.	MALF. MALE	MALF. FEM.
49	15	15	0	0	0	15	9	6	0	0	0	0
→ 50	17	17	9	5	4	8	6	2	0	0	1	0
51	8	8	1	1	0	7	5	2	0	0	0	0
→ 52	19	19	7	6	1	12	5	7	0	0	1	0
53	12	12	0	0	0	12	8	4	0	0	0	0
54 <RE>	10	9	3	3								
55	11	11	2	0	2	9	4	5	0	0	0	0
56	12	12	3	3	0	3	3	0	0	0	0	0
57	10	10	6	5	1	4	2	2	0	0	1	0
58	9	9	0	0	0	9	4	5	0	0	0	0
→ 59	17	16	5	1	4	11	6	5	0	0	0	0
→ 60	16	16	6	1	5	10	4	6	0	0	0	0
61	8	7	1	0	1	6	2	4	0	0	0	0
62	11	10	2	1	1	8	5	3	0	0	0	0
→ 63	15	15	4	4	0	11	4	7	0	0	0	0
64	9	9	1	1	0	8	5	3	0	0	0	0
TOTAL	189	186	47	28	19	133	72	61	0	0	3	0
MEAN	12.6	12.4	3.1	1.9	1.3	8.9	4.8	4.1			0.2	
ST DEV	3.6	3.7	2.9	2.1	1.7	3.2	1.9	2.1			0.4	

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CAE-REPS - 1
27-OCT-92

REPRODUCTION DATA SUMMARY

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	GROUP 1 0 MG/KG	GROUP 2 20 MG/KG	GROUP 3 60 MG/KG	GROUP 4 180 MG/KG
NUMBER OF DAMS	16	13	16	15
CORPORA LUTEA	201	141	194	189
MEAN (+)	12.6	10.8	12.1	12.6
ST.DEV.	2.2	2.5	2.7	3.6
PRE-IMPLANTATION LOSS	8	13	11	3
% OF CORP. LUTEA (#)	4.0	9.2 #	5.7	1.6
MEAN (+)	0.5	1.0	0.7	0.2
ST.DEV.	0.8	1.7	1.1	0.4
NUMBER OF DAMS AFFECTED	5	5	5	3
IMPLANTATION SITES	193	128	183	186
% OF CORP. LUTEA (#)	96.0	90.8 #	94.3	98.4
MEAN (+)	12.1	9.8	11.4	12.4
ST.DEV.	2.4	2.9	2.6	3.7
POST-IMPLANTATION LOSS	21	14	36	53
% OF IMPL. SITES (#)	10.9	10.9	19.7 #	28.5 ##
MEAN (+)	1.3	1.1	2.3	3.5
ST.DEV.	1.4	1.2	2.0	3.2
NUMBER OF DAMS AFFECTED	11	7	13	12
IMPLANTATION SITE SCARS	0	0	0	6
% OF IMPL. SITES				3.2
MEAN (+)				0.4
ST.DEV.				1.5
EMBRYONIC/FETAL DEATHS : TOTAL	21	14	36	47
% OF IMPL. SITES (#)	10.9	10.9	19.7 #	25.3 ##
MEAN (+)	1.3	1.1	2.3	3.1
ST.DEV.	1.4	1.2	2.0	2.9
NUMBER OF DAMS AFFECTED	11	7	13	12
EMBRYONIC RESORPTIONS	7	8	21	28
% OF IMPL. SITES (#)	3.6	6.3	11.5 ##	15.1 ##
MEAN (+)	0.4	0.6	1.3	1.9
ST.DEV.	0.8	1.0	1.5	2.1
NUMBER OF DAMS AFFECTED	5	4	10	10
FETAL RESORPTIONS	14	6	15	19
% OF IMPL. SITES (#)	7.3	4.7	8.2	10.2
MEAN (+)	0.9	0.5	0.9	1.3
ST.DEV.	1.3	0.7	1.3	1.7
NUMBER OF DAMS AFFECTED	9	5	7	8
FETUSES				
TOTAL FETUSES	172	114	147	133
% OF IMPL. SITES (#)	89.1	89.1	80.3 #	71.5 ##
MEAN (+)	10.8	8.8	9.2	8.9
ST.DEV.	2.3	3.3	2.4	3.2
LIVE FETUSES	172	114	147	133
DEAD FETUSES	0	0	0	0
ABNORMAL FETUSES	4	1	3	3
% OF FETUSES (#)	2.3	0.9	2.0	2.3
MEAN (+)	0.3	0.1	0.2	0.2
ST.DEV.	0.4	0.3	0.4	0.4
NUMBER OF DAMS AFFECTED	4	1	3	3
ABNORMAL LIVE FETUSES AT EXTERNAL EXAMINATION	4	1	3	3
ABNORMAL DEAD FETUSES AT EXTERNAL EXAMINATION	0	0	0	0

