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

PC 128831

2

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.: 40780401 Cyfluthrin: [Developmental Study in the Rat via Inhalation] **This supplement includes a revised executive summary and summary tables.**

STUDY TYPE: Developmental Toxicity via Inhalation - Rat
OPPTS Number: 870.3700 OPP Guideline Number: §83-3a

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128831 TOX. CHEM. NO.: 266E

TEST MATERIAL (PURITY): Cyfluthrin Technical: Cyano(fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropanecarboxylate (92.9% and 93%)

SYNONYMS: FCR 1272, Baythroid™

CITATION: Renhof, M.; Pauluhn, J. (1988) FCR 1272: Common Name Cyfluthrin: Study for Embryotoxic Effects on Rats after Inhalation. Bayer AG Toxicology Division, Federal Republic of Germany. Report No. 16391: Laboratory Project ID Report No. 97403. February 1, 1988. MRID 40780401. Unpublished study.

SPONSOR: Mobay Corporation, Agricultural Chemicals Division

EXECUTIVE SUMMARY: Two developmental toxicity studies via inhalation (MRID 40780401) were conducted. In the first study, 4 groups of 30 female Bor:WISW (SPF Cpb) rats were inseminated by being housed overnight with males. The presence of sperm in the vaginal smears following mating established gestation day 0. The dams were dynamically exposed head-only to cyfluthrin dissolved in a 1:1 mixture of Lutrol and ethanol at analytical concentrations of 0, 0.0011, 0.0047 or 0.0237 mg/L/day for 6 hours/day on gestation days 6 through 15. A second study was conducted in order to establish a NOAEL for offspring toxicity . In that study, the dams were exposed to analytical concentrations of 0, 0.00009, 0.00025, 0.00059 or 0.0042 mg/L of the test material. The MMAD was 1.23 - 1.45 µm in the first study and 1.29 - 1.53 µm in the second study. An oxygen enriched atmosphere (30%) was provided for the 0.0042 mg/L group to see if the embryotoxic effects seen in the first study at this concentration could be lessened. The rats were observed several times on the exposure days except during the exposures (because

of restraint for head-only exposure). They were weighed on gestation days 0, 6, 9, 12 and 20. The dams were sacrificed on day 20 and their pups removed by caesarian section. Their ovaries and uteri were examined for implantations, live young, embryonic and fetal deaths, fetal sex and weights, and external fetal abnormalities.

Combining the results of the two studies, maternal effects were observed at 0.0047 mg/L and above: reduced motility, dyspnea, piloerection, ungroomed coats and eye irritation. The symptoms were mainly observed after the end of exposure in the 0.0047 mg/L concentration group and were largely gone by the next exposure day. At 0.0237 mg/L concentration, the symptoms were observed at greater intensity over the entire exposure period. Effects in the pups were observed at 0.0011 mg/L and above. At 0.0011 mg/L and above, a dose-related increase in the incidence of runts and skeletal anomalies in the sternum were observed. At 0.0047 mg/L and above, biologically significant decreases in pup weights were observed ($p < 0.01$). At 0.0237 mg/L, increases in post-implantation loss, late embryonic deaths and in skeletal anomalies in the extremities were observed as well as microphthalmia.

The maternal NOAEL is 0.0011 mg/L and the maternal LOAEL is 0.0047 mg/L (reduced motility, dyspnea, piloerection, ungroomed coats and eye irritation.

The developmental NOAEL is 0.00059 mg/L and the developmental LOAEL is 0.0011 mg/L (increases in the incidence of runts and skeletal anomalies in the sternum).

An *ad hoc* committee met on 4/22/93 to discuss the developmental toxicity data base for cyfluthrin. At that time, the Committee recommended that due to deficiencies that were mentioned in the review of the study, this study should be re-examined if it is to be used as a regulatory endpoint. Although the study had been graded Acceptable and NOAELs and LOAELs had been established for maternal and developmental toxicity, comments had also been made that developmental anomalies in the study had not been adequately reported. The dams in this study had reflex apnea, although it was poorly characterized.

This study is classified as **acceptable guideline** and satisfies the guideline requirement for a developmental toxicity study in the rat via inhalation (870.3700, **§83-3a**).

