(EXCERPT)
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TASK: 107
September 3, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

28-Day Feeding Study in the Rat

STUDY IDENTIFICATION: Moyes, A., Godley, M. J., Hall, M., Pratt, I., Stonard, R. D., Tinston, D. J., and Forbes, D. 28-Day feeding study in the rat. (Unpublished study No. PR 0397 and report No. CTL/P/1013 by Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, U.K., for Imperial Chemicals Industries, Alderley Park, Macclesfield, Cheshire, U.K., dated May 15, 1984) Accession No. 073204.

APPROVED BY:

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Date: 9-3-85

1. CHEMICAL: Cyhalothrin [(RS)α-cyano-3-phenoxybenzyl(z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane-carboxylate].

2. TEST MATERIAL: Viscous dark brown liquid with a 89.2% (w/w) cyhalothrin content. Unspecified as to technical grade or formulation. The CTL reference number was Y00102/010/001.

3. STUDY/ACTION TYPE: Subchronic (28-day) feeding study in rats.

4. STUDY IDENTIFICATION: Moyes, A., Godley, M. J., Hall, M., Pratt, I., Stonard, R. D., Tinston, D. J., and Forbes, D. 28-Day feeding study in the rat. (Unpublished study No. PR 0397 and report No. CTL/P/1013 by Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, U.K., for Imperial Chemicals Industries, Alderley Park, Macclesfield, Cheshire, U.K., dated May 15, 1984) Accession No. 073204.

5. REVIEWED BY:

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7. CONCLUSIONS:

Feeding cyhalothrin to rats caused a significant decrease in mean body weight gain during the first week of the study in males receiving 250 ppm ($p \leq .05$) and in females receiving 10, 20 ($p \leq .05$), or 250 ($p \leq .01$) ppm. In addition, there was a significant reduction in mean weight gain over the 4 weeks of the study in males receiving 250 ppm ($p \leq .05$) and females receiving 20 or 250 ($p \leq .05$) ppm. Hepatic aminopyrine demethylase activity (HADA) was increased, and smooth endoplasmic reticulum (SER) was proliferated in the livers of rats of both sexes receiving the high dose of cyhalothrin. Liver weights were not significantly affected by the test substance, but liver-to-body weight ratios were higher ($p \leq .01$) in the male 250 ppm group. As defined within the scope of this study, the NOEL for cyhalothrin in female rats is 10 ppm and the LOEL is 20 ppm; and the NOEL in male rats is 20 ppm and the LOEL 250 ppm.

Item 8 - see footnote 1.

9. BACKGROUND:

In a previous 28-day feeding study in rats (Faupel, P. F., et al., 1980), male rats fed 20 ppm cyhalothrin showed a trend towards elevated hepatic aminopyrine-N-demethylase activity at termination. At dietary levels of 20 ppm and above, there was proliferation of hepatic smooth endoplasmic reticulum (SER) in male rats and in the female rats fed 250 ppm cyhalothrin. The present study was designed to establish a no effect level (NOEL) to be used in setting levels for a long-term study.

Item 10 - see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

1. The cyhalothrin used in the study was supplied by ICI, Ltd. pharmaceutical division. It was a dark brown viscous liquid with a cyhalothrin content of 89.2% (w/w).

2. The test animals were Wistar derived Alderley Park rats, bred as SPF animals. Dosing started when the animals were 5 weeks old.

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[1] Only items appropriate to the DER have been included.

3. The basal diet was Porton Combined Diet (PCD) manufactured by Special Diets Service. The test substance was applied to the diet as an acetone solution. Pellets were made and air dried in a furnace at 50°C. The dietary dosages of cyhalothrin were control, 1, 5, 10, 20, and 250 ppm.

4. Animals were randomly distributed to experimental groups using a shuffle card method. Body weights, body weight gains, liver weights, ratios, hepatic APDM, and quantified E.M. results were compared, test to control, using a two-sided Student's t-test.

5. Test and control diets were prepared for analysis of cyhalothrin by Soxhlet extraction, cleaned up through Florisil columns and the eluate analyzed by gas-liquid chromatography using an electron capture detector.

B. Protocol:

See Materials and Methods in Appendix A.

12. REPORTED RESULTS:

A. The cyhalothrin content of all but one of the test diets was found to be within ± 10% of the target cyhalothrin content; the 1 ppm diet was 81% of the target cyhalothrin content.

B. No deaths occurred. No signs of toxicity or clinical observations related to the test substance were seen at any dose level throughout the study. Mean body weights and mean body weight gains are presented in Table 1 and Table 2, respectively. There were statistically significant reductions in body weight gains during the first week of study for males and females receiving 250 ppm ($p \leq .01$) cyhalothrin and for the females receiving 10 and 20 ppm ($p \leq .05$). Also, there was a significant reduction ($p \leq .05$) in body weight gain from the start to completion of the study for males and females receiving 250 ppm cyhalothrin and for the females receiving 20 ppm. Mean body weight was significantly reduced ($p \leq .05$) at the 250 ppm level in weeks 1 and 2 of the study. In the males receiving 250 ppm cyhalothrin, liver-to-body weight ratios were increased ($p \leq .01$) while liver weight was lower than the control but not significantly reduced. There was a significant reduction ($p \leq .05$) in liver weight in females receiving 20 ppm cyhalothrin; the liver-to-body weight ratio was not affected. HADA activity was increased ($p \leq .01$) in both sexes receiving 250 ppm cyhalothrin. Mild but statistically significant ($p \leq .01$) pro- liferation of smooth endoplasmic reticulum (SER) in hepatocytes was seen in male and female rats receiving 250 ppm cyhalothrin. A few males in the 20 ppm group also showed SER proliferation but this was not statistically different from control values.