*/** : Dunnett-Test based on pooled variance significant at level 5% (*) or 1% (**)
#/## : Fisher's Exact Test significant at level 5% (#) or 1% (##)
+ : Steel Test significant at level 5%

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CAE-REPS - 2
27-OCT-92

REPRODUCTION DATA SUMMARY

	GROUP 1 0 MG/KG	GROUP 2 20 MG/KG	GROUP 3 60 MG/KG	GROUP 4 180 MG/KG
NUMBER OF DAMS	16	13	16	15
SEX OF FETUSES				
TOTAL MALES	86	71	80	72
% OF FETUSES (#)	50.0	62.3 #	54.4	54.1
MEAN	5.4	5.5	5.0	4.8
ST.DEV.	2.2	2.6	2.0	1.9
TOTAL FEMALES	86	43	67	61
% OF FETUSES (#)	50.0	37.7 #	45.6	45.9
MEAN	5.4	3.3	4.2	4.1
ST.DEV.	1.5	1.4	1.5	2.1
LIVE MALES	86	71	80	72
LIVE FEMALES	86	43	67	61
WEIGHTS OF LIVE FETUSES (LITTER BASIS)				
TOTAL FETUSES				
N (LITTERS)	16	13	16	15
MEAN (*)	29.2	32.4	30.3	30.9
ST.DEV.	3.3	4.4	4.4	4.2
MALES				
N (LITTERS)	16	12	16	15
MEAN (*)	30.0	31.4	30.9	30.6
ST.DEV.	4.0	2.9	4.6	4.5
FEMALES				
N (LITTERS)	16	13	16	14
MEAN (*)	28.8	32.7	29.6	31.6
ST.DEV.	3.7	5.2	4.9	4.3
WEIGHTS OF LIVE FETUSES (INDIVIDUAL BASIS)				
TOTAL FETUSES				
N (FETUSES)	172	114	147	133
MEAN (*)	28.8	31.1 **	29.6	30.4 *
ST.DEV.	4.9	4.7	5.4	5.8
MALES				
N (FETUSES)	86	71	80	72
MEAN (*)	29.2	31.0	30.4	30.0
ST.DEV.	4.7	4.1	5.2	6.2
FEMALES				
N (FETUSES)	86	43	67	61
MEAN (*)	28.3	31.5 **	28.5	30.8 *
ST.DEV.	5.2	5.7	5.4	5.4

*/** : Dunnett-Test based on pooled variance significant at level 5% (*) or 1% (**)
#/## : Fisher's Exact Test significant at level 5% (#) or 1% (##)
* : Steel Test significant at level 5%

RCC PROJECT 309914
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TERMINOLOGY USED IN THE ASSESSMENT OF THE DATA

Empty implantation site	- very early resorption or aborted implantation
Embryonic resorption	- amorphous mass being resorbed
Fetal resorption	- clearly defined fetal body being resorbed
Dead fetus	- appearance of live fetus but without respiration or movement
Live fetus	- breathing and/or moving fetus
Runt	- small fetus <19.0 grams (weight of a normally developed fetus, mean over several years: 31.5 - 36.8 grams)
Abnormal finding	- malformation and/or anomaly
Skeletal variant	- variations in the number of ribs and degree of ossification of phalangeal nuclei and/or sternebrae

STATISTICAL METHODS

The following statistical methods were used to analyze body weights, food consumption, reproduction and skeletal examination data:

Univariate one-way analysis of variance was used to assess the significance of intergroup differences.

