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Cyfluthrin **Reproduction Study (83-4); 870.3800**

for Reviewer: Laurence D. Chitlik, D.A.B.T. Pamela M Hurley, Date 2/28/2002
Toxicology Branch I (7509C)
Secondary Reviewer: Pamela M. Hurley, Ph.D. Pamela M Hurley, Date 2/28/2002
Registration Action Branch 2 (7509C)

Note: This supplement provides an Executive Summary and data not included in the original DER for MRID No. 00131532

DATA EVALUATION RECORD

STUDY TYPE :Multigeneration Reproduction - Rat OPPTS 870.3800 [§83-4]

TEST MATERIAL (PURITY): FCR 1272 (purity not reported in the test report)

SYNONYMS/CODES: Cyfluthrin

CITATION: Loeser E. and Eiben R. (1983) FCR 1272 Multigeneration Study on Rats. Bayer AG Institut Fuer Toxikologie, Wuppertal, Federal republic of Germany, Bayer Report Number 11870, Mobay ACD Report No. I 85881. June 8, 1983. MRID No. 00131532. Unpublished Report.

SPONSOR: Mobay Chemical Corporation

EXECUTIVE SUMMARY: In a 3-generation reproduction study (MRID 00131532) FCR 1272 (reported to be a composite of five batches 2/80, 3/80, 5/80, 6/80 and 7/80 as a 50% premix with Wessalon S; % a.i. not specified) was administered in the diet to groups of 10 male and 20 female BOR:WISW SPF rats per dose at concentrations of 0, 50, 150, or 450 ppm (equivalent to 0, 3.8/5.4, 12.3/15.1, or 37.2/48.5 (M/F) mg/kg/day) for three generations. Fresh mixtures of the test material were prepared weekly. During the mating period, two females were placed together with one male. From the F0 parental generation, F1a, F1b, F2a, F2b, and F3a and F3b generations were produced.

Parental toxicity was observed at the high dose level in all generations manifested by treatment related decreases in body weight gains. No deaths, gross pathology or histopathology findings associated with administration of the test material were noted. **The LOAEL for parental toxicity is 450 ppm (37.2/48.5 mg/kg/day) and the NOAEL is 150 ppm (12.3/15.1 mg/kg/day) based upon decreases in body weight gain.**

Offspring toxicity manifested as decreases in the 5 day viability indices at 15.1 and 48.5 mg/kg/day for the F1a, F2a, F3a, and F3b generations. The F3b 5 day viability index was 99.0,

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Parental toxicity was observed at the high dose level in all generations manifested by treatment related decreases in body weight gains. No deaths, gross pathology or histopathology findings associated with administration of the test material were noted. **The LOAEL for parental toxicity is 450 ppm (37.2/48.5 mg/kg/day) and the NOAEL is 150 ppm (12.3/15.1 mg/kg/day) based upon decreases in body weight gain.**

Offspring toxicity manifested as decreases in the 5 day viability indices at 15.1 and 48.5 mg/kg/day for the F1a, F2a, F3a, and F3b generations. The F3b 5 day viability index was 99.0,

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EXECUTIVE SUMMARY: In this study (MRID 00131532) FCR 1272 (reported to be a composite of five batches 2/80, 3/80, 5/80, 6/80 and 7/80 as a 50% premix with Wessalon S; % a.i. not specified) was administered in the diet to groups of 10 male and 20 female BOR:WISW SPF rats per dose at concentrations of 0, 50, 150, or 450 ppm (equivalent to 0, 2.5, 7.5, or 22.5 mg/kg/day) for three generations. Fresh mixtures of the test material were prepared weekly. During the mating period, two females were placed together with one male. From the F0 parental generation, F1a, F1b, F2a, F2b, and F3a and F3b generations were produced.

Parental toxicity was observed at the high dose level in all generations manifested by treatment related decreases in body weight gains. No deaths, gross pathology or histopathology findings associated with administration of the test material were noted. **The LOAEL for parental toxicity is 450 ppm (22.5 mg/kg/day) and the NOAEL is 150 ppm (7.5 mg/kg/day) based upon decreases in body weight gain.**

Offspring toxicity manifested as decreases in the 5 day viability indices at 7.5 and 22.5 mg/kg/day for the F1a, F2a, F3a, and F3b generations. The F3b 5 day viability index was 99.0, 92.3, 89.0, and 77.4 for the control, low, mid, and high doses, respectively. This persisted to some degree since the Lactation Index (viability at the end of the lactation period) was also reduced after 4 weeks in the F1a, F1b, F2b, and F3b litters. In addition, at the 150 and 450 ppm dose levels, pup body weight gains were decreased. Effects were not apparent on the fertility indices, gestation indices, sex ratios , number of pups per litter, stillbirths, pup body weights at birth, gross pathology and histopathology. **The LOAEL for offspring toxicity is 150 ppm (7.5 mg/kg/day based on decreased viability persisting through the lactation period and decreased body weight gains. The offspring NOAEL is 50 ppm (2.5 mg/kg/day).**

This reproduction study is **acceptable** and satisfies the guideline requirement for a reproduction study in the rat (§83-4).