Cyfluthrin Developmental Inhalation Study in the Rat: Clinical Signs in Dams

Clinical Sign	Number of Dams Affected (Earliest Gestation Day of Initiation)				
Study Number 1					
Dose (mg/L)	0	0.0011	0.0047[a]	0.0237	
Reduced motility	-	-	18/30 (6)	27/29 (6)	
Dyspnea	-	-	5/30 (7)	20/29 (6)	
Eye irritation	-	-	19/30 (6)	29/29 (6)	
Ungroomed coat	-	-	-	8 (8)	
Bristling coast (piloerection)	-	-	26/30 (7)	29/29 (6)	
Study Number 2					
Dose (mg/L)	0	0.00009	0.00025	0.00059	0.00416
Reduced motility	-	-	-	-	-
Dyspnea	-	-	-	-	-
Eye irritation	-	-	-	-	-
Ungroomed coat	-	-	-	-	-
Bristling coast (piloerection)	-	-	-	-	-

(-): no clinical signs observed.

[a] Data extracted from MRID number 40780401 from the individual animal data starting on page 64.

Cyfluthrin Developmental Inhalation Study in the Rat: Maternal Body Weight Gain (g)[a]

Interval	Dose (# of Dams)				
	Control (30)	LDT (30)	MDT (30)	HDT (30)	
Study Number 1					
Dose (mg/L)	0	0.0011	0.0047	0.0237	
Pretreatment: Days 0 - 6	19.3	17.6	17.9	19.5	
Treatment: Days 6 -15	4.3	1.5	-8.0	-11.6	
Posttreatment: Days 15 - 20	39.3	45.1	41.3	36.6	
Study Number 2					
Dose (mg/L)	0	0.00009	0.00025	0.00059	0.00416
Pretreatment: Days 0 - 6	15.6	17.8	18.3	17.6	18.4
Treatment: Days 6 -15	-2.1	3.7	-1.7	0.7	-7.3
Posttreatment: Days 15 - 20	27.8	39.2	32.0	39.0	29.4

a Data extracted from MRID number 40780401and table 3. Data were given in body weights. Estimated body weight gains were calculated by the reviewer from the mean body weights.

Cyfluthrin Developmental Inhalation Study in the Rat: Cesarian Section Observations[a]				
Study Number 1				
Dose (mg/L)	0	0.0011	0.0047	0.0237
# Animals Assigned	30	30	30	30
# Animals Inseminated	30	30	30	30
# Animals Fertilized	25 (83.3)	29 (96.7)	29 (96.7)	29 (96.7)
Pregnancy Rate (% Fertilization)	25 (100.0)	29 (100.0)	27 (93.1)	29 (100.0)
Maternal Wastage				
# Died	0	0	0	1
# # Died/Pregnant	0	0	0	1
# Non pregnant	5	1	1	1
# Aborted	0	0	0	0
# Premature Delivery	0	0	0	0
Total Corpora Lutea	Not available	Not available	Not available	Not available
Corpora Lutea/Dam				
Total Implantations	288	354	339	324
Implantations/Dam	11.5	12.2	11.7	11.6
Total Live Fetuses	271	329	292	261
Live Fetuses/Dam	10.8	11.3	10.8[b]	9.3
Total Resorptions	17	25	22[b]	63
Early	2	5	3[b]	6
Late	15	20	19	57
Resorptions/Dam	0.7	0.9	0.81[b]	2.3*
Total Dead Fetuses	0	0	0	0
Dead Fetuses/Dam	0	0	0	0
Mean Fetal Weight (g)	3.40	3.16*	2.89**	2.43**
Preimplantation Loss	Not available	Not available	Not available	Not available
Postimplantation Loss (%)				
Total	5.9	7.1	6.5[b]	19.4
Per Dam	6.1	7.4	6.9[b]	19.8
Sex Ratio (% Male)	53.7	50.4	54.5	46.2

[a]Data extracted from MRID number 40780401and Tables 6-9; Appendix, page 143

* $p < 0.05$; ** $p < 0.01$

[b] Does not include the two dams that fully resorbed their litters.