If the variables could be assumed to follow a normal distribution, the Dunnett-test (many-one t-test), based on a pooled variance estimate, was applied for intergroup comparisons (i.e. single treatment groups against the control group).

The Steel-test (many-one rank test) was applied when the data could not be assumed to follow a normal distribution.

Fisher's Exact test for 2x2 tables was applied if the variables could be dichotomized without loss of information.

Individual values, means, standard deviations and t-statistics were rounded off before printing.

References:

C. W. Dunnett, A Multiple Comparison Procedure for Comparing Several Treatments with a Control, J. Amer. Statist. Assoc. 50, 1096-1121 (1955).

Rupert G. Miller, Simultaneous Statistical Inference, Springer Verlag, New York (1981).

R.A. Fisher, Statistical Methods for Research Workers, Oliver and Boyd, Edinburgh (1950).

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

FEB - 8 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Cyfluthrin: review of a Developmental Toxicity Rabbit Study.

Tox.Chem No.: 266E
MRID No.: 42675401
DP Barcode: D195277
Submission No.: S448766
PC Code: 128831

From: John C. Redden, Toxicologist
Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

11/12/93

To: Sheila Moats
Insecticide-Rodenticide Branch
Registration Division (H7505)

Thru: Karen L. Hamernik, Ph.D.
Section Head Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

11/31/94

KLH 2/4/94

ACTION:

Review MRID No. 426754-01: a Developmental Toxicity Rabbit Study.

CONCLUSIONS:

In a developmental toxicity study, Chinchilla rabbits were administered cyfluthrin via gavage at doses of 0, 20, 60, or 180 mg/kg/day on gestational days 6-18, inclusively.

Maternal NOEL = 20 mg/kg/day
Maternal LOEL = 60 mg/kg/day based on decreased body weight gain and food consumption during the dosing period

Developmental NOEL = 20 mg/kg/day
Developmental LOEL = 60 mg/kg/day based on increased numbers of resorptions and percent incidence of postimplantation loss

The study is classified as **Guideline.** This study meets the minimum requirements set forth under EPA Guideline Series 83-3 for a developmental toxicity study in rabbits.

FINAL

DATA EVALUATION REPORT

CYFLUTHRIN

Study Type: Developmental Toxicity

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer Pia Lindström Date 10/25/93
Pia Lindström, DPH

Independent Reviewer Sanju Diwan Date 10/25/93
Sanju Diwan, Ph.D.

QA/QC Manager Sharon Segal Date 10/25/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-122
Clement Number: 386
Project Officer: Caroline Gordon

Guideline Series 83-3: Developmental Toxicity

EPA Reviewer: Myron Ottley, Ph.D. Signature: MSOttley
Review Section IV, Toxicology Branch I/HED Date: 11/29/93

EPA Section Head: Marion Copley, DVM Signature: MCopley
Review Section IV, Toxicology Branch I/HED Date: 12/3/93

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity (Rabbit); Guideline Series 83-3

EPA IDENTIFICATION NUMBERS

PC CODE: 128831

Tox Chem. No.: 266-E

MRID No.: 426754-01

TEST MATERIAL: Cyfluthrin

SYNONYMS: FCR 1272; Cyano(4-flouro-3-phenoxy-phenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropane carboxylate

SPONSOR: Bayer AG, Wuppertal, Germany

STUDY NUMBER: 309914

TESTING FACILITY: RCC, Research and Consulting Company, Ltd., Itingen, Switzerland

TITLE OF REPORT: Embryotoxicity Study (Including Teratogenicity) with FCR 1272 in the Rabbit

AUTHORS: H. Becker and K. Biedermann

REPORT ISSUED: December 3, 1992

CONCLUSIONS: In a developmental toxicity study, Chinchilla rabbits were administered cyfluthrin via gavage at doses of 0, 20, 60, or 180 mg/kg/day on gestational days (GDs) 6-18, inclusively.