COMPLIANCE: No signed and dated GLP, Quality Assurance, Statement of No Data Confidentiality, and Flagging statements were provided.

Body weights from a two-generation study of cyfluthrin (MRID# 00131532; Bayer report 11870, Mobay report 85881; authors Loeser, E. and Eigen, R. (1983)).

Dose Levels (ppm)	0	50	150	450
Male P_0				
Week 0	91	89	90	89
Week 14	333	348	330	312
Body wt gain (wk 0-14)	242	259	240	223 (92)[a]
Week 15	340	354	336	315*
Week 19	344	356	339	320
Week 34	386	405	371	356*
Body wt gain (wk 19-34)	42	49	32 (76)	36 (86)
Female P_0				
Week 0	85	85	85	84
Week 14	195	198	195	189
Body wt gain (wk 0-14)	110	113	110	105
Week 19	233	235	219	206** (88)
Week 33	261	263	246	237** (91)
Body wt gain (19-33)	28	28	27	31

[a](% control)

Dose Levels (ppm)	0	50	150	450
$F1_a$ M&F pup wt				
$F1_a$ Birth	5.9	5.9	5.5	5.5*
Week 1	12.9	12.5	12.1	9.9**
Week 2	23.9	23.4	21.5*	17.7**
Week 3	35.4	34.1	30.8**	25.4**
Week 4	53.6	54.9	47.9*	39.5**
$F1_b$ M&F pup wt				
Birth	5.6	5.9	5.8	5.6
Week 1	13.0	14.0	12.3	11.1**
Week 2	24.3	23.6	22.2	20.0**
Week 3	35.3	35.3	33.0	29.1**
Week 4	53.8	53.9	49.2	45.6**
$F1_b$ Males				
Week 5	85.1	86.1	83.6	69.8**
Week 9	200	184	149**	160**
Week 35	419	375*	330**	333**
Week 39	432	382*	342**	347**
Body wt. gain (5-39)	347	296 (85)[a]	258 (74)	277 (80)
$F1_b$ females				
Week 5	77.1	80.1	73.0	64.3**
Week 9	134	141	128	121**
Week 35	241	257	247	223*
Week 39	239	240	236	216*
Body wt. gain (5-39)	162	160	163	152 (94)

Dose Levels (ppm)	0	50	150	450
$F2_a$ M&F pup wt				
Birth	6.1	5.6*	5.9	5.5*
Week 1	14.0	12.3**	12.0**	11.5**
Week 2	24.5	21.1**	unreadable*	19.4**
Week 3	35.5	31.3*	32.6	27.1**
Week 4	54.1	48.7	49.0	44.7**
$F2_b$ M&F pup wt				
Birth	5.9	5.9	5.5	5.6
Week 1	14.5	12.8	11.3*	10.8*
Week 2	25.5	22.9	20.4*	20.2*
Week 3	40.0	36.6	33.9*	31.5*
Week 4	62.1	56.4	51.1**	47.1**
$F2_b$ males				
Week 9	192	210	193	163
Week 13	284	307	280	246*
Week 39	398	406	373*	349*
Body wt gain (9-39)	206	196	180 (87)	186 (90)
Female $F2_b$				
Week 9	142	139	132**	127**
Week 13	178	176	167**	161**
Week 39	232	227	224	215**
Body wt gain (9-39)	90	88	92	88
$F3_a$ M&F pup wt				
Birth	6.0	5.8	5.8	5.5

Dose Levels (ppm)	0	50	150	450
Week 1	14.6	13.3	11.8**	11.0**
Week 2	26.3	24.8*	22.3**	21.1**
Week 3	39.4	37.7	34.3*	32.3**
Week 4	58.5	55.3	51.5*	50.8**
$F3_b$ M&F pup wt				
Birth	5.8	5.4	5.4	5.7
Week 1	13.7	12.3	12.2*	12.4
Week 2	25.3	22.9	22.8*	22.8
Week 4	49.1	44.5	42.6*	42.9

[a]( ) = percent of control

The Lactation Index and offspring body weights were affected as shown in the following table:

Dose level	Lactation Index for F1a	Mean birth Wt for F1a (grams)	Lactation Index for F1b	Mean birth Wt for F1b (grams)	Lactation index for F2a	Mean Birth wt for F2a (grams)	Lactation Index for F2b	Mean Birth Wt for F2b (grams)	Lactation index for F3a	Mean birth Wt for F3a (grams)	Lactation Index for F3b	Mean birth Wt for F3b (grams)
0	99.5	5.9	96.0	5.6	95.1	6.1	93.1	5.9	94.3	6.0	97.7	5.8
50	97.7	5.9	95.5	5.9	91.9	5.6*	92.6	5.9	94.3	5.8	94.9	5.4
150	97.2	5.5ns	91.4	5.8	91.8	5.9	75.8**	5.5	90.4	5.8	98.3	5.4
450	87.1**	5.5*	83.5**	5.6	80.2**	5.5*	72.4**	5.6	92.3	5.5	91.5*	5.7

* Statistically Significant at P<0.05
**Statistically Significant at P<0.01

Note that birth weights were reduced only for the F1a and F2a generations at the high dose level.. However, during growth periods, weight gain was reduced in the F1a, F1b, F2b, F3a and F3b pups. Together, these data confirm offspring toxicity at the 450 dose level only.