C. Table 3 presents the results of mean liver weights, mean liver-to-body weight ratios, hepatic aminopyrine-N-demethylase activity (HADA), and smooth endoplasmic reticulum measurements (SER).

TABLE 1. Mean Body Weights for Rats Fed Cyhalothrin for 4 Weeks

Week	Dietary Concentration (ppm) 0	1	5	10	20	250
Males						
0	124.9	111.9	118.6	120.0	116.5	117.5
1	181.0	166.5	176.0	176.1	175.4	152.1*
2	233.0	215.4	230.4	228.4	230.8	204.4*
3	278.9	263.0	276.0	273.9	280.9	251.0
4	319.4	296.1 (93)[a]	319.9 (100)	314.4 (98)	323.0 (101)	286.0 (90)
Females						
0	94.6	96.8	106.9	109.6	107.9	104.5
1	142.3	140.8	145.4	142.8	141.0	131.0
2	167.8	164.3	171.8	167.4	163.1	160.1
3	190.0	185.3	196.5	186.6	185.0	182.1
4	210.4	201.9 (96)	215.8 (102)	203.8 (100)	197.9 (94)	197.0 (94)

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

[a]Percent of control.

TABLE 2. Mean Body Weight Gain for Rats Fed Cyhalothrin for 4 Weeks

Week	Dietary Concentration (ppm) 0	1	5	10	20	250
Males						
0 - 1	56.1	54.6	57.4	56.1	58.9	34.6**
1 - 2	52.1	48.9	54.4	52.3	55.4	52.3
2 - 3	45.8	47.6	45.6	45.5	50.1	46.6
3 - 4	40.5	33.1	43.9	40.5	42.1	35.0
0 - 4	194.5	184.3	201.3	194.4	206.5	168.5*
Females						
0 - 1	47.6	44.0	38.5	33.1*	33.1*	26.5**
1 - 2	25.5	23.5	26.4	24.6	22.1	29.1
2 - 3	22.3	21.0	24.8	19.3	21.9	22.0
3 - 4	20.4	16.6	19.3	17.1	12.9	14.9
0 - 4	115.8	105.1	108.9	94.1	90.0*	92.5*

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

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

TABLE 3. Selected Liver Data for Rats Fed Cyhalothrin for 4 Weeks

Effect Measured	Dietary Concentration (ppm) 0.0	1.0	5.0	10	20	250
Males						
Liver Weight (g)	15.581	14.364	15.723	15.703	16.323	14.926
Liver/Body Wt. Ratio	4.871	4.852	4.913	4.977	5.049	5.212**
HADA[a]	30.9	30.2	29.5	32.5	30.5	43.9**
SER[b]	134.3	--	--	131.8	146.3	169.7**
Females						
Liver Weight (g)	9.923	9.551	9.988	9.553	8.925*	9.076
Liver/Body Wt. Ratio	4.720	4.727	4.632	4.690	4.508	4.608
HADA	12.6	12.4	12.0	14.1	13.6	17.7**
SER	109.4	--	--	--	105.8	130.9**

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

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

[a] Hepatic Aminopyrine Demethylase Activity expressed as µmol formaldehyde/hour/g tissue.

[b] Smooth Endoplasmic Reticulum.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. "In conclusion, cyhalothrin produced definite toxicological effects at a dietary level of 250 ppm. This level is recommended as the maximum level for a long-term feeding study. The no effect level achieved in this study is 10 ppm cyhalothrin." Principal toxic effects included weight gain suppression and liver toxicity consisting of increased SER proliferation and increased HADA activity.

B. The draft and final reports were audited for good laboratory practice and the methods and results given in the report were felt to reflect the data produced during the study.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. This specific study design was based on results obtained from a prior study in which liver alterations were found. There was no effect on survival at any dosage level. No judgment can be made on signs of toxicity as no data were included. Body weight was statistically decreased ($p \leq .05$) in male rats at 250 ppm for the first 2 weeks. The male 250 ppm group's weight gain was decreased at week one only, while the females' weight gains were decreased at 10, 20, and 250 ppm for week one. When weight gains were examined over the entire study, there was a decrease for the males at 250 ppm and for the females at 20 and 250 ppm. Although no food consumption measurements were taken, it appears that body weight and body weight gains were compound affected early in the study, with accommodation taking place.

The liver is clearly affected due to dietary exposure to cyhalothrin. The significantly reduced liver weight for the female 20 ppm group appears not to follow a dose-effect relationship and does not appear to be compound related. The male rats at 250 ppm showed an increased liver weight-to-body weight ratio, increased HADA, and proliferation of the SER. The female rats at the 250 ppm level showed increased HADA and proliferation of the SER. The SER proliferation occurred without a concommitant increase in liver weight.

B. There are no substantive differences between conclusions reported by the study authors and those of the reviewer.

C. The study was not designed as a core study but as a follow-up to set the NOEL and LOEL for cyhalothrin in rats. As defined within the scope of this study, the NOEL for cyhalothrin in rats is 10 ppm and the LOEL is 20 ppm based on body weight and liver effects.

Item 15 - see footnote 1.

16. CBI APPENDIX:

Appendix A (CBI pp. 2-7) Materials and Methods.

Core Classification: Core supplemental because the design and conduct of the study were so limited.