Maternal NOEL = 20 mg/kg/day
Maternal LOEL = 60 mg/kg/day based on decreased body weight gain and food consumption during the dosing period

Developmental NOEL = 20 mg/kg/day
Developmental LOEL = 60 mg/kg/day based on increased numbers of resorptions and % incidence of postimplantation loss

CLASSIFICATION: Core Guideline Data. This study meets the minimum requirements set forth under EPA Guideline Series 83-3 for a developmental toxicity study in rabbits.

A. MATERIALS

Test Compound

Purity: 96%
Description: Viscous oil with crystalline parts
Batch number: 238 005 176
Receipt date: Not reported
Contaminants: None reported
Storage: Room temperature/in dark

Vehicle: Corn oil

Test Animals

Species: Rabbit
Strain: Chinchilla (CHbb: CH, Hybrids, SPF Quality)
Source: Dr. Karl Thomae GmbH, and SAVO Med. Versuchstier zuchten GmbH, Germany
Age: 16-27 Weeks at mating
Weight: 3189-4626 g on GD 0
Males used: Proven fertile residents at RCC

B. STUDY DESIGN

This study was designed to assess the potential of cyfluthrin to cause developmental toxicity in rabbits when administered daily via gavage from GDs 6-18, inclusively.

Mating: Following approximately one week of acclimation, females were housed with males in a ratio of 1:1. The fertility of the males used in this study was continuously monitored. The day copulation was observed was designated GD 0. Specific details of how mating was confirmed were not stated.

Animal husbandry: Food (Kliba 341 rabbit maintenance diet) and tap water were available ad libitum throughout the study. A 12/12-hour light/dark cycle was maintained. Temperature was maintained at 20°±3°C and humidity was maintained at 40%-70%. There were 10-15 air changes per hour.

Group arrangement: Animals were manually assigned to the following dose groups based on the distribution of males to which the females were mated:

Test Group	Dose Level (mg/kg/day)	Number Assigned per Group
Control	0	25
Low-dose	20	25
Mid-dose	60	25
High-dose	180	25

Dose administered: Doses were prepared and administered daily via gavage from GDs 6 through 18 in a volume of 2 mL/kg. Individual doses were calculated based on the most recently recorded body weight data. Dosing solutions were not adjusted for active ingredient. Analyses for concentration, stability and homogeneity were conducted in a previous range-finding study and were confirmed once in this study.

Dose rationale: Doses were selected based on the results of two range-finding studies (RRC Project Nos. 309903 and 316855). The results of these studies were not presented.

Observations: Animals were observed twice daily for mortality, moribundity, and clinical signs. Body weight data were recorded daily throughout the study. Food consumption data were recorded for the following intervals: GDs 0-6, 6-11, 11-15, 15-19, 19-24, and 24-28. On GD 28 animals were sacrificed by cervical dislocation and litters were delivered by cesarean section. Examination of the does at sacrifice included the following:

- Gross pathological observations of all internal organs
- Gravid uterine weights
- Number of corpora lutea
- Number of implantation sites
- Numbers of resorptions (early and late) and live and dead fetuses

Uteri from apparently nonpregnant animals were stained with ammonium sulfide using the method described by Salewski (1964) to detect early embryonic loss.

Examination of live fetuses included the following:

- Individual fetal weight and sex
- External anomalies for all fetuses
- Visceral anomalies for all fetuses
- Heads for approximately one-half of the fetuses using the method described by Wilson (1965)
- Skeletal anomalies for all fetuses using a modified method described by Dawson (1926)

Statistical analysis: The following methods were used.