Cyfluthrin Developmental Inhalation Study in the Rat: Cesarian Section Observations[a]					
Study Number 2					
Dose (mg/L)	0	0.00009	0.00025	0.00059	0.00416
# Animals Assigned	30	30	30	30	30
# Animals Inseminated	30	30	30	30	30
# Animals Fertilized	23 (76.7)	29 (96.7)	25 (83.3)	29 (96.7)	22 (73.3)
Pregnancy Rate (% Fertilization)	23 (100.0)	29 (100.0)	25 (100.0)	29 (100.0)	22 (100.0)
Maternal Wastage					
# Died	0	0	0	0	0
# # Died/Pregnant	0	0	0	0	0
# Non pregnant	7	1	5	1	8
# Aborted	0	0	0	0	0
# Premature Delivery	0	0	0	0	0
Total Corpora Lutea	Not available	Not available	Not available	Not available	Not available
Corpora Lutea/Dam					
Total Implantations	246	330	280	320	246
Implantations/Dam	10.7	11.4	11.2	11.0	11.2
Total Live Fetuses	206	277	221	268	209
Live Fetuses/Dam	9.0	9.6	8.8	9.2	9.5
Total Resorptions	40	52	59	52	37
Early	3	10	8	6	5
Late	37	42	51	46	32
Resorptions/Dam	1.7	1.8	2.4	1.8	1.7
Total Dead Fetuses	0	0	0	0	0
Dead Fetuses/Dam	0	0	0	0	0
Mean Fetal Weight (g)	3.48	3.51	3.53	3.47	3.29[b]*
Preimplantation Loss	Not available	Not available	Not available	Not available	Not available
Postimplantation Loss (%)					
Total	16.3	15.8	21.1	16.3	15.0
Per Dam	15.9	15.8	21.4	16.4	15.2
Sex Ratio (% Male)	48.9	54.2	50.0	53.3	54.7

[a]Data extracted from MRID number 40780401and Tables 10-14: Appendix, pages 144-145

* $p < 0.05$

[b] This exposure group provided with an oxygen rich atmosphere (30%).

Cyfluthrin Developmental Inhalation Study in the Rat: External Examinations

Study Number 1

Observations*	Control	0.0011 mg/L	0.0047 mg/L	0.0237 mg/L
#fetuses(litters) examined	188 (25)[a]	228 (29)	204 (27)	184 (29)
Runts	5 (4)[b]	58 (16)	132 (21)	212 (27)

(*) some observations may be grouped together
([a]) fetal [litter] incidence
([b])Data extracted from MRID number 40780401 from the individual animal data starting on page 112

Study Number 2

Dose Level (mg/L)	Control	0.00009	0.00025	0.00059	0.00416
Observations*					
#fetuses(litters) examined	145 (23)[a]	193 (29)	156 (25)	104 (29)	146 (22)
Runts	8(5)[b]	11(8)	8 (6)	6 (5)	25 (11)

(*) some observations may be grouped together
([a]) fetal [litter] incidence
([b]) Data extracted from MRID number 40780401 from the individual animal data starting on page 118.

Cyfluthrin Developmental Inhalation Study in the Rat
Skeletal Examinations (Bone Alterations)

Study Number 1

Observations*	Control	0.0011 mg/L	0.0047 mg/L	0.0237 mg/L
#fetuses(litters) examined	188 (25)[a]	228 (29)	204 (27)	184 (29)
Sternum	4 (1)[b]	17 (10)	31 (16)	124 (25)
Extremities	1 (1)	0 (0)	1 (1)	8 (4)
Pelvis	0 (0)	0 (0)	0 (0)	3 (2)
Skull	8 (2)	13 (12)	5 (3)	1 (1)

([a]) fetal [litter] incidence
[b] Data extracted from MRID number 40780401 from the individual animal data starting on page146.

Cyfluthrin Developmental Inhalation Study in the Rat
Skeletal Examinations (Bone Alterations)

Study Number 2

Dose (mg/L)	Control	0.0.00009	0.00025	0.00059	0.00416
Observations[+]					
#fetuses(litters) examined	145 (23)[a]	193 (29)	156 (25)	104 (29)	146 (22)
Sternum	0 (0)[b]	5 (5)	4 (2)	4 (4)	7 (6)
Extremities	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Pelvis	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Skull	17 (8)	11 (8)	10 (7)	4 (4)	7 (5)

([+]) some observations may be grouped together
([a]) fetal [litter] incidence
([b]) Data extracted from MRID number 40780401 from the individual animal data starting on page 146.