Day 5 viability data are presented below:

Viability Indices at day 5

Dose level (PPM)	F1a	F1b	F2a	F2b	F3a	F3b
0	100	91.2	98.6	88.0	96.1	99.0
50	99.5	98.0**	96.2	93.7	94.1	92.3**
150	93.9**	97.6*	94.1	83.2	77.0**	89.0**
450	96.7*	91.4	91.9*	88.0	77.8**	77.4**

*Statistically significant at p 0.05
**Statistically significant at p<0.01

When the day 5 viability index is examined for all matings/generations as noted in the table above, it is apparent that offspring toxicity is also affected in a reasonably consistent manner at the 150 ppm dose level. These data together suggest that the NOAEL for offspring toxicity is the 50 ppm dose level (2.5 mg/kg/day).

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FCR 1272 (Proposed Common Name: Cyfluthrin) Multigeneration Study in Rats.

Bayer, A.G., Institute fur Toxikologie, Report No. 11870 (also Mobil No. 85881), June 8, 1983. EPA Acc. No. 072009, Tab. 3.6.2.

1. The test material used for this study was FCR 1272 and was from five batches designated as 2/80, 3/80, 5/80, 6/80 and 7/80. The purity of the material was not stated because the batches were as "pre-mix concentrates" at 50% with Wessalon S. The report stated that stability and homogeneity in the feed were checked before the start of the study but supporting data were not provided in the report.

2. The test animals used were SPF rats of the BOR:WISW strain and were bred by a German supplier. At the start of the study, the rats were 5-6 weeks old. There were 4 groups of 10 males and 20 females in each test group and they were dosed as either 0, 50, 150 or 450 ppm. Six sets of litters were bred. F_1a and F_2b from the F_0 parental groups; F_2a and F_2b from the F_1b parental groups and F_3a and F_3b from the F_2b parental groups. For each mating one male rat was mated with 2 female rats.

3. Survival, general appearance and behavioral reactions in adult rats. No test chemical related deaths were reported. Body weight gain for the adults was definitely depressed at 450 ppm for all groups.

4. Reproductive performance

   a. Fertility index (number of pregnant females/number of mated females.) No consistent change in the fertility index was noted. Usually 90-100% pregnancies resulted. The F_1b parents had occasions of 65-85% pregnancies and the F_2b generation high dose group resulted in the lowest rate (65%). This trend was not evident in the F_3a or b generations.

   b. Gestation index (number of females with live litters/number of pregnant females). No effects were noted and the gestation index was usually 90-100%.

   c. Viability index (number of live pups after 5 days/number of pups born). Indication of decreased viability was evident for the F_1a, F_2a, F_3a and F_3b generations. The F_3a and F_3b generations were most noticeably affected. For example, the F_3b generation had viability

indexes of 99.0, 92.3, 89.0, and 77.4 for the control, low, mid and high dose groups.

For the purpose of this study, the NOEL is set at 50 ppm because the decrease at 50 ppm is not consistent through the 6 litter sets and it is considered by this reviewer to be reasonably close to and within control range values.

NOEL = 150

d. Lactation index (number of live pups after 4 weeks/no. of live pups at day 5, after reduction to 10): decreases in the lactation index were evident for the F_1a, F_1b, F_2a, F_2b and F_3b litter sets. The maximum difference was found for the F_2a and F_2b groups which were 75.8 and 72.4% for the mid and high dose levels versus 93.1% for the control group.

LOEL = 150

5. Condition of the pups

a. Sex ratio - was not affected, there were approximately equal numbers of males and females.

b. Number of pups - For the F_1b and the F_3a groups there appeared to be few pups in the high dose group, but this trend was not evident in the other 4 litter sets.

c. Stillbirths - The F_1b group had 6 stillbirths in the high dose test group but the other litter sets did not show evidence of dose related stillbirths.

d. Body weight at birth - Body weight of the pups at birth was small for some occasions but this was not consistent for the high dose test group for all 6 of the litter sets.

e. Body weight gain of the pups - A NOEL for decrease or retarded weight gain is set at 50 ppm. At 150 and 450 ppm there was noted consistent effects and slower weight gain.

LOEL = 150

6. Gross necropsy and histopathology. The 4-week-old pups from the F_3b generation and their parents (the F_2b generation) were necropsied and subjected to histopathology. A single male and female from each of 10 dams from the control and high dose groups were examined histologically.

No dose related changes were noted by either gross necropsy or histopathology of the parents or pups examined.

The livers, kidneys and testes or ovaries of the parental rats were determined but no test chemical effects were noted.

Conclusion: This study is Core Minimum. The NOEL for a decrease in the viability index is set at 50 ppm. There were noted occasions of pup deaths at 150 and 450 ppm. A NOEL for systemic effects is set at 50 ppm. Body weight decreases in the pups are noted at 150 and 450 ppm.

Pages 13-25 - *Access to FIFRA health and safety data is restricted under FIFRA

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