- Normally distributed data--ANOVA and Dunnett's test
- Non-normally distributed data--Steele's test
- Dichotomized data--Fischer's Exact test

Compliance

- A signed Statement of No Data Confidentiality Claims, dated February 16, 1993, was provided.
- A signed Statement of Compliance with EPA, OECD, and Swiss GLPs, dated February 16, 1993, was provided.
- A signed Quality Assurance Statement, dated December 3, 1992, was provided.

C. RESULTS

Test Material Analysis

Concentration, homogeneity, and stability analyses revealed values ranging from 96% to 102% of target.

Maternal Toxicity

Mortality: No mortality was observed at any dose level.

Abortion: No abortions were reported at any dose level.

Clinical observations: No compound-related clinical signs were observed at any dose level.

Body weight: Compound-related effects on body weight gain were observed at 180 and 60 mg/kg/day. A summary of body weight gain for selected intervals is presented in Table 1. Body weight gain decreased significantly at 180 and 60 mg/kg/day during the dosing period. During the postdosing period, nonsignificant increases were noted. Corrected body weight gain was comparable in all dose groups. Body weights were similar to control for all dose groups throughout the study.

Food consumption: Compound-related effects on food consumption (g/animal/day) were observed at 180 and 60 mg/kg/day. A summary of food consumption for selected intervals is presented in Table 2. Food consumption decreased significantly during the following intervals: GDs 6-11 at 180 and 60 mg/kg/day and GDs 11-15 at 180 mg/kg/day. It increased significantly during GDs 24-28. Food efficiency was not determined.

Gross pathological observations: No compound-related gross pathology was observed.

Cesarean section observations: Compound-related effects were observed at 180 and 60 mg/kg/day. A summary of cesarean section data is presented in Table 3. Postimplantation loss increased significantly at 180 and 60 mg/kg/day. In addition, the total number of resorptions was significantly ($p \leq 0.05$) greater than control and the total number of fetuses was significantly ($p \leq 0.05$) lower than control at 180 and 60 mg/kg/day, when expressed as a percentage of the number of implantation sites (data not shown). Incidental (but statistically significant) changes were

noted at 20 mg/kg/day in sex ratio (Table 3) and in percent implantation sites of corpora lutea (data not shown).

Developmental Toxicity

No compound-related effects were observed at any dose level. A summary of gross, visceral, and skeletal malformations is presented in Table 4.

External examinations: External malformations in the control group consisted of four fetuses from different litters, two runts and two with multiple malformations (Table 4). At 20 mg/kg/day, one fetus had omphalocele. At 60 and 180 mg/kg/day, three fetuses per dose group, all from different litters, were runts. External variations were not reported.

Visceral examinations: Visceral malformations were limited to one fetus at 180 mg/kg/day with a hemidiaphragm. Visceral variations were not reported.

Skeletal examinations: Skeletal malformations at 0 and 20 mg/kg/day consisted of three fetuses from different litters at each dose level with multiple malformations (Table 4). At 60 mg/kg/day, three fetuses from the same litter had fused ribs or sternebrae. At 180 mg/kg/day, two fetuses from one litter had bifurcated ribs or multiple malformations; and three additional fetuses from different litters had either a single or multiple malformation(s). Skeletal variations, including incomplete ossification and flying ribs, were noted in all dose groups.

D. DISCUSSION/CONCLUSIONS

Acceptance Criteria

The reviewers have completed an Acceptance Criteria check list (Attachment I) to be included with the evaluation of the study. All criteria were satisfied.

Test Material Analyses

Analyses for concentration revealed values within ±5% of nominals. Stability analysis revealed that the test material was stable in the vehicle for at least 2 hours at room temperature. Homogeneity of the test material in the vehicle was confirmed.