Cyfluthrin Developmental Inhalation Study in the Rat: Malformations

Study Number 1

Observations[+]	Control	0.0011 mg/L	0.0047 mg/L	0.0237 mg/L
#fetuses(litters) examined	188 (25)[a]	228 (29)	204 (27)	184 (29)
Microphthalmia	1 (1)[b]	2 (2)	1 (1)	8 (5)

([+]) some observations may be grouped together
([a]) fetal [litter] incidence
([b]) Data extracted from MRID number 40780401 from the individual animal data starting on page 31.

Study Number 2

Dose Levels (mg/L)	Control	0.00009	0.00025	0.00059	0.00416
Observations[+]					
#fetuses(litters) examined	145 (23)[a]	193 (29)	156 (25)	104 (29)	146 (22)
Microphthalmia	1 (1)[b,c]	1 (1)	2 (2)	1 (1)	1 (1)

([a]) fetal [litter] incidence
([b]) anophthalmia in this case
([c]) Data extracted from MRID # 40780401 from the individual animal data starting on page 31.

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

NOV 28 1989

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Cyfluthrin - Review of an Inhalation Teratology Study in Rats

EPA Nos. 3125-356
Record Nos. 229600

Project No. 8-1060
Tox. Chem. No. 266E

TO: George LaRocca (PM Team #15)
Registration Division (TS-767c)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section I, Insecticide, Rodenticide Branch
Health Effects Division (TS-769c)

7-21-89

THRU: Edwin R. Budd, Section Head
Section I, Insecticide, Rodenticide Branch
Health Effects Division (TS-769c)

7/31/89

Acting

The Registrant, Mobay Chemical Company, submitted an Inhalation Teratology study of FCR 1272 (cyfluthrin) in rats. This study was reviewed and classified Core Minimum. Despite its deficiencies, this study was accepted because it demonstrated cyfluthrin's teratogenic potential by the inhalation route. Skeletal anomaly incidence was presented by general structure only, so there was no way of knowing the nature or location of the anomalies. The visceral anomaly data were also not clearly presented. The criteria used for defining a runt, a key finding in this study, were not given.

Thus, the exact nature of the terata is unclear. These positive findings stand in contrast to the negative findings seen in an oral teratology study performed at the same laboratory. The defined doses for these two studies are as follows:

Rat Oral Teratology [Bayer AG Institut Fur Toxicologie; Report No. 10562; 1-20-82]

Maternal NOEL = 3 mg/kg/day
Maternal LEL = 10 mg/kg/day (behavioral changes in gait and coordination)
Fetotoxic NOEL >30 mg/kg/day
Teratogenic NOEL >30 mg/kg/day

Rat Inhalation Teratology [Bayer AG Toxicology Division; Report Nos. T 0020125 & T 3021686]

Maternal NOEL = 0.0011 mg/l
Maternal LEL = 0.0047 mg/l (reduced motility, dyspnea, piloerection, ungroomed coats, and eye irritation)
Developmental NOEL = 0.00059 mg/l
Developmental LEL = 0.0011 mg/l (unspecified sternal anomalies, increased runt incidence)

Unlike the oral study, cyfluthrin caused developmental toxicity at or below the maternal LEL when administered by inhalation. It is possible that using inhalation to bypass portal circulation may have exposed both the dams and their pups to more parent compound and less metabolite. The two metabolism studies reviewed to date are inadequate to confirm or deny this theory, however.

Section II, Tox. Branch I (TS-769C)
Secondary reviewer: Edwin R. Budd
Section II, Tox. Branch I (TS-769C)

7/31/89

Acting

DATA EVALUATION REPORT

STUDY TYPE: Teratology Study in Rats by Inhalation

ACCESSION NUMBER: 407804-01

TOX. CHEM. NO.: 266E

TEST MATERIAL: FCR 1272 (93% pure)
Batch No. 233490583
Brownish viscous substance

MRID NO.: N/A

SYNONYMS: Cyfluthrin

STUDY NUMBER(S): Bayer No. T 0020125, T 3021686
Mobay No. 97403

SPONSOR: Mobay Corporation

TESTING FACILITY: Bayer AG Toxicology Division (Fed. Rep. of Germany)