Maternal Toxicity

Compound-related and dose-dependent maternal toxicity was observed at 180 and 60 mg/kg/day. It was manifested as significantly decreased body weight gain and food consumption during the dosing period which was followed by increases in these parameters during the postdosing period. Based on these results, the NOEL and LOEL for maternal toxicity were 20 and 60 mg/kg/day, respectively.

Developmental Toxicity

Developmental toxicity was observed at 180 and 60 mg/kg/day in a dose-dependent manner. It was manifested as significantly increased numbers of resorptions (total, as well as per litter). This effect was also reflected in the increased postimplantation loss at these dose levels.

Study/Reporting Deficiencies

Study deficiencies included failure to submit a protocol and failure to provide standard deviations for body weight gain and food consumption data. However, these deficiencies did not affect the interpretation of study results.

E. CORE CLASSIFICATION: Core Guideline Data.

Maternal NOEL = 20 mg/kg/day
Maternal LOEL = 60 mg/kg/day (based on decreased body weight gain and food consumption)

Developmental Toxicity NOEL = 20 mg/kg/day
Developmental Toxicity LOEL = 60 mg/kg/day (based on increased resorptions and % incidence of postimplantation loss)

F. RISK ASSESSMENT: Not applicable

TABLE 1. Mean Body Weight Gain (g)[a,b]

Dose Group (mg/kg/day)	Prior to Dosing Period (GDs 0-6)	Dosing Period (GDs 6-19)	Post-Dosing Period (GDs 19-28)	Gestation Period (GDs 6-28)	Corrected Body Weight Gain (GDs 6-28)
0	176	-40	127	87	-421 ± 162[c]
20	212	-34	177	143	-307 ± 221
60	185	-189**	231	42	-412 ± 269
180	194	-233**	227	-6	-471 ± 292

[a]Data were extracted from Study No. 309914, pg. 38-42.

[b]S.D. not provided for most intervals

[c]Mean ± S.D.

**Significantly different from control ($p \leq 0.01$)

TABLE 2. Mean Food Consumption (g/animal/day)[a]

Exposure Periods	Dose groups (mg/kg/day) 0	20	60	180
GDs 0-6	219 ± 39	216 ± 26	215 ± 30	233 ± 26
GDs 6-11	146 ± 45	124 ± 41	107 ± 52	76 ± 41**
GDs 11-15	140 ± 46	132 ± 35	100 ± 64	82 ± 47**
GDs 15-19	102 ± 42	105 ± 52	78 ± 51	74 ± 52
GDs 19-24	150 ± 33	164 ± 27	169 ± 50	167 ± 51
GDs 24-28	121 ± 34	146 ± 36	161 ± 29**	178 ± 32**

[a]Data were extracted from Study No. 309914, pg. 27.

TABLE 3. Cesarean Section Observations[a]

Parameter	Dose Level (mg/kg/day) 0	20	60	180
No. animals mated	16	16	16	16
No. animals pregnant	16	13	16	16
Pregnancy rate (%)[b]	100	81	100	100
Maternal wastage				
No. died/nonpregnant	0	0	0	0
No. died/pregnant	0	0	0	0
No. nonpregnant	0	3	0	0
No. aborted	0	0	0	0
Gravid uterine weight(g)	508 ± 75[c]	450 ± 132	455 ± 87	464 ± 112
Does with 100% resorptions	0	0	0	1
Does with live litters	16	13	16	15
Total corpora lutea	201	141	194	189
Corpora lutes/doe	12.6 ± 2.2	10.8 ± 2.5	12.1 ± 2.7	12.6 ± 3.6
Total implantations	193	128	183	186
Implantations/doe	12.1 ± 2.4	9.8 ± 2.9	11.4 ± 2.6	12.4 ± 3.7
Total live fetuses	172	114	147	133
Live fetuses/doe	10.8 ± 2.3	8.8 ± 3.3	9.2 ± 2.4	8.9 ± 3.2
Total resorptions	21	14	36	47
Early resorptions	7	8	21	28
Late resorptions	14	6	15	19
Resorptions/doe	1.3 ± 1.4	1.1 ± 1.2	2.3 ± 2.0	3.1 ± 2.9
Total dead fetuses	0	0	0	0
Fetal weight/litter (g)	29.2 ± 3.3	32.4 ± 4.4	30.3 ± 4.4	30.9 ± 4.2
Preimplantation loss (%)	4	9*	6	2
Postimplantation loss (%)	11	11	20*	29**
Sex ratio (% male)	50	62*	54	54

[a]Data were extracted from Study No. 309914, pg. 21, 38-42, and 46-47.

[b]Calculated by the reviewers; not statistically analyzed

[c]Mean ± S.D.

*Significantly different from control ($p \leq 0.05$)

**Significantly different from control ($p \leq 0.01$)

TABLE 4. Incidences of Fetal Malformations[a]

Findings[b]	Dose Level (mg/kg/day) 0	20	60	180
No. fetuses (litters) examined	172 (16)	114 (13)	147 (16)	133 (15)
External Malformations				
Runt	2 (2)	0	3 (3)	3 (3)
Omphalocele	1	1	0	0
Cheilognathopalatoschisis	1	0	0	0
Cranioschisis	1	0	0	0
Arthrogryposis	1	0	0	0
Open eye	2 (2)	0	0	0
Total No. fetuses (litters) with any external malformation	4 (4)	1	3 (3)	3 (3)
Visceral Malformations				
Hemidiaphragm	0	0	0	1
Total No. fetuses (litters) with any visceral malformation	0	0	0	1
Skeletal Malformations				
Fused sternebra	1	0	1	2 (2)
Fused vertebral arches	1	0	0	0
Missing, fused or bipartite vertebral body and/or arches	1	3 (3)	0	2 (2)
Partial aplasia of cranium	1	0	0	0
Abnormal structure of vertebral column and ribs	0	1	0	0
Scoliosis	0	1	0	0
Shortened trunk	0	1	0	0
Bifurcated or missing ribs	0	3 (3)	0	2 (2)
Fused ribs	0	2 (2)	2 (1)	2 (2)
Tip of tail missing	0	0	0	1
Fused vertebral bodies	0	0	0	1
Total No. fetuses (litters) with any skeletal malformation	3 (3)	3 (3)	3 (1)	5 (4)
Total No. fetuses (litters) with any malformation	6 (6)	3 (3)	6 (4)	8 (6)

[a]Data were extracted from Study No. 3309914, pg. 52-66.

[b]More than one type of malformation may be found in one fetus.

ATTACHMENT I

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.	YES	Technical form of the active ingredient tested.
2.	YES	At least 20 pregnant animals/dose group for mice, rats, or hamsters are available. At least 12 pregnant animals/dose group for rabbits are available (three test groups and control group).
3.	YES	At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg).
4.*	YES	At the low dose, no developmental toxicity is reported.
5.	YES	Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6.*	YES	Analysis for test material stability, homogeneity, and concentration in dosing medium.
7.	YES	Individual daily observations.
8.	YES	Individual body weights.
9.	YES	Individual food consumption.
10.	YES	Necropsy on all animals.
11.	YES	Individual uterine examination, including numbers of fetal deaths, early and late resorptions, and viable fetuses per sex.
12.	YES	All ovaries examined to determine number of corpora lutea.
13.	YES	Individual litter weights and/or individual fetal weights/sex/litter.
14.	YES	Individual fetal external examination.
15.	YES	Individual fetal skeletal examination for 1/3 to 1/2 of each litter for rodents and all for rabbits.
16.	YES	Individual fetal soft tissue examination.

Criteria marked with an asterisk (*) are supplemental, may not be required for every study.

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Chemical:	**Cyfluthrin**
PC Code:	**128831**
HED File Code	**13000 Tox Reviews**
Memo Date:	**02/14/2001 12:00:00 AM**
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