TITLE OF REPORT: Study for Embryotoxic Effects on Rats After Inhalation

AUTHOR(S): M. Renhof and J. Pauluhn

REPORT ISSUED: February 1, 1988

CONCLUSIONS: Despite the deficiencies of this study, it is evident that FCR 1272 is teratogenic when administered by inhalation. Striking differences between this study and an oral teratology study performed at the same laboratory suggest that bypassing portal circulation may expose the rats to more parent compound and less metabolite. The defined doses are as follows:

Maternal NOEL = 0.0011 mg/l
Maternal LEL = 0.0047 mg/l (reduced motility, dyspnea, piloerection, ungroomed coats, and eye irritation)
Developmental NOEL = 0.00059 mg/l
Developmental LEL = 0.0011 mg/l (unspecified sternal anomalies, increased runt incidence)

STUDY CLASSIFICATION: This study is classified CORE MINIMUM. Despite its deficiencies, this study is acceptable because it demonstrated cyfluthrin's teratogenic potential. Skeletal anomaly incidence was presented by general structure only (e.g. sternum, skull, extremities, etc.); there was no way of telling where the anomalies were found, or what the anomalies actually were (e.g. fusions, delayed ossifications, etc.). There was also no presentation of visceral anomaly data, although some data were combined with the list of external malformations. The criteria used for defining a runt were not given. Historical control data would have been useful. This study received Quality Assurance review.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: This study was performed in two parts, the first study and the second study. In the First Study, four groups of 30 female (187-250 g) Bor:WISW (SPF Cpb) rats were inseminated by being housed overnight with males (>300 g). The presence of sperm in the vaginal smears following mating established gestation day 0. The females were exposed head-only to the test article in a 20 liter PVC dynamic inhalation chamber for 6 hours/day on gestation days 6 through 15. The nominal FCR 1272 chamber concentrations were 0 (vehicle control), 0.001, 0.005, and 0.025 mg/l. In the Second study, additional groups of 30 inseminated females were similarly exposed to nominal chamber concentrations of 0 (vehicle control), 0.0001, 0.0003, 0.0006, and 0.005 mg/l. An oxygen enriched atmosphere (30%) was provided for the 0.005 mg/l group to see if the embryotoxic effects seen in the first study at this concentration could be lessened.

The test article was dissolved in a 1:1 mixture of Lutrol (polyethylene glycol E 400) and ethanol. The test article formulations were prepared daily, and aerosolized with binary spray nozzles. Samples of the chamber atmospheres were collected on cotton wool in glass tubes placed in the rats' breathing zone. Analytical measurements were made using gas chromatography and high pressure liquid chromatography. Particle size measurements were made with an APS 3300 aerodynamic particle sizer and a Berner cascade impactor. The integrity of the aerosol generator was assured during exposure with a Ratfisch RS 55 total hydrocarbon analyser. Food and water were available ad libitum.

The rats were observed several times on the exposure days except during the exposures (because of restraint for head-only exposure). They were weighed on gestation days 0, 6, 9, 12, and 20.

The dams were sacrificed on day 20 and their pups removed by caesarean section. Their ovaries and uteri were examined for implantations, live young, embryonic and fetal deaths, fetal sex and weights, and external fetal abnormalities. Approximately a third of the fetuses were examined by the method of Wilson (1965) for visceral malformations, and the remaining fetuses were eviscerated, clarified, stained with alizarin red S, and examined for skeletal defects by the method of Dawson.

RESULTS: The results from the first and second studies will be presented together. Dose concentration analyses measured analytical concentrations to be within 13% and 17% of nominal in the first and second studies, respectively. The majority of aerosol particles in all concentrations were in the respirable range (<1 um). The nominal and analytical concentrations, mass median aerodynamic diameter (MMAD) values with geometric standard deviations, and mortality were as follows:

Concentration (mg/l/day) Nominal	Analytical	MMAD (Gsd)	Mortality
FIRST STUDY:			
0	0	1.40 (1.41) um	0/30
0.001	0.0011	1.23 (1.33) um	0/30
0.005	0.0047	1.45 (1.42) um	0/30
0.025	0.0237	1.23 (1.34) um	1/30*

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R058522

Chemical:	**Cyfluthrin**
PC Code:	**128831**
HED File Code	**13000 Tox Reviews**
Memo Date:	**02/13/2001 12:00:00 AM**
File ID:	**00000000**
Accession Number:	**412-04-0046**

HED Records Reference Center
03/25/2004